SUPPLEMENTARY APPENDIX 6: Evidence Report/Summary of Findings Tables

2020 American College of Rheumatology Guideline for the Management of Reproductive Health in Rheumatic and Musculoskeletal Diseases

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OBJECTIVES

The objective of this project is to develop recommendations related to the management of reproductive health issues for rheumatic disease patients. Specifically, we aim to focus on the following areas:

- PART I: REPRODUCTIVE HEALTH MANAGEMENT
  - **Pre-pregnancy:**
    - Contraception safety and efficacy
    - Fertility preservation in the setting of cyclophosphamide therapy
    - Assisted reproductive technology safety and management
    - Counseling in anticipation of pregnancy
  - **Pregnancy:**
    - Pregnancy management including management of antiphospholipid antibody-positive patients
    - Management and monitoring of the anti-Ro/La+ mother
    - Menopause and use of hormone replacement therapy
    - Long-term issues

- PART II: MEDICATION USE BEFORE, DURING, AND AFTER PREGNANCY
    - Safety of paternal medication exposure
    - Medication safety during pregnancy
    - Corticosteroid safety in pregnancy
    - Medication safety during lactation
    - Long-term issues in the offspring

Using this evidence report

Navigation through this document will be most efficient if the reader uses the navigation pane (Found under View→show Navigation Pane). Each section is linked to via different headings with the top level heading being the main part of the report (Part I, Part II) and each lower-level heading links to the main topic area and then each individual set of questions.

When reviewing this report and the guideline statement, the most efficient way to find the evidence linked with a given statement is to search (Find) for the guideline statement number (e.g. GS2, GS2A, GS2B).

METHODS

Identification of Studies

Literature search strategies, based on PICO questions (Population/patients, Intervention, Comparator, and Outcomes; *see Appendix A*) were developed by the principal investigators, systematic literature review leader, and a research librarian, with input from the Core Team. The search

strategies were peer reviewed by another medical librarian using Peer Review of Electronic Search Strategies (PRESS) (1). Searches were performed in OVID Medline (1946 +), Embase (1974 +), the Cochrane Library, and PubMed (mid-1960s +).

The search strategies were developed using the controlled vocabulary or thesauri language for each database: Medical Subject Headings (MeSH) for OVID Medline, PubMed and Cochrane Library; and Emtree terms for Embase. Text words were also be used in OVID Medline, PubMed, and Embase, and keyword/title/abstract words in the Cochrane Library.

Search Limits

Only English language articles were retrieved.

Grey Literature

The websites of appropriate agencies, such as the Agency for Healthcare Research and Quality (AHRQ), were searched for peer-reviewed reports not indexed by electronic databases.

Literature Search Update

Literature searches will be updated just before the voting panel meeting to ensure completeness.

Inclusion/Exclusion Criteria

Each PICO question outlines the defined patient population, interventions, comparators and outcomes, and each PICO is provided at the beginning of each summary, below.

Management of Studies and Data

References and abstracts were imported into bibliographic management software (Reference Manager) (2), duplicates removed, and exported to Distiller SR, a web-based systematic review manager (3). Screening and data abstraction forms were created in Distiller SR. Search results were divided among reviewers, and two reviewers screened each title/abstract, with disagreements at the title/abstract screening stage being resolved by the Methodological Lead (K.E.D.). Following the same dual review process, disagreements at the full manuscript screening stage were discussed and adjudicated by the literature review leadership, if necessary.

Analysis and Synthesis

The literature review team analyzed and synthesized data from included studies that address the PICO questions. This evidence profile, including a GRADE Summary of Findings table, was prepared for each PICO question using Review Manager (RevMan) (2, 4) and GRADEprofiler (GRADEpro) software (5). The Summary of Findings table contains the benefits and harms for each outcome across studies, the assumed and

corresponding risk for comparators and interventions (95% CI), the absolute risk and relative effect (95% CI), the number of participants/number of studies, and the certainty in the evidence for each critical and important outcome (i.e., high, moderate, low or very low).

Quality Assessment

- Quality assessment was performed separately for each outcome using the GRADE system, which results in one of four possible evidence grades that reflect level of confidence in the effect estimate: high, moderate, low, and very low.
- Study design is the starting point for quality assessment: randomized controlled trials (RCTs) start at high quality and observational studies start at low quality.
- Five factors can lower the quality of evidence grade: risk of bias, inconsistency, indirectness, imprecision, and publication bias.
- Risk of bias refers to limitations in study design or execution (e.g. lack of allocation concealment or blinding).
- Inconsistency refers to unexplained heterogeneity in results of studies evaluating the same outcome.
- Indirectness refers to lack of direct comparisons of interventions of interest (e.g. studies comparing drug A vs. placebo and drug B vs. placebo when the comparison of interest is drug A vs. drug B), lack of applicability in the interventions or populations being evaluated, or use of indirect (surrogate) outcome measures.
- Imprecision refers to uncertainty in the estimate of effect due to very low numbers of patients or events and/or wide 95% confidence intervals that cross a clinical decision threshold (i.e. between recommending and not recommending treatment).
- Publication bias refers to selective publication of studies that show greater treatment effects (i.e. negative studies are suppressed).
- Quality of evidence can vary from outcome to outcome. The final quality assessment for the PICO question is based on the critical outcome with the lowest quality assessment.

Interpreting the evidence

- It is important to take into account the information presented specifically as it relates to the question of interest. For example, when we are asking in PICO 1. A.16 what the impact of estrogen-progestin contraception versus no hormonal contraception use is on risk of thrombosis in women with APS with or without underlying RD, but the available evidence does not include the appropriate comparison group for this question, this evidence is indirect, and appropriately gets downgraded for indirectness as shown under the column labeled “indirectness.” The quality of evidence takes these sorts of things into account, and is appropriately rated as high, moderate, low or very low. This quality of evidence is key to your decisions.

Moving from evidence to recommendations

- In GRADE, recommendations can be either strong or conditional. Generally, strong recommendations are restricted to high or moderate quality evidence. Low quality evidence almost invariably mandates a weak recommendation.
- There are, however, situations in which low quality evidence can lead to strong recommendations. For instance, if we have low quality evidence favoring an intervention but high quality evidence of important harm we may make a strong recommendation against the intervention.

References

References for each summary are located at the end of the summary and appear in order of first mention. A complete list of references is located at the end of the evidence report and is organized alphabetically.

References

1. Sampson M, McGowan J, Lefebvre C, Moher D, Grimshaw J. PRESS: Peer Review of Electronic Search Strategies. Ottawa: Canadian Agency for Drugs and Technologies in Health; 2008.
2. Review Manager [software]. Oxford (UK): Cochrane Collaboration; 2013. http://ims.cochrane.org/revman
3. DistillerSR. Ottawa, Canada: Evidence Partners; 2013. http://systematic-review.net/
4. Reference Manager [software]. Thomson Reuters; 2013. http://www.refman.com/
5. GRADEprofiler [software]. Oxford (UK): Cochrane Collaboration; 2013. http://ims.cochrane.org/revman/gradepro

PART I: REPRODUCTIVE HEALTH MANAGEMENT

1. Contraception

1A.

In women with RD who are of childbearing age [variables listed] what is the impact of hormonal contraception use [variables listed] versus no hormonal contraception use on risk of thrombosis?

Populations: Women with RD at risk for pregnancy
- RD without aPL (aCL, ab2GPI, LAC)
- SLE without aPL
- RD with aPL but no APS
- APS with or without underlying RD (history of thrombosis or obstetrical complication)

Interventions: Use of specific forms of effective hormonal birth control including:
- Estrogen-progestin pill, patch or vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- Depot medroxyprogesterone acetate (DMPA)

Comparators: RD patients at risk for pregnancy not using hormonal birth control, including:
- Male contraception/ sterilization
- Copper IUD
- Not sexually active/abstinence
- Barrier contraception
- Tubal ligation/hysterectomy

Outcome:
- Risk of thrombosis

1. In women with RD who are of childbearing age with non-lupus rheumatic disease and negative aPL antibodies, what is the impact of estrogen-progestin contraception (pill, patch or vaginal ring) versus no hormonal contraception use on risk of thrombosis? **QUESTIONS 1-5 RELEVANCE: GS1, BUT NO EVIDENCE**
No evidence

2. In women with RD who are of childbearing age with non-lupus rheumatic disease and negative aPL antibodies, what is the impact of the progestin IUD versus no hormonal contraception use on risk of thrombosis?
No evidence

3. In women with RD who are of childbearing age with non-lupus rheumatic disease and negative aPL antibodies, what is the impact of the progestin pill versus no hormonal contraception use on risk of thrombosis?
No evidence

4. In women with RD who are of childbearing age with non-lupus rheumatic disease and negative aPL antibodies, what is the impact of the progestin subdermal implant versus no hormonal contraception use on risk of thrombosis?
No evidence

5. In women with RD who are of childbearing age with non-lupus rheumatic disease and negative aPL antibodies, what is the impact of IM depo-medroxyprogesterone acetate versus no hormonal contraception use on risk of thrombosis?
No evidence

6. In women with RD who are of childbearing age with SLE and negative aPL antibodies, what is the impact of estrogen-progestin contraception (pill, patch or vaginal ring) versus no hormonal contraception use on risk of thrombosis? **EVIDENCE FOR: GS2, GS2A, GS2B**

Summary: This PICO was addressed by one RCT[1] and one observational study[2] with direct evidence. Evidence was supplemented by one RCT[3] and two observational studies with indirect evidence.[4,5]

Results from one RCT compared the risk of thrombosis in aPL negative women with SLE taking combined estrogen-progestin contraception (COC) to placebo[1]. After one year, 2.2% of patients in the COC group experienced thrombosis compared to 3.3% of patients in the placebo group (OR: 0.67; 95% CI: 0.11, 4.09). One DVT was experienced in each group (OR: 1.01; 95% CI: 0.06, 16.41).

One observational study[2] provided direct evidence for the risk of DVT with COC use. In a cross-sectional survey combined with retrospective chart review, 31 of 85 women with SLE had ever used COC during or after the onset of SLE for a total of 93 person-years. Two women experienced a DVT while on COC (2.2 DVT per 100 PY). Comparatively, after the onset of SLE, 10 DVTs were experienced during 1060 person-years while not using COCs (0.94 per 100 PY). The risk of DVT was higher in patients using COCs (RR: 2.3; 95% CI: 0.5, 10.3).

Additional indirect evidence from a RCT of women with SLE was provided by Sanchez-Guerrero 2005,[3] where patients were randomized to combined estrogen-progestin contraception (COC) or copper IUD. In the COC group, 26% of patients had positive anticardiolipin antibodies and 18.5% had positive anti-β2GPI antibodies. In the copper IUD group, 31.5% of patients had positive anticardiolipin antibodies and 11.1% had positive anti-β2GPI antibodies. Two patients in the COC group experienced thrombosis (3.7% compared to no patients in the copper IUD group (OR: 5.19; 95% CI: 0.24, 110.69). The incidence of thrombosis in the COC group was 4.75 events per 100 patient-years.

Two observational studies provided additional indirect evidence. In a cross-sectional interview of women with SLE,[4] 31 of 85 women self-reported history of taking COCs, of which 2 experienced a DVT (6%). These are likely the same two patients from Julkunen 1993.[2] A cross-sectional survey of women with SLE found that no women with a self-reported history of COC use at the time of SLE diagnosis had thrombosis as a presenting feature of SLE.[5]

Quality of Evidence across outcomes: Very low.

Estrogen-progestin contraception compared to placebo/non-hormonal contraception in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1a Impact of estrogen-progestin contraception on thrombosis risk in women with SLE and negative aPL antibodies.

Certainty assessment							Summary of findings				
Nº of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo/non-hormonal contraception	**With Estrogen-progestin contraception**		**Risk with placebo/non-hormonal contraception**	**Risk difference with Estrogen-progestin contraception**
Thrombosis - COC vs. Copper IUD											
108 (1 RCT)	serious [a,b]	very serious [c]	serious [d]	very serious [c]	none	⨁◯◯◯ VERY LOW	0/54 (0.0%)	2/54 (3.7%)	**OR 5.19** (0.24 to 110.69)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Thrombosis - COC vs. Placebo											
183 (1 RCT)	not serious [e]	very serious [c]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	3/92 (3.3%)	2/91 (2.2%)	**OR 0.67** (0.11 to 4.09)	33 per 1,000	**11 fewer per 1,000** (29 fewer to 89 more)
DVT - COC vs. Placebo											
183 (1 RCT)	not serious [e]	very serious [c]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	1/92 (1.1%)	1/91 (1.1%)	**OR 1.01** (0.06 to 16.41)	11 per 1,000	**0 fewer per 1,000** (10 fewer to 142 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No placebo used.
b. 28% in cOC group and 21% in IUD group did not complete the study. Some reasons provided for withdrawal/loss to follow-up. ITT analysis used
c. Only one study
d. In COC group, 26% of patients had positive anticardiolipin antibodies and 18.5% had positive anti-β2GPI antibodies. In copper IUD group, 31.5% of patients had positive anticardiolipin antibodies and 11.1% had positive anti-β2GPI antibodies.
e. OC group: 42% discontinued (reasons provided). 14% lost to follow-up Placebo group: 40% discontinued (reasons provided). 20% lost to follow-up.

References
54 Petri 2005
55 Sanchez-Guerrero 2005

Observational Studies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Combined Oral Contraceptives						
Risk of DVT	104 Julkunen 1993[2]	Cross-sectional survey combined with retrospective chart review	Retrospective review – unknown time period reviewed	85 women with **SLE** 31 patients had used cOCs during or after the onset of SLE	History of taking combined oestrogen-progestagen oral contraceptives (COCs; 30-50 mg of ethinyloestradiol) during or after SLE diagnosis	31 patients had used COCs during or after the onset of SLE for a total of 93 woman-years. N=2 patients had a DVT while on COCs (2.2 per 100 PY). 7 of the 85 patients had 10 DVTs after the onset of SLE while not using COCs (1060 woman years) = (0.94 per 100 PY) The risk of having DVT was higher in patients using COCs (RR 2.3,95% CI 0.5 to 10.3).
Risk of DVT	105 Julkunen 1991[4]	Cross-sectional interview of SLE patients	March 1989 – April 1990	85 women with **SLE** aged 18-44 31 patients used cOCs during or after SLE onset 32 (38%) of patients ever used PCs for a mean duration of 17.5 months (range 1 month – 11 years).	Self-reported history of taking estrogen-containing combined oral contraceptives (COCs)	2 patients experienced a DVT (6%) while on COCs. No data available on person-time for cOCs after diagnosis of SLE to calculate incidence.
Risk of thrombosis	71, Lakasing 2001[5]	Cross-sectional survey	Cross-sectional; time of survey unknown	Women with **SLE only** SLE group: n=39; median age: 31 (range: 21-42); median age at diagnosis: 25 (range: 11-36)	Self-reported history of combined oral contraceptive pill	SLE group: no report of thrombosis at diagnosis

7. In women with RD who are of childbearing age with SLE and negative aPL antibodies, what is the impact of the progestin IUD versus no hormonal contraception use on risk of thrombosis? **RELEVANCE: GS2 AND GS2A, BUT NO EVIDENCE**
No evidence

8. In women with RD who are of childbearing age with SLE and negative aPL antibodies, what is the impact of the progestin pill versus no hormonal contraception use on risk of thrombosis? **EVIDENCE FOR: GS2, GS2A**

Summary: This PICO was addressed by one RCT[3] and three observational studies[2,4,6] with indirect evidence.

An RCT randomized women with SLE to progestin-only contraception or copper IUD. In the progestin-only group, 33% of patients had positive anticardiolipin antibodies and 18.5% had positive anti-β2GPI antibodies. In the copper IUD group, 31.5% of patients had positive anticardiolipin antibodies and 11.1% had positive anti-β2GPI antibodies. Two patients in the progestin-only group experienced thrombosis (3.7%) compared to no patients in the copper IUD group (OR: 5.19; 95% CI: 0.24, 110.69). The incidence of thrombosis in the progestin-only group was 5.44 events per 100 patient-years.

Three observational studies provided additional indirect evidence. In a cross-sectional interview of women with SLE,[2,4] 32 of 85 women self-reported a history of taking progestin-only contraception for an average duration of 17.5 months, of which 1 experienced a DVT (3%). In a prospective cohort study follow-up of 187 women with SLE patients who completed a randomized trial,[6] patients took either chlormadinone acetate (CMA, 10 mg/day) or cyproterone acetate (CPA, 50 mg/day). There was 1 case of DVT (0.8%) during 2942 person-months of CPA treatment (0.4 DVT per 100 person-years). There were no DVTs reported during 3912 person-months of CMA treatment.

Quality of Evidence across outcomes: Very low.

Progestin-only contraception compared to copper IUD in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1a Impact of progestin-only contraception on thrombosis risk in women with SLE and negative aPL antibodies.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With copper IUD	**With progestin-only contraception**		**Risk with copper IUD**	**Risk difference with progestin-only contraception**
SLE - Thrombosis - Progestin Only vs. Copper IUD											
108 (1 RCT)	serious [a,b]	very serious [c]	serious [d]	very serious [c]	none	⨁◯◯◯ VERY LOW	0/54 (0.0%)	2/54 (3.7%)	**OR 5.19** (0.24 to 110.69)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No placebo used

b. 53% in progestin only and 21% in IUD group did not complete the study. Some reasons provided for withdrawal/loss to follow-up. ITT analysis used
c. Only one study
d. In progestin-only group, 33% of patients had positive anticardiolipin antibodies and 18.5% had positive anti-β2GPI antibodies. In copper IUD group, 31.5% of patients had positive anticardiolipin antibodies and 11.1% had positive anti-β2GPI antibodies.

References
55 Sanchez-Guerrero 2005

Observational Studies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Progestin Only Pill						
Risk of DVT	104 Julkunen 1993[2]	Cross-sectional survey combined with retrospective chart review	Retrospective review – unknown time period reviewed	85 women with **SLE** 834 healthy women 32 patients ever used progestin-only contraception	History of taking progestagen-only contraceptives (PCs; low dose preparations containing lynestrenol, levonorgestrol or norethisterone)	1 DVT while on PCs (3%)
Risk of DVT	105 Julkunen 1991[4]	Cross-sectional interview of SLE patients	March 1989 – April 1990	85 women with **SLE** aged 18-44 32 (38%) of patients ever used PCs for a mean duration of 17.5 months (range 1 month – 11 years).	Self-reported history of taking progesterone-only contraceptives (PCs)	Progesterone Only: 1 patient had a DVT (3%). Estimating total person-time of exposure (mean 17.5 months x 32 patients = 46.7 person-years), incidence of DVT with PC use is 1 / 46.7 person-years = 2.1 DVT per 100 person-years
Risk of DVT	27, Chabbert-Buffet 2011[6]	Prospective cohort study follow-up of patients who completed a randomized trial	Mean follow-up: 46±34.6 months (total of 6854 person-months)	n=187 women with **SLE** Mean age: 31±7.1 years Mean duration of SLE: 57.6±46.5 months	CPA (Androcur®; Schering, 50 mg daily for the first 6 weeks, then 50 mg/day, 20 of 27 days) for 1 year CMA (Luteran®; Aventis, 5 mg twice daily, 20 of 27 days) unless SLE was active Choice between CPA and CMA was made according to the SLE disease activity level. Patients receiving CMA continued the same therapeutic regimen as long as tolerability was good and SLE disease activity was acceptable. If a SLE flare occurred, CMA was switched to CPA. 124 received CPA (mean 23.17±24.3 months of treatment; 2942 person-months)	CPA: 1 case of DVT (0.8%) during 2942 person-months of treatment: 0.4 DVT per 100 person-years CMA: No DVT during 3912 person-months of treatment CPA or CMA: 1 DVT during 6854 person-months: 0.2 DVT per 100 person-years

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					151 received CMA (mean 25.98±28.24 months of treatment; 3912 person-months) 60 received both CPA and CMA	

9. In women with RD who are of childbearing age with SLE and negative aPL antibodies, what is the impact of the progestin subdermal implant versus no hormonal contraception use on risk of thrombosis? **QUESTIONS 9 AND 10 RELEVANCE: GS2 AND GS2A, BUT NO EVIDENCE**
No evidence

10. In women with RD who are of childbearing age with SLE and negative aPL antibodies, what is the impact of IM depo-medroxyprogesterone acetate versus no hormonal contraception use on risk of thrombosis?
No evidence

11. In women with RD who are of childbearing age with positive aPL antibodies but not APS, what is the impact of estrogen-progestin contraception (pill, patch or vaginal ring) versus no hormonal contraception use on risk of thrombosis? **QUESTIONS 11-15 RELEVANCE: GS3,GS4, GS4A BUT NO EVIDENCE**
No evidence

12. In women with RD who are of childbearing age with positive aPL antibodies but not APS, what is the impact of the progestin IUD versus no hormonal contraception use on risk of thrombosis?
No evidence

13. In women with RD who are of childbearing age with positive aPL antibodies but not APS, what is the impact of the progestin pill versus no hormonal contraception use on risk of thrombosis?
No evidence

14. In women with RD who are of childbearing age with positive aPL antibodies but not APS dies, what is the impact of the progestin subdermal implant versus no hormonal contraception use on risk of thrombosis?
No evidence

15. In women with RD who are of childbearing age with positive aPL antibodies but not APS, what is the impact of IM depo-medroxyprogesterone acetate versus no hormonal contraception use on risk of thrombosis?
No evidence

16. In women with APS with or without underlying RD who are of childbearing age (history of thrombosis or obstetrical complication), what is the impact of estrogen-progestin contraception (pill, patch or vaginal ring) versus no hormonal contraception use on risk of thrombosis? **EVIDENCE FOR GS3, GS4, GS4A**

Summary: This PICO was addressed by one observational study with indirect evidence.[5] In this cross-sectional survey, 30 women with APS only and 17 women with APS + SLE self-reported a history of taking an estrogen-progestin contraception pill (COC). In the APS group, n=7 (23%) of patients had thrombosis as a presenting symptom of APS. Of these, 4 were using COCs at the time of thrombosis and 3 were not. In the SLE + APS group, n=3 (18%) of patients had thrombosis as a presenting symptom of APS. All three of these patients were using COC at the time of thrombosis.

Quality of Evidence across outcomes: Very low.

Observational Studies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Combined Oral Contraceptives						
Risk of thrombosis	71, Lakasing 2001[5]	Cross-sectional survey	Cross-sectional; time of survey unknown	Women with **(1) APS only, or (2) SLE and APS** APS group: n=30; median age: 31 (range: 25-42); median age at diagnosis: 30 (range: 23-38) SLE and APS group: n=17; median age: 30 (range: 22-39); median age at diagnosis: 25 (range: 11-37)	Self-reported history of combined oral contraceptive pill	APS group: 23% of patients (n=7) had thrombosis as presenting symptom of APS 4 were using COCP at time of thrombosis 3 were not using COCP at time of thrombosis SLE and APS group: 18% of patients(n=3) had thrombosis as presenting symptom of APS ALL 3 were using COCP at time of thrombosis INDIRECT EVIDENCE

17. In women with APS with or without underlying RD who are of childbearing age (history of thrombosis or obstetrical complication), what is the impact of the progestin IUD versus no hormonal contraception use on risk of thrombosis? **QUESTONS 17-20 RELEVANCE: GS3, GS4,GS4A BUT NO EVIDENCE**
No evidence

18. In women with APS with or without underlying RD who are of childbearing age (history of thrombosis or obstetrical complication), what is the impact of the progestin pill versus no hormonal contraception use on risk of thrombosis?
No evidence

19. In women with APS with or without underlying RD who are of childbearing age (history of thrombosis or obstetrical complication), what is the impact of the progestin subdermal implant versus no hormonal contraception use on risk of thrombosis?
No evidence

20. In women with APS with or without underlying RD who are of childbearing age (history of thrombosis or obstetrical complication), what is the impact of IM depo-medroxyprogesterone acetate versus no hormonal contraception use on risk of thrombosis?
No evidence

References:

1. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. The New England journal of medicine. 2005;353(24):2550-2558.
2. Julkunen HA, Kaaja R, Friman C. Contraceptive practice in women with systemic lupus erythematosus. British journal of rheumatology. 1993;32(3):227-230.
3. Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. The New England journal of medicine. 2005;353(24):2539-2549.
4. Julkunen HA. Oral contraceptives in systemic lupus erythematosus: side-effects and influence on the activity of SLE. Scandinavian journal of rheumatology. 1991;20(6):427-433.
5. Lakasing L, Khamashta M. Contraceptive practices in women with systemic lupus erythematosus and/or antiphospholipid syndrome: what advice should we be giving? The journal of family planning and reproductive health care. 2002;27(1):7-12.
6. Chabbert-Buffet N, Amoura Z, Scarabin PY, Frances C, Levy DP, Galicier L, et al. Pregnane progestin contraception in systemic lupus erythematosus: a longitudinal study of 187 patients. Contraception. 2011;83(3):229-237.

1B.

In women of childbearing age with SLE and RA, what is the impact of hormonal contraception use versus no hormonal contraception use on risk of disease flare?

Populations: Women with SLE at risk for pregnancy

Interventions: Use of specific forms of effective hormonal birth control including:

- Estrogen-progestin pill, patch or vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- Depot medroxyprogesterone acetate (DMPA)
- Emergency contraception (morning after pill, mifepristone)

Comparators: SLE patients at risk for pregnancy not using hormonal birth control, including:

- Male contraception/ sterilization
- Copper IUD
- Not sexually active/abstinence
- Barrier contraception
- Tubal ligation/hysterectomy

Outcomes:

- SLE flare excluding nephritis (for SLE)
- Lupus nephritis flare (for SLE)

21. In women of childbearing age with SLE, what is the impact of use of estrogen-progestin contraception (pill, patch or vaginal ring) versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare? **EVIDENCE FOR GS2, GS2C**

Summary: For the population of women with SLE, this PICO was addressed by two RCTs[1,2] and two observational studies[3,4] with direct evidence. One additional observational study provided indirect evidence.[5]

Results from one RCT compared the risk any flare, mild or moderate flare, and severe flare in women with SLE taking combined estrogen-progestin contraception (COC) to placebo.[1] After one year, 75.8%% of patients in the COC group experienced a flare of any severity compared to 68.5% of patients in the placebo group (OR: 1.44; 95% CI: 0.75, 2.77). For the outcome of mild or moderate flare, 69.2% of patients in the COC experienced a flare compared to 59.8% of patients in the placebo group (OR: 1.51; 95% CI: 0.82, 2.79). Finally, 7.7% of patients in the COC group experienced a severe flare compared to 7.6% of patients in the placebo group (OR: 1.01; 95% CI: 0.34, 3.01). The 12-month severe flare rate in the COC group was 0.084 compared to 0.087 in the placebo group.

Another RCT of women with SLE was provided by Sanchez -Guerrero 2005,[2] where patients were randomized to combined estrogen-progestin contraception (COC) or copper IUD. In this study, there were 36 flares during 489 person-years of follow-up in the COC group (7.36 flares per 100 person-years) compared to 40 flares during 525 person-years of follow-up in the copper IUD group (7.62 per 100 person-years). The rate ratio of

flares in the COC group compared to the copper IUD group was 0.94 (95% CI: 0.58, 1.52). The study also found no increased rate of severe flare for patients taking COC, with only 2 severe flares in each group. The rate of severe flares in the COC group was 0.40 per 100 person-years compared to 0.38 per 100 person-years in the copper IUD group (RR: 1.09; 95% CI: 0.08, 14.80).

Two observational studies provided additional direct evidence. In an observational study of 26 women with SLE, 20 patients took 21 courses of estrogen-containing contraception.[3] Disease flares were noted in 9 patients within 3 months of starting COC (43%), and 4 patients experienced major renal flares (19%). Compared to 30 randomly selected women with SLE who never took estrogen-containing contraception, the 12-month incidence of flare was 0.88 per person-year among COC users, compared to 0.2 per person-year among non-users.

In a cross-sectional interview of women with SLE,[4] 31 of 85 women self-reported a history of taking COCs during or after the onset of SLE. Three women had an SLE flare during the first 12 months of COC therapy (9.7%), with a rate of 0.02 flares per patient-month. Comparatively, the 12-month incidence of flares in patients who had never used COCs was 0.01 flares per patient-month.

A cross-sectional survey of women with SLE provided indirect evidence for the association of COC use and disease flares.[5] Among 39 women with SLE, 9 were diagnosed with SLE while using combined oral contraception, and 2 of these patients discontinued COCs due to lupus symptoms. In 17 women with SLE + APS, 4 were using combined oral contraception at diagnosis, while no report of increased SLE activity at time of diagnosis.

In women with RA, one observational study directly addressed the PICO question.[6] In this prospective study of an inception cohort of 112 RA patients, 54 women used COC after RA diagnosis for a median of 34 months. There was no significant difference in Sharp score modification van der Heijde, Larsen score for large joints, or Health Assessment Questionnaire score between COC users and non-users. Additionally, the months of COC use was not associated with Sharp score tertile.

Quality of Evidence across outcomes: Very low.

Estrogen-progestin contraception compared to placebo/non-hormonal contraception in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1b Impact of estrogen-progestin contraception on disease flare in women with SLE.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With placebo/non-hormonal contraception	With estrogen-progestin contraception		Risk with placebo/non-hormonal contraception	Risk difference with estrogen-progestin contraception
Any Flare - COC vs Placebo											

Estrogen-progestin contraception compared to placebo/non-hormonal contraception in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1b Impact of estrogen-progestin contraception on disease flare in women with SLE.

Certainty assessment							Summary of findings				
183 (1 RCT)	not serious [a]	very serious [b]	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	63/92 (68.5%)	69/91 (75.8%)	**OR 1.44** (0.75 to 2.77)	685 per 1,000	**73 more per 1,000** (65 fewer to 173 more)
Rate of Any Flare - COC vs Copper IUD											
108 (1 RCT)	serious [c,d]	very serious [b]	not serious	serious [b]	none	⊕◯◯◯ VERY LOW	40/525	36/489	**Rate ratio 0.94** (0.58 to 1.52)	76 per 1,000	**5 fewer per 1,000** (32 fewer to 40 more)
Mild or Moderate Flare - COC vs Placebo											
183 (1 RCT)	not serious [a]	very serious [b]	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	55/92 (59.8%)	63/91 (69.2%)	**OR 1.51** (0.82 to 2.79)	598 per 1,000	**94 more per 1,000** (48 fewer to 208 more)
Severe Flare - COC vs Placebo											
183 (1 RCT)	not serious [a]	very serious [b]	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	7/92 (7.6%)	7/91 (7.7%)	**OR 1.01** (0.34 to 3.01)	76 per 1,000	**1 more per 1,000** (49 fewer to 123 more)
Rate of Severe Flare - COC vs Copper IUD											
108 (1 RCT)	serious [c,d]	very serious [b]	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	2/525	2/489	**Rate ratio 1.09** (0.08 to 14.80)	4 per 1,000	**0 fewer per 1,000** (4 fewer to 53 more)
12-Month Severe Flare Rate - KM - COC vs Placebo											
183 (1 RCT)	not serious [a]	very serious [b]	not serious	very serious [b]	none	⊕◯◯◯ VERY LOW	0.087	0.084	-	The mean 12-Month Severe Flare Rate - KM - COC vs Placebo was **0**	MD **0** (0.09 lower to 0.08 higher)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. OC group: 42% discontinued (reasons provided). 14% lost to follow-up Placebo group: 40% discontinued (reasons provided). 20% lost to follow-up.
b. Only 1 study
c. No placebo used
d. 28% in cOC group, 53% in progestin only, and 21% in IUD group did not complete the study. Some reasons provided for withdrawal/loss to follow-up. ITT analysis used

References
54 Petri 2005
55 Sanchez-Guerrero 2005

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Estrogen-progestin pill, patch or vaginal ring						
SLE flare excluding nephritis (for SLE)	71, Lakasing 2001[5]	Cross-sectional survey	Cross-sectional; time of survey unknown	Women with (1) SLE only, (2) APS only, or (3) SLE and APS SLE group: n=39; median age: 31 (range: 21-42); median age at diagnosis: 25 (range: 11-36) SLE and APS group: n=17; median age: 30 (range: 22-39); median age at diagnosis: 25 (range: 11-37)	Self-reported history of combined oral contraceptive pill	SLE group: n=9 women were diagnosed while using COCP; 2 discontinued due to lupus symptoms (22%) SLE and APS group: n=4 women were diagnosis while using COCP; no report of SLE flare at diagnosis INDIRECT EVIDENCE
	156, Jungers 1982[3]	Observational study	January 1968 - June 1980	n=26 women with SLE 20 patients took 21 courses of estrogen-containing contraception	Estrogen-containing: ethinyl-estradiol, with a daily dose of 50 mcg in 14 treatments and 30 mcg in 7	Over 21 hormonal courses, exacerbations of lupus activity were observed within 3 months of the start of oral contraceptive therapy in 9 patients: • Any flare: 9 (43%) **note: in 3 patients, flare was recorded at the diagnosis of SLE Compared to 30 randomly selected women who with SLE who never took estrogen-containing contraceptives, the 12-month incidence of flares was: • No estrogen-containing contraceptives: 0.2 per person-year (6 flares in 360 patient-months) • Estrogen-containing contraceptives: 0.88 per person-year among users (7 flares in 96 patient-months)
	105 Julkunen 1991[4]	Cross-sectional interview of SLE patients	March 1989 – April 1990	85 women with **SLE** aged 18-44	Self-reported history of taking estrogen-	cOCs started after SLE diagnosis in 11 patients. N=4 (36%) of patients had exacerbations of SLE while using cOCs (all

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				31 patients used cOCs during or after SLE onset	containing combined oral contraceptives (cOCs)	occurred after more than 6 months from starting cOCs) SLE flare during the first 12 months of cOC therapy: n=3 of 31 patients (9.7%). 3 flares per 144 patient-months (rate = 0.02 flares per patient month) Incidence of flares during a 12-month period in patients who had never used cOCs: 5 flares per 373 patient-months (rate = 0.01 flares per patient month)
Renal flare (for SLE)	156, Jungers 1982[3]	Observational study	January 1968 - June 1980	n=26 women with SLE 20 patients took 21 courses of estrogen-containing contraception 11 patients took progestin-only pills, 5 of whom also previously took estrogen-containing pills	Estrogen-containing: ethinyl-estradiol, with a daily dose of 50 mcg in 14 treatments and 30 mcg in 7	Over 21 hormonal courses, exacerbations of lupus activity were observed within 3 months of the start of oral contraceptive therapy in 9 patients: • Mild, extra-renal manifestations: 5 (24%) • Major renal flares: 4 (19%) **note: in 3 patients, flare was recorded at the diagnosis of SLE
RA Flare	3737 Drossaers-Bakker 2002[6]	Prospective inception cohort of RA patients	12 years	Women with **RA** seen at an outpatient rheumatology clinic between 1982 and 1986 with onset of symptoms 0-5 years at first visit and aged 20-50 years at first visit included n=131 women followed for 12 years; n=112 women included in study n=54 use OC after RA diagnosis (48%) Median use of OC after RA diagnosis: 34 months (range: 0-144)	n/a	Median (range) Sharp score modification van der Heijde • No OC use: 146 (0-392) • OC use: 78 (0-428) Median (range) Larsen score for large joints (0–60) • No OC use: 5 (0-48) • OC use: 3 (0-55) Median (range) Health Assessment Questionnaire • No OC use: 1.0 (0-2.88) • OC use: 0.75 (0-3) *no significant differences between OC users and non-users for any outcomes. Months of OC use (OR=0.99, p=0.11) were not associated with SHS tertile.

22. In women of childbearing age with SLE, what is the impact of use of the progestin IUD versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare? **RELEVANCE: GS2, GS2A NO NO EVIDENCE**

No evidence

23. In women of childbearing age with SLE, what is the impact of use of the progestin pill versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare? **EVIDENCE FOR GS2**

Summary: This PICO question was directly addressed by one RCT[2] and one observational study.[7] One additional observational study indirectly addressed the question.[3]

A RCT randomized women with SLE to progestin-only contraception or copper IUD.[2] There were 40 flares of any severity during 421 person-years of follow-up in the progestin-only group (9.5 flares per 100 person-years) compared to 40 flares during 525 person-years of follow-up in the copper IUD group (7.6 flares per 100 PY). The rate ratio of flares in the progestin-only group compared to the copper IUD group was 1.24 (95% CI: 0.78, 1.98).

In a prospective cohort study follow-up of 187 women with SLE patients who completed a randomized trial,[7] patients took either chlormadinone acetate (CMA, 10 mg/day) or cyproterone acetate (CPA, 50 mg/day). The number of flares were combined for both CMP and CPA, and the rate of flares during progestin treatment was compared to 1-year prior to progestin treatment. For the outcome of renal flare, there were 4.2 flares per 100 person-years in the 1-year prior to progestin therapy, compared to 3.3 flares per 100 person-years during progestin therapy. For the outcome of neurological flare, there were 1.2 flares per 100 person-years in the 1-year prior to progestin therapy, compared to 0.4 flares per 100 person-years during progestin therapy.

One observational study provided additional indirect evidence. In an observational study of 26 women with SLE,[3] 11 patients took a progestin-only pill. There were no observed flares in patients treated with a progestin-only pill over a follow-up period of 5 to 30 months.

Quality of Evidence across outcomes: Very low.

Progestin-only contraception compared to copper IUD in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1b Impact of progestin-only contraception on disease flare in women with SLE.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With copper IUD	With progestin-only contraception		Risk with copper IUD	Risk difference with progestin-only contraception
Any Flare - Rate											

Progestin-only contraception compared to copper IUD in women with RD who are of childbearing age with SLE and negative aPL antibodies

Bibliography: Pico1b Impact of progestin-only contraception on disease flare in women with SLE.

Certainty assessment							Summary of findings				
108 (1 RCT)	serious [a,b]	very serious [c]	not serious	very serious [c]	none	⨁◯◯◯ VERY LOW	40/525	40/421	**Rate ratio 1.24** (0.78 to 1.98)	76 per 1,000	**18 more per 1,000** (17 fewer to 75 more)

CI: Confidence interval

Explanations

a. No placebo used
b. 53% in progestin only, and 21% in IUD group did not complete the study. Some reasons provided for withdrawal/loss to follow-up. ITT analysis used
c. Only 1 study

References

55 Sanchez-Guerrero 2005

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Progestin only pill						
SLE flare excluding nephritis (for SLE)	156, Jungers 1982[3]	Observational study	January 1968 - June 1980	n=26 women with SLE 11 patients took progestin-only pills, 5 of whom also previously took estrogen-containing pills	Progestin-only: discontinuous progestogens at normal dosage (lynestrenol in 3 patients, chlormadinone acetate in 2) or continuous low-dose norsteroids (norethisterone in 3 patients; norgestrienone in 3)	No observed flares in patients treated with progestin-only medications over a follow-up period of 5-30 months
Renal flare flare (for SLE)	27, Chabbert-Buffet 2011[7]	Prospective cohort study follow-up of patients who completed a randomized trial	Mean follow-up: 46±34.6 months (total of 6854 person-months)	n=187 women with SLE Mean age: 31±7.1 years Mean duration of SLE: 57.6±46.5 months	CPA (Androcur®; Schering, 50 mg daily for the first 6 weeks, then 50 mg/day, 20 of 27 days) for 1 year CMA (Luteran®; Aventis, 5 mg twice daily, 20 of 27 days) unless SLE was active Choice between CPA and CMA was made according to the SLE disease activity level. Patients receiving CMA continued the same therapeutic regimen as long as tolerability was good and SLE disease activity was	Disease flare: defined as any worsening of previous clinical state concerning SLE attributable symptoms (cutaneous symptoms, arthritis, renal, CNS or vascular flare) or new SLE-related clinical event according to the SLE expert in charge of the patient or increase in corticosteroid dose or initiation of immunosuppressive therapy **Results for the outcome of flare group both medications together and compare 1-year before and during progestin treatment** Renal flare

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					acceptable. If a SLE flare occurred, CMA was switched to CPA. – 124 received CPA (mean 23.17±24.3 months of treatment; 2942 person-months) – 151 received CMA (mean 25.98±28.24 months of treatment; 3912 person-months) – 60 received both CPA and CMA	Prior to PP Treatment: 4.2 flares per 100 person-years During PP Treatment: 3.3 per 100 person-years
Neurological flare	27, Chabbert-Buffet 2011[7]	Prospective cohort study follow-up of patients who completed a randomized trial	Mean follow-up: 46±34.6 months (total of 6854 person-months)	n=187 women with SLE Mean age: 31±7.1 years Mean duration of SLE: 57.6±46.5 months	CPA (Androcur®; Schering, 50 mg daily for the first 6 weeks, then 50 mg/day, 20 of 27 days) for 1 year CMA (Luteran®; Aventis, 5 mg twice daily, 20 of 27 days) unless SLE was active Choice between CPA and CMA was made according to the SLE disease activity level. Patients receiving CMA continued the same therapeutic regimen as long as tolerability was good and SLE disease activity was acceptable. If a SLE flare occurred, CMA was switched to CPA. – 124 received CPA (mean 23.17±24.3 months of treatment; 2942 person-months) – 151 received CMA (mean 25.98±28.24 months of treatment; 3912 person-months) 60 received both CPA and CMA	Disease flare: defined as any worsening of previous clinical state concerning SLE attributable symptoms (cutaneous symptoms, arthritis, renal, CNS or vascular flare) or new SLE-related clinical event according to the SLE expert in charge of the patient or increase in corticosteroid dose or initiation of immunosuppressive therapy **Results for the outcome of flare group both medications together and compare 1-year before and during progestin treatment** Neurological flare Prior to PP Treatment: 1.2 flares per 100 person-years During PP Treatment: 0.4 per 100 person-years

24. In women of childbearing age with SLE, what is the impact of use of the progestin subdermal implant versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare? **QUESTIONS 24-26 RELEVANCE: GS2, GS2A, GS2C BUT NO EVIDENCE**
No evidence

25. In women of childbearing age with SLE, what is the impact of use of IM depo-medroxyprogesterone acetate versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare?
No evidence

26. In women of childbearing age with SLE, what is the impact of use of emergency contraception (morning after pill, mifepristone) versus no hormonal contraception use on risk of nephritis and non-nephritis disease flare?
No evidence

References:

1. Petri M, Kim MY, Kalunian KC, Grossman J, Hahn BH, Sammaritano LR, et al. Combined oral contraceptives in women with systemic lupus erythematosus. The New England journal of medicine. 2005;353(24):2550-2558.
2. Sanchez-Guerrero J, Uribe AG, Jimenez-Santana L, Mestanza-Peralta M, Lara-Reyes P, Seuc AH, et al. A trial of contraceptive methods in women with systemic lupus erythematosus. The New England journal of medicine. 2005;353(24):2539-2549.
3. Jungers P, Dougados M, Pelissier C, Kuttenn F, Tron F, Lesavre P, et al. Influence of oral contraceptive therapy on the activity of systemic lupus erythematosus. Arthritis and rheumatism. 1982;25(6):618-623.
4. Julkunen HA. Oral contraceptives in systemic lupus erythematosus: side-effects and influence on the activity of SLE. Scandinavian journal of rheumatology. 1991;20(6):427-433.
5. Lakasing L, Khamashta M. Contraceptive practices in women with systemic lupus erythematosus and/or antiphospholipid syndrome: what advice should we be giving? The journal of family planning and reproductive health care. 2002;27(1):7-12.
6. Drossaers-Bakker KW, Zwinderman AH, Zeben Dv, Breedveld FC, Hazes JM. Pregnancy and oral contraceptive use do not significantly influence outcome in long term rheumatoid arthritis. Annals of the rheumatic diseases. 2002;61(5):405-408.
7. Chabbert-Buffet N, Amoura Z, Scarabin PY, Frances C, Levy DP, Galicier L, et al. Pregnane progestin contraception in systemic lupus erythematosus: a longitudinal study of 187 patients. Contraception. 2011;83(3):229-237.

1C: No evidence

1C. In women with RD of childbearing age [variables listed], what is the impact of IUD use versus no IUD use on risk of pelvic infection?

Populations: Women with RD at risk for pregnancy
- On immunosuppressive medications
- Not on immunosuppressive medications

Intervention: Use of specific forms of effective birth control, including:
- IUD with copper
    - With or without prophylactic antibiotics at insertion
- IUD with progestin
    - With or without prophylactic antibiotics at insertion

Comparator:
- Similar patients not using an IUD

Outcome:
- Infection (pelvic inflammatory disease)

RELEVANCE: GS7 BUT NO EVIDENCE

1D: No evidence

1D. In RD patients of childbearing age [variables listed], what is the impact of having a sterilization procedure, versus non-RD patients, on likelihood of infection and thrombosis?

Populations: Patients with RD at risk for pregnancy

- Women
  - On immunosuppressive medications
  - Not on immunosuppressive medications
- Men
  - On immunosuppressive medications
  - Not on immunosuppressive medications

Intervention: Use of specific forms of permanent birth control including:

- Tubal ligation (women)
- Vasectomy (men)

Comparator:

- General population patients without RD having these procedures

Outcome:

- Infection or complication

RELEVANCE: GS7,GS8 BUT NO EVIDENCE

1E: No evidence

1E. In women with RD of childbearing age, what is the impact of using progestin-only contraception [listed] versus not using progestin-only contraception on bone density and fracture rate?

Population:
- Women with RD of childbearing age

Intervention: Using progestin contraception
- IUD with progestin
- Progestin-only pill
- Progestin implant
- DMPA

Comparator:
- Women with RD not using any progestin-only contraception
- Women without RD using any progestin-only contraception

Outcomes:
- Bone density as defined by bone density test (DEXA)
- Fracture rate: vertebral and non-vertebral (including fragility and insufficiency fractures)

RELEVANCE: GS10 BUT NO EVIDENCE

1F: No evidence

1F. In women with RD of childbearing age who are using hormonal contraception [listed], what is the impact of concomitant rheumatology medication use versus no rheumatology medication use on the risk of contraception failure?

Population: Women with RD using hormonal contraception

- Estrogen-progestin pill
- Estrogen-progestin patch
- Estrogen-progestin vaginal ring
- IUD with progestin
- Progestin pill
- Progestin implant
- DMPA
- Emergency contraception (morning after pill, mifepristone)

Intervention: Use of rheumatology medications

- Mycophenolate mofetil or mycophenolic acid
- Methotrexate
- Cyclophosphamide
- Leflunomide
- Tocilizumab
- Thalidomide
- Lenalidomide

RELEVANCE: GS11 – GS23, BUT NO EVIDENCE

2. Assisted reproductive technologies

2A.

2A. In women with SLE who are undergoing assisted reproductive technology, what is the effect of ART /ovarian stimulation versus no ART /ovarian stimulation on maternal and pregnancy outcomes?

Population: Women with SLE who are undergoing ART/ovarian stimulation

Interventions:
- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Assisted reproductive technologies: ovulation induction with in vitro fertilization / embryo transfer

Comparator:
- Similar patients who are not having ART (flare or damage of RD)

Outcomes:
- Flare of SLE (compare to SLE patients not having the procedure)
- Damage of SLE (including renal failure): compare to SLE patients not having the procedure
- Renal risks
- Fetal outcomes, with healthy singleton pregnancy as ideal outcome (i.e. what is the risk to the fetus?)

All studies for PICO 2a provide indirect evidence.

27. In women with SLE who are undergoing assisted reproductive technology, what is the effect of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) versus no ovarian stimulation on patient/maternal and (if relevant) pregnancy outcomes? **EVIDENCE FOR GS24**

No studies address use of ovulation induction therapy alone. One study addresses use of ovulation induction therapy with in vitro fertilization in 7 women with SLE for 16 cycles.[1] The study does not include a control group. 4 SLE flares were seen in the 3 of the 7 women. One woman developed renal disease. Three pregnancies were multiple gestations.

One study addresses the use of ovulation induction in 65 out of 97 in vitro fertilization cycles.[2] The study does not include a control group. 4 SLE flares were seen in 3 women. 2 women with SLE and APS had a thromboembolic event. Fetal and maternal outcomes were otherwise not separated between SLE and APS patients.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ovulation induction agents (clomiphene, aromatase inhibitors, gonadotropin therapy)						
Flare of SLE	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction (clomid, metrodin, Lupron, or repronex), IVF	4 SLE flares in 3 patients/16 cycles
Renal Risks	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction, IVF	1 patient with Cr elevation during OI/IVF, 1 with FSGS postpartum
Fetal Outcomes	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction, IVF	2/7 pregnancies twin, 1/7 triplets 2 patients with gestational HTN 1 patient with spontaneous abortion
Assisted reproductive technologies: ovulation induction with in vitro fertilization / embryo transfer						
Flare of SLE	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction (clomid, metrodin, Lupron, or repronex), IVF	4 SLE flares in 3 patients/16 cycles
Flare of SLE	Orquevaux 2017[2]	Observational	duration varies, not reported	27 women with SLE - 65 IVF cycles, background rx HCQ,	Agonist GnRH, antagonist GnRH, oocyte donation	4 SLE flares in 3 patients

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				steroids, ASA		
Renal Risks	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction, IVF	1 patient with Cr elevation during OI/IVF, 1 with FSGS postpartum
Maternal Outcomes	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction, IVF	2 patients with gestational HTN
Maternal Outcomes	Orquevaux 2017[2]	Observational	duration varies, not reported	27 women with SLE - 65 IVF cycles, background rx HCQ, steroids, ASA	Agonist GnRH, antagonist GnRH, oocyte donation	2 pts with pre-eclampsia but not clear if SLE or APS or both
Fetal Outcomes	Guballa, 2000[1]	Observational	Duration varies	7 women with SLE = 16 IVF cycles, background steroids	ovulation induction, IVF	2/7 pregnancies twin, 1/7 triplets 1 patient with spontaneous abortion
Maternal Outcomes	Orquevaux 2017[2]	Observational	duration varies, not reported	27 women with SLE - 65 IVF cycles, background rx HCQ, steroids, ASA	Agonist GnRH, antagonist GnRH, oocyte donation	2 miscarriages but not clear if SLE or APS or both 10 preterm birth but not clear if SLE or APS or both

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results

28. In women with SLE who are undergoing assisted reproductive technology, what is the effect of ovulation induction therapy with IVF and embryo transfer versus no ART on patient/maternal and (if relevant) pregnancy outcomes? **EVIDENCE FOR GS24**

The evidence is the same as for question 27 as OI and IVF were not separated in the two studies.

29. In women with SLE who are undergoing assisted reproductive technology, what is the effect of frozen embryo transfer versus no ART on patient/maternal and (if relevant) pregnancy outcomes? **RELEVANCE GS24 BUT NO EVIDENCE**

No evidence is available.

References:

1. Guballa N, Sammaritano L, Schwartzman S, Buyon J, Lockshin MD. Ovulation induction and in vitro fertilization in systemic lupus erythematosus and antiphospholipid syndrome. Arthritis and rheumatism. 2000;43(3):550-556.
2. Orquevaux P, Masseau A, Guern VL, Gayet V, Vauthier D, Guettrot-Imbert G, et al. In Vitro Fertilization in 37 Women with Systemic Lupus Erythematosus or Antiphospholipid Syndrome: A Series of 97 Procedures. The Journal of rheumatology. 2017;44(5):613-618.

2B.

2B. In women with RD [aPL variable] what is the impact of ART/ovarian stimulation, versus no ART/ovarian stimulation, on risk of maternal thrombosis?

Population: Women with RD who are undergoing assisted reproductive technology (ART)
- With aPL (any)
- With aPL (meet criteria for APS)

Interventions:
Assisted Reproductive Technology to include
- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Preparation for donor egg/embryo transfer (donor egg recipient)
- Assisted reproductive technologies with In vitro fertilization

Comparator:
- Similar RD patients not undergoing ART

- Non-RD patients having ART
- Among RD patients undergoing ART (study pop) compare with and without aPL

Outcome:
- Thrombosis

All evidence for PICO 2b is indirect and derives from two studies (Guballa 2000 and Orquevaux 2017).

30. In women with RD and any positive aPL, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) versus no ovarian stimulation therapy, on likelihood of maternal thrombosis? **RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE**

No evidence available.

31. In women with RD who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) versus no ovarian stimulation therapy, on likelihood of maternal thrombosis? **EVIDENCE FOR GS25, GS25A GS25B**

No studies address use of ovulation induction therapy alone. One study addresses use of ovulation induction therapy with in vitro fertilization in 14 women with APLS (10 SLE, 4 primary APLS).[1] The study does not include a control group. 4 thromboembolic events were noted

One study addresses the use of ovulation induction in 48 IVF cycles of 10 women with primary APS.[2] The study does not include a control group. No thromboembolic events were seen.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Ovulation induction agents (clomiphene, aromatase inhibitors, gonadotropin therapy)						
Thrombosis	Guballa, 2000[2]	Observational	Duration varies	10 women with primary APS = 48 IVF cycles, background steroids	ovulation induction, IVF	0 thromboembolic events
Assisted reproductive technologies: ovulation induction with in vitro fertilization / embryo transfer						
Thrombosis	Orquevaux, 2017[1]	observational,	duration varies, not reported	14 pt with APLS (10 with SLE, 4 with primary APLS),	Agonist GnRH, antagonist GnRH, oocyte donation	4 thromboembolic events

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				background ASA + prophylactic heparin		
Thrombosis	Guballa, 2000[2]	Observational	Duration varies	10 women with primary APS = 48 IVF cycles, background steroids	ovulation induction, IVF	0 thromboembolic events

32. In women with RD and any positive aPL, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) versus no ART on likelihood of maternal thrombosis? **QUESTIONS 32-36 RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE**

No evidence available

33. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) versus no ART on likelihood of maternal thrombosis?

No evidence available

34. In women with RD and any positive aPL, what is the impact of preparation for frozen embryo transfer, versus no ART on likelihood of maternal thrombosis?

No evidence available

35. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for embryo transfer versus no ART on likelihood of maternal thrombosis?

No evidence available

36. In women with RD and any positive aPL, what is the impact of ovulation induction therapy with IVF and embryo transfer versus no ART on likelihood of maternal thrombosis?

No evidence available

37. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy with IVF and embryo transfer versus no ART on likelihood of maternal thrombosis?

The evidence is the same as for question 31 as OI and IVF were not separated in the two studies. EVIDENCE FOR GS25, GS25A GS25B

38. In women with RD and any positive aPL, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) compared to non-RD patients (without aPL) undergoing this procedure, on likelihood of maternal thrombosis? **QUESTIONS 38-42 RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE**

No evidence available

39. In women with RD who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) compared to non-RD patients (without aPL) undergoing this procedure, on likelihood of maternal thrombosis?

No evidence available

40. In women with RD and any positive aPL, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

41. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

42. In women with RD and any positive aPL, what is the impact of preparation for frozen embryo transfer, compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

43. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for frozen embryo transfer compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

44. In women with RD and any positive aPL, what is the impact of ovulation induction therapy with IVF and embryo transfer compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

45. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy with IVF and embryo transfer compared to non-RD patients (without aPL) undergoing this procedure on likelihood of maternal thrombosis?

The evidence is the same as for question 31 as OI and IVF were not separated in the two studies. EVIDENCE FOR GS25, GS25A GS25B

46. In women with RD and any positive aPL, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) compared to RD patient without aPL undergoing this procedure, on likelihood of maternal thrombosis? **RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE**

No evidence available

47. In women with RD who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy (including use of clomiphene, aromatase inhibitors, or gonadotropin therapy) compared to RD patients without aPL undergoing this procedure, on likelihood of maternal thrombosis?

The evidence is the same as for question 31 as OI and IVF were not separated in the two studies. EVIDENCE FOR GS25, GS25A GS25B

48. In women with RD and any positive aPL, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) compared to RD patients without aPL undergoing this procedure on likelihood of maternal thrombosis? **QUESTIONS 22-26 RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE**

No evidence available

49. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for donor egg/embryo transfer (i.e. donor egg recipient) compared to RD patients without aPL undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

50. In women with RD and any positive aPL, what is the impact of preparation for frozen embryo transfer, compared to RD patients without aPL undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

51. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of preparation for frozen embryo transfer compared to RD patients without aPL undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

52. In women with RD and any positive aPL, what is the impact of ovulation induction therapy with IVF and embryo transfer compared to patients without aPL undergoing this procedure on likelihood of maternal thrombosis?

No evidence available

53. In women with RD and positive aPL who meet revised Sapporo criteria for APS, what is the impact of ovulation induction therapy with IVF and embryo transfer compared to RD patients without aPL undergoing this procedure on likelihood of maternal thrombosis?

The evidence is the same as for question 31 as OI and IVF were not separated in the two studies. RELEVANCE: GS25 GS25A, GS25B BUT NO EVIDENCE

References:

1. Orquevaux P, Masseau A, Guern VL, Gayet V, Vauthier D, Guettrot-Imbert G, et al. In Vitro Fertilization in 37 Women with Systemic Lupus Erythematosus or Antiphospholipid Syndrome: A Series of 97 Procedures. The Journal of rheumatology. 2017;44(5):613-618.
2. Guballa N, Sammaritano L, Schwartzman S, Buyon J, Lockshin MD. Ovulation induction and in vitro fertilization in systemic lupus erythematosus and antiphospholipid syndrome. Arthritis and rheumatism. 2000;43(3):550-556.

2C: No Evidence

2C. In women with RD who are undergoing assisted reproductive technology, what is the impact of stable/well-controlled disease activity [listed] versus active disease on maternal and pregnancy outcomes?

Population: Women with RD who are considering assisted reproductive technology (ART)

- Stable/well-controlled disease for <1 month on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy
- Stable/well controlled disease for one-three months on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy
- Stable/well controlled disease for 4-6 months on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy
- Stable/well-controlled disease for at least 6 months on
  - no medication
  - low-dose prednisone
  - background medications c/w pregnancy

Interventions:

- Ovulation induction agents (clomiphene, aromatase inhibitors, gonatotropin therapy)
- Assisted reproductive technologies: ovulation induction with in vitro fertilization/embryo transfer

Comparator (varies with outcome):

- Similar patients with active disease

Outcomes:

Success of procedure (likelihood of pregnancy)

- Fetal outcomes
- Flare of RD
- Damage of RD

RELEVANCE GS26 BUT NO EVIDENCE

2D: No Evidence

2D. In women with RD who are aPL positive (any) without history of thrombosis who are undergoing assisted reproductive technology, what is the impact of anticoagulation [listed] versus no anticoagulation on maternal and pregnancy outcomes [listed]?

Population:

- Women with RD, aPL positive but no history of thrombosis and not on chronic anticoagulation, who are undergoing ovarian stimulation/assisted reproductive technology (ART)

Interventions**:**

- Low-dose aspirin 81 mg
- Prophylactic LMWH/UF
- Therapeutic LMWH/UF
- LDA +LMWH/UF
-

Comparator:

- Similar patients undergoing ART and not treated with anticoagulation

Outcomes:

- Thrombosis

RELEVANCE: GS25, GS25A, GS25A-1, GS25A-2 BUT NO EVIDENCE

2E: No Evidence

2E. In women with RD who are undergoing assisted reproductive technology (ART), what is the impact of discontinuing or changing medications prior to ART if plan is for oocyte or embryo freezing without transfer, versus continuing medications, on maternal and procedure outcomes [listed]?

Population:
- Women with RD on rheumatic disease medications (define)

Intervention:
- Medication adjustment prior to intervention

Comparator:
- No medication adjustment prior to ART

Outcomes:
- Success of procedure (collectively and/or separately: no oocytes recovered, poor fertilization, no embryos)
- Blastocyst or embryo grade/aneuploidy
- Flare of RD
- Damage of RD

RELEVANCE GS28 BUT NO EVIDENCE

2F: No Evidence

2F. In women with SLE who are undergoing assisted reproductive technology (ART), what is the impact of prophylactic prednisone, versus no prophylactic prednisone, on maternal and procedure outcomes?

Population:
- Women with SLE undergoing ART

Intervention:
- Prophylactic prednisone during ovarian stimulation

Comparator:
- No prophylactic prednisone during ovarian stimulation

Outcomes:
- Success of procedure (likelihood of pregnancy)
- Flare of SLE

RELEVANCE GS 29, GS30 BUT NO EVIDENCE

3. Fertility Preservation

3A.

3A. In premenopausal women receiving CYC [variables listed] what is the impact of administration of a medication intended to preserve fertility [listed] versus no medication to preserve fertility on maternal outcomes?

- Population: Any pre-menopausal woman with RD receiving CYC
  - Monthly IV
  - Euro-lupus
  - Oral

- Ages:
  - Teen years
  - Women 20-29
  - Women 30-39
  - Women 40 and older

Intervention:

- GnRH analog (antagonist / agonist) co-therapy during cyclophosphamide
- Oral contraception co-therapy during cyclophosphamide.

Comparator: No hormonal co-therapy

Outcomes:

- Return of menstruation following cessation of CYC therapy
- Ability to conceive
- Premature ovarian insufficiency
- RD flare
-

54. In women in their teens receiving CYC by monthly IV infusion, what is the impact of receiving GnRH analog (antagonist/agonist) co-therapy verses not receiving GnRH analog (antagonist/agonist) co-therapy on: **EVIDENCE FOR GS31**

a. Return of menstruation following cessation of Cyc therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

One randomized, double-blind placebo-controlled dose-escalation study[1] examined return of menstruation following cessation of CYC therapy in women who received GnRH. The evidence was indirect for this outcome, as the study did not report the outcome of return of menstruation in the placebo group. 16/16 patients who received GnRH + CYC had return of menses.

In 2 observational studies[2,3] with direct comparisons (n=82), 19.4% (6/31) of women who received IV CYC without GnRH had ability to conceive. 29.4% (15/51) women who received IV CYC + GnRH had ability to conceive. OR 1.69 (0.53-5.44) for ability to conceive in women who received GnRH co-therapy with IC CYC.

One retrospective observational[4] provided indirect evidence about ability to conceive. 11 women (19 pregnancies) with PAN, GPA, EGPA, or MPA diagnosed during pregnancy or who had a pregnancy after diagnosis were identified. 6/11 (55%) of those women had previously received IV CYC; this group conceived and delivered 8 healthy children. 5/6 of those women had been prescribed continuous oral progestative drugs or a GnRH agonist.

In 2 observational studies[2,3] with direct comparisons (n=82), 35.5% (11/31) of women who received IV CYC without GnRH developed premature ovarian failure. 3.9% (2/51) women who received IV CYC + GnRH developed premature ovarian failure. OR 0.07 (0.01-0.36) for developing premature ovarian failure in women who received GnRH co-therapy with IC CYC.

Quality of Evidence across outcomes: Low

GnRh compared to no hormonal co-therapy for preserving fertility in premenopausal women receiving Monthly IV CYC

Bibliography: Bettendorf B. PICO 3a: medication versus no medication for preserving fertility in premenopausal women receiving CYC.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no hormonal co-therapy	**With GnRh**		**Risk with no hormonal co-therapy**	**Risk difference with GnRh**
Premature ovarian failure											
82 (2 observational studies)	serious [a]	not serious	not serious	not serious	very strong association	⨁⨁⨁◯ MODERATE	11/31 (35.5%)	2/51 (3.9%)	**OR 0.07** (0.01 to 0.36)	355 per 1,000	**318 fewer per 1,000** (349 fewer to 190 fewer)
Ability to conceive											
82 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	6/31 (19.4%)	15/51 (29.4%)	**OR 1.69** (0.53 to 5.44)	194 per 1,000	**95 more per 1,000** (81 fewer to 373 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. study participants chose whether they wanted GnRH or not, no blinding was possible- allocation bias and performance bias was present. Retrospective data

References:

Premature ovarian failure outcome: 241 Blumenfield 2011, 307 Somers 2005

Ability to conceive outcome: 241 Blumenfield 2011, 307 Somers 2005

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
GnRH analog (antagonist / agonist) co-therapy during cyclophosphamide						
INDIRECT EVIDENCE						
Return of menstruation following cessation of Cyc therapy	189 Brunner 2015[1]	randomized, double-blind placebo-controlled dose-escalation study	24 week CYC induction therapy followed by CYC every 6-12 weeks for maintenance therapy or until CYC was discontinued. Ovarian function following CYC therapy was measured at > 3 months after discontinuation of GnRH	females <21 years old with childhood-onset SLE who require CYC therapy	triptorelin (GnRH agonist) at escalated doses versus placebo	Study does not report outcomes of return of menstruation in placebo group. 16 patients received GnRH along with CYC therapy and all 16 had return of menses
Ability to conceive	3592 Pagnoux 2011[4]	Retrospective observational study	15-year period	Women diagnosed with PAN,GPA, EGPA or microscopic polyangiitis (MPA) during pregnancy or who had a pregnancy after diagnosis were identified in patient databases. Median age: 29 (range: 20-40 years)	n=6 (55%) had previously received IV CYC, with a cumulative dose of 55 g for one EGPA patient	n=11 women had 19 pregnancies after diagnosis (8 pregnancies in 4 GPA patients, 6 in 3 EGPA patients, 2 in 1 MPA patient, 2 in 2 PAN patients and 1 in 1 cutaneous PAN patient 6 women had previously received IV CYC but conceived and delivered eight healthy children. 5 of those women had been prescribed continuous oral progestative drugs or a gonadotropin-releasing hormone agonist, like triptorelin, to try to preserve ovarian function when receiving CYC Two patients conceived while taking CYC: one had a therapeutic abortion at 8 weeks and the other had a live birth at 37 weeks

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Median time from diagnosis to pregnancy: 36 months (range: 4-348)		

55. In women in their teens, aged 20-29, aged 30-39, aged 40 or older receiving CYC by monthly IV infusion, what is the impact of receiving oral contraception co-therapy verses not receiving oral contraceptive co-therapy during cyclophosphamide on: **EVIDENCE FOR GS31**

a. Return of menstruation following cessation of CYC therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

Return of menstruation following cessation of CYC therapy was indirectly reported in 1 observational study[5] of 84 premenopausal women (56 with SLE and 28 with other inflammatory diseases). 26/56 (46.4%) SLE patients received contraceptive pills. 23/30 (76.6%) of SLE patients who did not use contraceptive pills had return of menses, 20/26 (76.9%) of women with SLE who used contraceptive pills had return of menses. 10/28 (35.7%) non-SLE patients with other inflammatory disease received contraceptive pills. 12/18 (66.6%) of non-SLE patients who did not use contraceptive pills had return of menses, 10/10 (100%) of women with non-SLE who used contraceptive pills had return of menses.

Ability to conceive was reported in 2 observational studies with indirect evidence[4,5]. In 1 study[4], 11 women (19 pregnancies) with PAN, GPA, EGPA, or MPA diagnosed during pregnancy or who had a pregnancy after diagnosis were identified. 6/11 (55%) of those women had previously received IV CYC; this group conceived and delivered 8 healthy children. 5/6 of those women had been prescribed continuous oral progestative drugs or a GnRH agonist. In 1 study[5], 13/56 (23.6%) SLE patients who received IV CYC had ability to conceive and 5/28 (17.8%) patients with non-SLE inflammatory disease who received IV CYC had ability to conceive. Ability to conceive was not reported based on whether patients received hormonal co-therapy or not. Overall very low quality of evidence for this outcome.

Premature ovarian failure was reported in 1 observational study with indirect evidence[5]. 13 out of 56 SLE patients who received IV CYC developed ovarian failure. 6/26 (23.0%) of SLE patients using oral contraceptives developed ovarian failure compared to 7/30 (23.3%) of SLE patients not using oral contraceptives. 6 out of 28 patients with other inflammatory diseases (not SLE) who received IV CYC developed ovarian failure. 0/10 non-SLE patients using oral contraceptives developed ovarian failure compared to 6/18 (33.3%) of non-SLE patients not using oral contraceptives.

Quality of evidence across outcome: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Oral contraceptive pill co-therapy during cyclophosphamide						
INDIRECT EVIDENCE						
Return of menstruation following cessation of CYC therapy	2845, Huong, 2002[5]	Retrospective observational	Prior to and after 1997 Group Hospitalier Pitie-Salpetriere, Paris	84 premenopausal women with SLE (n=56) and other inflammatory diseases (n=28) treated with IVCY therapy	Hormonal co-therapy SLE patients 26 (46.4%) used contraceptive pills Non-SLE patients 10 (35.7%) used contraceptive pills	SLE patients (n=56) Return of menstruation: 23/30 (76.6%) of women who did not use contraceptive pills had return of menses; 20/26 (76.9%) women who used contraceptive pills had return of menses. Non-SLE patients (n=28) Return of menstruation: 12/18 (66.6%) of women who did not use contraceptive pills had return of menses; 10/10 (100%) women who used contraceptive pills had return of menses.
Ability to conceive	3592 Pagnoux 2011{Pagnoux, 2010 #186}	Retrospective observational study	15-year period	Women diagnosed with PAN,GPA, EGPA or microscopic polyangiitis (MPA) during pregnancy or who had a pregnancy after diagnosis were identified in patient databases. Median age: 29 (range: 20-40 years) Median time from diagnosis to pregnancy: 36 months (range: 4-348)	n=6 (55%) had previously received IV CYC, with a cumulative dose of 55 g for one EGPA patient	n=11 women had 19 pregnancies after diagnosis (8 pregnancies in 4 GPA patients, 6 in 3 EGPA patients, 2 in 1 MPA patient, 2 in 2 PAN patients and 1 in 1 cutaneous PAN patient 6 women had previously received IV CYC but conceived and delivered eight healthy children. 5 of those women had been prescribed continuous oral progestative drugs or a gonadotropin-releasing hormone agonist, like triptorelin, to try to preserve ovarian function when receiving CYC Two patients conceived while taking CYC: one had a therapeutic abortion at 8 weeks and the other had a live birth at 37 weeks
	2845, Huong, 2002[5]	Retrospective observational	Prior to and after 1997 Group Hospitalier Pitie-Salpetriere, Paris	84 premenopausal women with SLE (n=56) and other inflammatory diseases (n=28) treated	Hormonal co-therapy SLE patients 26 (46.4%) used contraceptive pills Non-SLE patients	SLE patients (n=56) Ability to conceive: 13 (23.6%) Non-SLE patients (n=28) Ability to conceive: 5 (17.8%) Ability to conceive was not reported based on whether patients received hormonal co-therapy or not.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				with IVCY therapy	10 (35.7%) used contraceptive pills	
Premature ovarian insufficiency	2845, Huong, 2002[5]	Retrospective observational	Prior to and after 1997 Group Hospitalier Pitie-Salpetriere, Paris	84 premenopausal women with SLE (n=56) and other inflammatory diseases (n=28) treated with IVCY therapy	Hormonal co-therapy <u>SLE patients</u> 26 (46.4%) used contraceptive pills <u>Non-SLE patients</u> 10 (35.7%) used contraceptive pills	<u>SLE patients (n=56)</u> Ovarian failure: 13 patients 6/26 (23.0%) contraceptive users developed ovarian failure 7/30 (23.3%) non-contraceptive users developed ovarian failure <u>Non-SLE patients (n=28)</u> Ovarian failure: 6 patients 0/10 contraceptive users developed ovarian failure 6/18 (33.3%) non-contraceptive users developed ovarian failure

56. In women in their teens, aged 20-29, aged 30-39, aged 40 or older receiving the Euro-lupus CYC protocol, what is the impact of receiving GnRH analog (antagonist/agonist) co-therapy verses not receiving GnRH analog (antagonist/agonist) co-therapy on: **RELEVANCE: GS32 BUT NO EVIDENCE**

a. Return of menstruation following cessation of Cyc therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

No evidence

57. In women in their teens, aged 20-29, aged 30-39, aged 40 or older receiving Euro-lupus CYC protocol, what is the impact of receiving oral contraception co-therapy verses not receiving oral contraceptive co-therapy co-therapy during cyclophosphamide on: **RELEVANCE GS32 BUT NO EVIDENCE**

a. Return of menstruation following cessation of CYC therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

No evidence

58. In women in their teens, aged 20-29, aged 30-39, aged 40 or older receiving oral CYC, what is the impact of receiving GnRH analog (antagonist/agonist) co-therapy verses not receiving GnRH analog (antagonist/agonist) co-therapy on: **RELEVANCE GS33 BUT NO EVIDENCE**

a. Return of menstruation following cessation of CYC therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

No evidence

59. In women in their teens, aged 20-29, aged 30-39, aged 40 or older receiving oral CYC, what is the impact of receiving oral contraception co-therapy verses not receiving oral contraceptive co-therapy co-therapy during cyclophosphamide on: **RELEVANCE GS32 BUT NO EVIDENCE**

a. Return of menstruation following cessation of CYC therapy
b. Ability to conceive
c. Premature ovarian insufficiency
d. Rheumatic disease flare

No evidence

References:

1. Brunner HI, Silva CA, Reiff A, Higgins GC, Imundo L, Williams CB, et al. Randomized, double-blind, dose-escalation trial of triptorelin for ovary protection in childhood-onset systemic lupus erythematosus. Arthritis & rheumatology (Hoboken, N.J.). 2015;67(5):1377-1385.
2. Blumenfeld Z, Mischari O, Schultz N, Boulman N, Balbir-Gurman A. Gonadotropin releasing hormone agonists may minimize cyclophosphamide associated gonadotoxicity in SLE and autoimmune diseases. Seminars in arthritis and rheumatism. 2011;41(3):346-352.

3. Somers EC, Marder W, Christman GM, Ognenovski V, McCune WJ. Use of a gonadotropin-releasing hormone analog for protection against premature ovarian failure during cyclophosphamide therapy in women with severe lupus. Arthritis and rheumatism. 2005;52(9):2761-2767.
4. Pagnoux C, Guern VL, Goffinet F, Diot E, Limal N, Pannier E, et al. Pregnancies in systemic necrotizing vasculitides: report on 12 women and their 20 pregnancies. Rheumatology (Oxford, England). 2010;50(5):953-961.
5. Huong DL, Amoura Z, Duhaut P, Sbai A, Costedoat N, Wechsler B, et al. Risk of ovarian failure and fertility after intravenous cyclophosphamide. A study in 84 patients. The Journal of rheumatology. 2002;29(12):2571-2576.

3B.

3B. In a man with RD receiving CYC, what is the impact of administration of testosterone co-therapy versus no testosterone co-therapy on paternal fertility outcomes [listed]?

Population: Any man receiving CYC for RD interested in fathering a child in the future

- Monthly IV
- Euro-lupus
- Oral

Intervention: Testosterone co-therapy during cyclophosphamide

Comparator: Similar patients without testosterone co-therapy

Outcomes:

- Sperm quality:
  - Sperm count following CYC therapy
  - Sperm motility
  - DNA fragmentation of chromatin
- Low testosterone level

60. In men with RD receiving monthly IV CYC therapy and interested in fathering a child in the future, what is the impact of receiving testosterone co-therapy versus not receiving testosterone co- therapy on sperm quality (including sperm count, sperm motility and DNA fragmentation of chromatin) or testosterone level? **EVIDENCE FOR GS35**

No direct or indirect evidence was found to answer this PICO question. One study examined the use of testosterone co-therapy in male patients with SLE who were receiving IV cyclophosphamide, however the comparator group was healthy, age-matched controls who did not receive cyclophosphamide (nor testosterone). Sperm quality (including sperm count and sperm motility) was lower in men receiving CYC+testosterone compared to those who did not receive CYC/testosterone. This was statistically significant. However, given that there was no comparison group of men receiving CYC who did not receive testosterone co-therapy, there is no evidence available to make an assessment of the impact of testosterone co-therapy on future fertility in men who received IV CYC. This evidence merely supports the fact that receiving IV CYC decreases sperm quality.[1]

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Testosterone co-therapy during cyclophosphamide						
Sperm quality (including sperm count, sperm motility and DNA fragmentation of chromatin)	283 Soares 2007[1]	Prospective observational cohort	3 years	35 consecutive male patients with SLE compared with 35 age-matched healthy controls	IV CYC or no CYC	- Sperm concentration (x10^6/mL): 2 in CYC patients (n=14), 82 in non CYC patients (n=21), p=0.0001 - Total sperm count(x10^6/mL): 6 in CYC patients (n=14), 150 in non CYC patients (n=21), p=0.0001 - Total motile sperm count (x10^6/mL): 2.5 in CYC patients (n=14), 94 in non CYC patients (n=21), p=0.0001 - Sperm motility, %: 48.5 in CYC patients (n=14), 64.5 in non CYC patients (n=21), p=0.004 - No data on DNA fragmentation of chromatin
Low testosterone level	No data					

61. In men with RD receiving Euro-lupus CYC therapy and interested in fathering a child in the future, what is the impact of receiving testosterone co-therapy verses not receiving testosterone co- therapy on sperm quality (including sperm count, sperm motility and DNA fragmentation of chromatin) or testosterone level? **RELEVANCE GS36 BUT NO EVIDENCE**

No evidence

62. In men with RD receiving oral CYC therapy and interested in fathering a child in the future, what is the impact of receiving testosterone co-therapy verses not receiving testosterone co- therapy on sperm quality (including sperm count, sperm motility and DNA fragmentation of chromatin) or testosterone level? **RELEVANCE GS37 BUT NO EVIDENCE**

No evidence

References

1. Soares PM, Borba EF, Bonfa E, Hallak J, Correa AL, Silva CA. Gonad evaluation in male systemic lupus erythematosus. Arthritis and rheumatism. 2007;56(7):2352-2361.

3C: No evidence

3C. In a man with RD, what is the impact of receiving rheumatology medications [listed], versus no rheumatology medications, on paternal fertility outcomes?

Population:

- Any man receiving rheumatology medications for RD interested in fathering a child in the future

Intervention:

- MTX
- Sulfasalazine
- Leflunomide
- CYC
    - IV pulse
    - Eurolupus
    - Oral

Comparator:

- Similar patients not taking that medication

Outcomes:

- Sperm quality:
    - Sperm count
    - Sperm motility
    - DNA fragmentation of chromatin
- Low testosterone level

RELEVANCE GS39-41 ……

BUT NO EVIDENCE.

4. Counseling in Anticipation of Pregnancy

4A

4A. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to alternative immunosuppressive agents [listed] prior to attempting conception versus continuing mycophenolate on maternal and pregnancy outcomes [listed]?

Population: Women with RD taking mycophenolate for maintenance of quiescent disease who wish to conceive.

Intervention: Stop mycophenolate prior to pregnancy and start alternative agent including azathioprine, cyclosporin, tacrolimus, prior to pregnancy

Comparator:
Stop mycophenolate prior to pregnancy without replacing it with alternative agent
Continue mycophenolate through pregnancy

Outcomes: Maternal and pregnancy outcomes to include…

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (infection)
- Maternal mortality

63. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to azathioprine prior to attempting conception versus stopping mycophenolate without a replacement agent on maternal and pregnancy outcomes? **EVIDENCE FOR GS42**

Summary:

This PICO was addressed by 1 observational study[1] with indirect evidence. In this study, medical records of women with lupus nephritis counselled for pregnancy wish were reviewed. Women included in the study were receiving treatment with either MMF or AZA with inactive lupus (SLEDAI <= 4) and quiescent lupus nephritis. 18 women treated with MMF were identified (and 31 treated with AZA). MMF was tapered and

patients were transitioned to AZA (2mg/kg), which was maintained throughout pregnancy. Pregnancy and maternal outcomes in this group as follows: 1 first trimester SAB (5.5%), 3 preterm deliveries (17.6%), 0 cases of pre-eclampsia (0%), 3 small for gestational age infants (17.6%), 0 flares during pregnancy (0%), 1 flare 2 months post-partum (5.5%).

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Stop mycophenolate prior to pregnancy and start azathioprine						
Pregnancy loss	Fischer-Betz 2013[1]	Observational	1 year	18 pregnancies among women with LN transitioned from MMF to AZA; patients all had inactive lupus (SLEDAI <= 4) and quiescent LN prior to conception	AZA (2mg/kg) throughout pregnancy	1 first trimester SAB (5.5%)
Preterm delivery	Fischer-Betz 2013[1]	Observational	1 year	18 pregnancies among women with LN transitioned from MMF to AZA; patients all had inactive lupus (SLEDAI <= 4) and quiescent LN prior to conception	AZA (2mg/kg) throughout pregnancy	3 preterm deliveries (17.6%)
Pre-eclampsia	Fischer-Betz 2013[1]	Observational	1 year	18 pregnancies among women with LN transitioned from MMF to AZA; patients all had inactive lupus (SLEDAI <= 4) and quiescent LN prior to conception	AZA (2mg/kg) throughout pregnancy	0 cases of pre-eclampsia (0%)
SGA infants	Fischer-Betz 2013[1]	Observational	1 year	18 pregnancies among women with LN transitioned from MMF to AZA; patients	AZA (2mg/kg) throughout pregnancy	3 small for gestational age infants (17.6%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				all had inactive lupus (SLEDAI <= 4) and quiescent LN prior to conception		
Flares	Fischer-Betz 2013[1]	Observational	1 year	18 pregnancies among women with LN transitioned from MMF to AZA; patients all had inactive lupus (SLEDAI <= 4) and quiescent LN prior to conception	AZA (2mg/kg) throughout pregnancy	0 flares during pregnancy (0%), 1 flare 2 months post-partum (5.5%)

64. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to cyclosporine prior to attempting conception versus stopping mycophenolate without a replacement agent on maternal and pregnancy outcomes**? QUESTIONS 64-68 RELEVANCE TO GS42 BUT NO EVIDENCE**
No evidence

65. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to tacrolimus prior to attempting conception versus stopping mycophenolate without a replacement agent on maternal and pregnancy outcomes?
No evidence

66. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to azathioprine prior to attempting conception versus continuing mycophenolate on maternal and pregnancy outcomes?
No evidence

67. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to cyclosporine prior to attempting conception versus continuing mycophenolate on maternal and pregnancy outcomes?
No evidence

68. In women with RD taking mycophenolate mofetil (or mycophenolic acid) for maintenance of quiescent disease who wish to conceive, what is the impact of switching to tacrolimus prior to attempting conception versus continuing mycophenolate on maternal and pregnancy outcomes?
No evidence

References:

1. Fischer-Betz R, Specker C, Brinks R, Aringer M, Schneider M. Low risk of renal flares and negative outcomes in women with lupus nephritis conceiving after switching from mycophenolate mofetil to azathioprine. Rheumatology (Oxford, England). 2013;52(6):1070-1076.

4B: No evidence

4B. In women with RD taking a non-TNF-i biologic or new small molecule drug who wish to conceive, what is the impact of switching to a TNF-i or pregnancy compatible drug prior to conception versus not switching on maternal and pregnancy outcomes [listed]?

Population:
- Women with RD taking a non-TNF-i biologic or new small molecule drug who wish to conceive

Intervention:
- Stop the non-TNF-i biologic or small molecule and change to a TNF-i or pregnancy-compatible synthetic DMARD prior to conception

Comparator:
- Stop a non-TNF-I biologic or small molecule for pregnancy and don't replace it with another immunosuppressant
- Continue the initial medication

Outcome:
- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

RELEVANCE TO GS43 BUT NO EVIDENCE

4C: No evidence

4C. In women who have taken leflunomide within 2 years of wanting to conceive, what is the impact of checking drug level or administering washout [listed] versus not checking drug level or administering washout on maternal and pregnancy outcomes [listed]?

Population:
- Women with RD who have taken leflunomide within 2 years of wanting to conceive

Intervention:
- Check leflunomide blood level prior to conception
- Administer cholestyramine prior to conception if leflunomide level is over acceptable range

Comparator:
- Not checking leflunomide blood level prior to conception
- Not administering cholestyramine prior to conception

Outcome:
- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality

RELEVANCE TO GS109 AND GS110 BUT NO EVIDENCE

4D.

4D. In women with RD on NSAIDS who plan to conceive, what is the impact of stopping the NSAID prior to attempting conception versus not stopping the NSAID on maternal and pregnancy outcomes?

Population: women with RD who are trying to conceive and are on NSAIDs

Intervention: Stop NSAID prior to attempting pregnancy

Comparator: Continue NSAID until after conception has occurred

Outcome: Maternal and pregnancy outcomes to include…

- Time to conception
- Spontaneous abortion

69. In women with RD on NSAIDS who plan to conceive, what is the impact of stopping the NSAID prior to attempting conception versus not stopping the NSAID until after pregnancy has occurred on maternal and pregnancy outcomes? **EVIDENCE FOR GS86,GS87,GS88**

Summary: This PICO was addressed by one observational study[1] with direct evidence. This study prospectively followed 245 female RA patients who were actively trying to conceive or already pregnant. 101 patients were noted to be subfertile (time to conception > 12 months) and 141 patients were not subfertile NSAID use was significantly higher in the subfertile group (58%) v the not subfertile group (37%). The OR of NSAID use in the subfertile v not subfertile group was 2.35 (1.30-4.26).

Quality of Evidence across outcomes: Very low

NSAID use in subfertile (time to conception > 12 months) v fertile patients											
Certainty assessment							**Summary of findings**				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							Fertile patients (% NSAID use)	**Subfertile patients (% NSAID use)**		**Risk with placebo**	**Risk difference with NSAID use in subfertile v fertile patients**
Subfertile (time to conception > 12 months)											

NSAID use in subfertile (time to conception > 12 months) v fertile patients											
Certainty assessment							Summary of findings				
245 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	69/185 (37.3%)	35/60 (58.3%)	OR 2.35 (1.30 to 4.26)	373 per 1,000	**210 more per 1,000** (63 more to 344 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

References

1. Brouwer J, Hazes JM, Laven JS, Dolhain RJ. Fertility in women with rheumatoid arthritis: influence of disease activity and medication. Annals of the rheumatic diseases. 2014;74(10):1836-1841.

4E. In patients with RD [listed], what is the impact of having a RD diagnosis compared to not having a RD diagnosis on long-term outcomes in offspring [listed]? THE CORE TEAM DECIDED TO HAVE THESE QUESTIONS REPRESENTED AS A DISCUSSION STATEMENT, AND NOT A VOTE-ABLE GUIDELINE STATEMENT.
DATA WILL BE SUMMARIZED FOR DISCUSSION PURPOSES IN THE PAPER.
APPLIES TO QUESTIONS 70-79, BELOW.

Population:

- Women with RD with
  - SLE
  - RA
  - Other RD
  - APS
  - Anti-Ro/La
- Men with RD with
  - SLE
  - RA
  - Other RD
  - APS
  - Anti-Ro/La

Intervention: having a RD

Comparator: Similar patients without these disease states.

Outcomes: Long-term outcomes to include…

- Risk of neurodevelopmental delays in offspring
- Risk of autoimmune disease in offspring

70. In women with SLE, what is the impact of having the diagnosis of SLE compared to not having this diagnosis on long-term outcomes in offspring?

Summary: The PICO for the risk of neurodevelopmental delays in offspring was addressed by two observational studies with direct evidence.[1,2] Evidence was supplemented by 4 observational studies with indirect evidence,[3-6] and 1 RCT.[7]

In an observational cohort study,[1] 49 children of mothers with SLE aged 2-26 years were matched to controls by age, sex, race, and socio-economic factors. Compared to controls, children of mothers with SLE had significant impairment in learning & memory, as well for behaviors. No difference was seen in intellectual function, attention, executive functioning, language, visuospatial, academic achievement, and sensorimotor. In a case-control study, children of mothers with SLE aged 8-15 years were matched to children of healthy mothers by age and sex.[2] There was no observed difference between the groups for IQ, academic achievement, or learning disability.

Four observational studies provided supplemental indirect evidence. One observational study included 30 children of mothers with SLE or APS, with a median age of 9 years.[3] Intellectual functioning was within the normal range in all children as per the Wechsler scale. Another cohort study included 60 children from 30 mothers with SLE, with a median age of 5.7 years.[4] For children under the age of 2, 17% used special education services, 2% had hearing impairment, 3% had fine motor skill deficit, 2% had gross mother skill deficit, and 5% had speech delay. For children aged 2 and older, 23% used special education services, 5% needed aid with reading, 3% required occupation therapy, 18% had speech therapy, and 5% had ADHD. In an observational study of 19 children over the age of 4 who were born to women with SLE,[5] no complaints of communication disability referable to the ears were detected in any children, and all children met expected child development and school performance for their age. Although no routine eye examinations were performed, no visual abnormalities were reported. In a study of 203 pregnancies to 143 women with connective tissue disease (77% with SLE), data were collected for each child at a mean age of 26 months (median 24 months, range 12–108 months). No visual, hearing, growth, or developmental abnormalities were reported by the mothers, general practitioners, or pediatricians.[6]

Finally, in a follow-up of children born to 20 women with SLE who participated in a RCT of hydroxychloroquine use during pregnancy,[7] children were examined between the age of 1.5 and 3 years. All children had normal cognitive development and did not have any visual, hearing, or growth abnormalities.

For the outcome of the risk of autoimmune disease in offspring, direct evidence was provided by 1 observational study,[1] in which 49 children of mothers with SLE aged 2-26 years were matched to controls by age, sex, race, and socio-economic factors. No children of mothers with SLE were diagnosed with SLE.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Having the diagnosis of SLE						
Risk of neurodevelopmental delays in offspring	3636 Urowitz, 2008[1]	Cohort study	1973 - 1998	Children of SLE mothers (n=49); age range 2–26 years Controls matched for age, sex, race, and socio-economics (n=49)	Treatment during pregnancy: • Steroids: 31 (69%) • Max steroids dose >10: 16/30 (53.3%) • Antimalarials: 11 (24%) • Immunosuppressives: 1 (2%)	Statistically significant impairment in SLE children in learning & memory (p=0.01) and behaviors (p=0.02) compared to controls. No difference seen in intellectual function, attention, executive functioning, language, visuospatial, academic achievement, and sensorimotor
	3724 Ross, 2003[2]	Case-control study		Age 8-15 y/o Children of SLE mothers (n=58)	Use of steroids during pregnancy: 20 (34%	No difference between groups for IQ/academic achievement or learning disability.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Control children from healthy mothers (n=58) matched by age and sex		
	4048 Nalli, 2014[3]	Observational study		Children of SLE or APS mothers (n=30) Median age=9	--	Intellectual functioning was within the normal range in all children as per the Wechsler scale
	2532, Marder, 2013[4]	Cohort study	Median 5.7 yrs	38 pregnant women with SLE, 60 pregnancies	Plaquenil exposure, steroids, 13 children with in utero AZA exposure vs 47 nonexposed children	Outcomes: use of special education services <u>Age <2 years</u> • 17% using SE services • Hearing impairment 2% • Fine motor skill deficit 3% • Gross motor skill deficit 2% • Speech delay 5% <u>Age >2 years</u> • 23% using SE services • Aid with reading 5% • OT 3% • speech therapy 18% • ADHD 5%
	2814 Borba 2004[5]	observational	Children over age 4, retrospective review of pregnancies	19 children born from consecutive SLE patients at University of Sao Paulo, all mothers fulfilled ACR criteria. Children > age 4 with no previous h/o recurrent otitis, acoustic trauma and ototoxic antibiotic treatment.	Children were divided according to gestational chloroquine use into: CDP group (n=9), control group not exposed to CDP (n=10)	No complaints of communication disability referable to the ears were detected in any children and they all presented an expected child development and school performance for their age. Although no routine eye examinations were performed, no visual abnormalities were reported.
	2824, Costedoat-Chalumeau 2003[6]	Case-control	Perinatal period	203 pregnancies to 143 women with connective tissue disease Maternal diagnosis: • SLE: 110 (77%) • UCTD: 21 (15%) • Sjogren's syndrome: 12 (8%) • APS: 28 (20%)	90 women (133 pregnancies treated with HCQ) or 53 women (70 pregnancies) with no HCQ	Data for each child were collected at a mean age of 26 months (median 24 months, range 12–108 months). No visual, hearing, growth, or developmental abnormalities were reported by the mothers, general practitioners, or pediatricians.
	2875 Levy 2001[7]	RCT	Perinatal period	20 patients with SLE	HCQ vs placebo n=8 HCQ	Children examined at ages of 1.5 - 3 y. No health compromise

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					n=12 placebo	was found. All children achieved percentiles above 50 in the National Center for Health Statistics Percentiles curve for height and weight. All children achieved satisfactory cognitive development and were able to perform activities expected for their ages. No visual or hearing abnormalities were observed on clinical exam
Risk of autoimmune disease in offspring	3636 Urowitz, 2008[1]	Cohort study	1973 - 1998	Children of SLE mothers (n=49) Controls matched for age, sex, race, and socio-economics (n=49)	Treatment during pregnancy: • Steroids: 31 (69%) • Max steroids dose >10: 16/30 (53.3%) • Antimalarials: 11 (24%) • Immunosuppressives: 1 (2%)	None of the SLE offspring were diagnosed with SLE

71. In women with RA, what is the impact of having the diagnosis of RA compared to not having this diagnosis on long-term outcomes in offspring?

Summary: One observational study directly addressed the PICO question.[8] In an administrative claims analysis, women with JIA (n=1681) were matched to a control group (n=6724) by date of first birth, maternal age, and area of residence. In infants born to women with JIA, 1.8% had a neurologic malformation, compared to 0.04% of infants born to women without JIA.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Having the diagnosis of RA						
Risk of neurodevelopmental delays in offspring	3438 Ehrmann Feldman 2016[8]	Observational – administrative claims analysis	1983 – 2010	Cohort formed through administrative claims databases. Patients with **JIA** identified by 3 ICD-9 codes of 714 and ≤16 years old at the time of the first billing code. Only first births were included. JIA patients matched to control group by date of first birth, maternal age, and area of residence. n=1681 women with JIA Mean age at delivery (SD): 24.7 (4.3) years Hypertension/heart disease: 8.5% Diabetes: 0.9%	n/a	**JIA** Major congenital malformation: 9.0% Neurologic malformation: 1.8% Congenital heart defect: 1.1% Neural tube defect: 1.6% **No JIA**

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=6724 women without JIA Mean age at delivery (SD): 25.0 (4.5) years Hypertension/heart disease: 4.6 % Diabetes: 0.6%		Major congenital malformation: 1.4% Neurologic malformation: 0.04% Congenital heart defect: 0.6% Neural tube defect: 0.03%

72. In women with non-SLE, non-RA, non-APS (i.e. other) RD, what is the impact of having this diagnosis of RD compared to not having this diagnosis on long-term outcomes in offspring?

No evidence.

73. In women with APS, what is the impact of having the diagnosis of APS compared to not having this diagnosis on long-term outcomes in offspring?

Summary: This PICO was addressed by three indirect observational studies.[3,6,9]

In an observational study of 15 children born to mothers with APS with a mean age of 11.74 years (SD: 2.41), all children were found to have a normal intelligence level by the Wechsler Intelligence Scale for Children Revised (WISC-R). Learning disabilities were assessed by the Sartori test, which identified 4 cases (26.7%). Three children had dyslexic syndrome and 1 had dyscalculia syndrome.[9]

In a study of 203 pregnancies to 143 women with connective tissue disease (20% with APS), data were collected for each child at a mean age of 26 months (median 24 months, range 12–108 months). No visual, hearing, growth, or developmental abnormalities were reported by the mothers, general practitioners, or pediatricians.[6]

One observational study included 30 children of mothers with SLE or APS, with a median age of 9 years.[3] Intellectual functioning was within the normal range in all children as per the Wechsler scale.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Having the diagnosis of APS						
Risk of neurodevelopmental delays in offspring	4305 Nacinovich, 2008[9]	Observational study		Children of APS mothers (n=17)		Wechsler Intelligence Scale for Children Revised (WISC-R) normal in all children

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Mean age 11.74 +/- 2.41 15 mothers had IgG aCL 2 mothers had IgM aCL Testing was done on the 15 children		Learning disabilities performed by the Sartori test which identified 4 cases (26.7%). 3 with dyslexic syndrome and 1 with dyscalculia syndrome
	2824, Costedoat-Chalumeau 2003[6]	Case-control	Perinatal period	203 pregnancies to 143 women with connective tissue disease Maternal diagnosis: SLE: 110 (77%) UCTD: 21 (15%) Sjogren's syndrome: 12 (8%) APS: 28 (20%)		Data for each child were collected at a mean age of 26 months (median 24 months, range 12–108 months). No visual, hearing, growth, or developmental abnormalities were reported by the mothers, general practitioners, or pediatricians.
	4048 Nalli, 2014[3]	Observational study		Children of SLE or APS mothers (n=30) Median age=9	--	Intellectual functioning was within the normal range in all children as per the Wechsler scale

74. In women with positive anti-Ro and/or La antibodies, what is the impact of having these antibodies compared to not having these antibodies on long-term outcomes in offspring?

Summary: For the outcome of risk of neurodevelopmental delays in offspring, the PICO was addressed by one indirect observational study. In a case-control study, children of mothers with SLE aged 8-15 years were matched to children of healthy mothers by age and sex.[2] There was no observed difference between the groups for IQ, academic achievement, or learning disability. Within the SLE group, 15 women had positive Ro/La antibodies and 43 were Ro/La negative. Children born to mothers who had Ro/La antibodies were significantly more likely to have a learning disability (47% compared to 16%).

For the outcome of risk of autoimmune disease in offspring, one study directly addressed the PICO question,[10] with an additional observational study providing indirect evidence.[11]

A cohort of 13 children born to 12 women with positive Ro/La antibodies were compared to 6 children born to 6 women with negative Ro/La antibodies.[10] Of the Ro/La positive mothers, 7 children had fetal or neonatal lupus (54%). All 6 of the children born to Ro/La negative mothers were healthy.

In a retrospective review of children with neonatal lupus enrolled in the Research Registry for Neonatal Lupus,[11] 47 children with a skin rash in the absence of congenital heart block were included. All mothers had documented anti-SSA/Ro, anti-SSB/La, and/or anti-U1RNP autoantibodies: 96% SSA/Ro and 72% SSB/La. After an average 77 months of follow-up, 4 children had signs of autoimmune disease (7% of children): 1 developed Hashimoto's thyroiditis at age 7; 2 developed juvenile RA (at 2 years and 5 years); and 1 developed Raynaud's.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Women with positive anti-Ro and/or La antibodies						
Risk of neurodevelopmental delays in offspring	3724 Ross, 2003[2]	Cohort study		Age 8-15 y/o Children of SLE mothers (n=58) Control children from healthy mothers (n=58)	Use of steroids during pregnancy: 20 (34%	No difference between groups for IQ/academic achievement or learning disability. Within the SLE children group, those that were born to mothers who had Anti-Ro/La were significantly more likely to have a learning disability. **Anti-Ro/La antibodies:** 7/15 vs. 7/43
Risk of autoimmune disease in offspring	4370, Strandberg 2006[10]	Cohort study	Mean 60 months duration (range 2-84 months)	12 SSA/SSB positive mothers and their 13 offspring. • Maternal diagnoses: n=6 with SLE, n=5 with Sjogren's syndrome, n=1 with UCTD. 6 SSA/SSB negative mothers and their 6 offspring • Maternal diagnoses: n=2 with aPL, n=1 with Sjogren's, n=2 with MCTD, n=1 with SLE	Exposure to SSA/SSB antibodies during pregnancy	Out of the 12 SSA/SSB positive mothers, 6 women gave birth to 7 children with fetal or neonatal lupus. (4 children born to 3 mothers with Sjogren's, and 3 children born to 3 mothers with SLE diagnosis.) Out of the 6 SSA/SSB negative mothers, all 6 of their offspring were healthy
	4555 Neiman 2000[11]	Retrospective medical record review from the Research Registry for Neonatal Lupus	1981 – 1997	Children with neonatal lupus enrolled in the Research Registry for Neonatal Lupus. cohort included mothers and their children with cutaneous manifestations of NLE (without CHB), in the presence or absence of hepatic or hematologic involvement. Cohort followed up for a mean period of 77 months (range, 1-204 months)	60% of children were treated; 91% of those (54% of all children) were given low to medium potency topical steroids. No children received systemic glucocorticoid therapy	All mothers had documented anti-SSA/Ro, anti-SSB/La, and/or anti-U1RNP autoantibodies: 96% SSA/Ro and 72% SSB/La All children had erythema as part of the rash. In 67%, the lesions were described as annular and in 32% as having an irregular outline. NLE rash resolved in all children. Of 51 with follow-up data,

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Data were obtained from an interview with mothers and through a medical record review n=47 mothers with 57 children with a skin rash in the absence of CHB Mean maternal age: 31 years (range: 17-41) Diagnosis at time of delivery: • Undifferentiated autoimmune syndrome: 23% • Asymptomatic: 28% • Sjogren's syndrome: 15% • SLE: 19% • SLE/Sjogren's: 13% • RA/Sjogren's: 2%		• 73% had rashes resolve without sequelae (57% of these children received treatment). • 27% of children had residual skin abnormalities (10 had telangiectasia; 2 had hyperpigmentation of the affected areas; and 10 had what was described as pitting, scarring, or atrophy after at least 2 years of follow-up). 71% of these children received treatment After an average 77 months of follow-up 4 children had signs of autoimmune disease (7% of children): • 1 developed Hashimoto's thyroiditis at age 7 • 2 developed juvenile RA (at 2 years and 5 years) • 1 developed Raynaud's

75. In men with SLE, what is the impact of having the diagnosis of SLE compared to not having this diagnosis on long-term outcomes in offspring?

No evidence.

76. In men with RA, what is the impact of having the diagnosis of RA compared to not having this diagnosis on long-term outcomes in offspring?

No evidence.

77. In men with non-SLE, non-RA, non-APS (i.e. other) RD, what is the impact of having this diagnosis of RD compared to not having this diagnosis on long-term outcomes in offspring?

No evidence.

78. In men with APS, what is the impact of having the diagnosis of APS compared to not having this diagnosis on long-term outcomes in offspring?

No evidence.

79. In men with positive anti-Ro and/or La antibodies, what is the impact of having these antibodies compared to not having these antibodies on long-term outcomes in offspring?

No evidence.

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4F: No evidence

4F. In women with RD on medication affecting folate metabolism [listed] before pregnancy, what is the impact of taking high-dose folic acid versus not taking high-dose folic acid on pregnancy outcome [listed]?

Population:
- Women with RD on medication [listed] prior to pregnancy
    - MTX
    - Sulfasalazine

Intervention:
- Addition of high-dose folic acid (pre-pregnancy and pregnancy)

Comparator:
- Women with RD on MTX or sulfasalazine before pregnancy not receiving high dose folic acid

Outcomes:
- MBD
- Spontaneous abortion
- Long term offspring outcomes (neurodevelopmental)

RELEVANCE: GS95, GS95A, GS104

5. Pregnancy Management

5A.

5A. In women with positive aPL [variables listed], does treating with certain medications during pregnancy [listed] versus not treating impact the maternal and pregnancy outcomes [listed]?

Population:

- Women with positive aPL (aCL, ab2GPI or positive LAC)
    - Not meeting clinical or laboratory criteria for APS (low positive aCL or ab2GPI with negative LAC, or presence of non-standardized aPLs) RA
    - Not meeting criteria for OB/thrombotic-APS (revised Sapporo criteria)
    - Meeting criteria for OB-APS (revised Sapporo criteria)
    - Meeting criteria for OB-APS (revised Sapporo criteria) and having failed standard heparin + low-dose aspirin (Hep+LDA)
    - Meeting thrombotic APS criteria

Intervention:

- LDA during pregnancy (for women not meeting OB-APS criteria)
- Prophylactic Hep+LDA during pregnancy (for women meeting and not meeting OB-APS criteria)
- Hydroxychloroquine (with or without other treatments) (all groups)
- Prophylactic Hep+LDA with other agent (IVIG, prednisone) during pregnancy (for women meeting OB-APS criteria and failing standard Hep+LDA therapy)
- Full dose Hep+LDA (for thrombotic APS: group 5)

Comparator:

- No treatment during pregnancy (for intervention group A, low-dose aspirin)
- LDA treatment (for intervention group B)
- Prophylactic hep+LDA (for intervention groups D,E)
- No hydroxychloroquine (vs HCQ, Group C)

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth

- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal/neonatal effects, including immunosuppression, organ failure, adverse vaccine reactions in infant (e.g., BCG)
- Long-term offspring effects
- Maternal morbidity (including infection and thrombosis)
- Maternal mortality
- Maternal thrombosis
- Maternal hemorrhage

THIS SECTION FOR TEMPLATE QUESTION 5A PROVIDES EVIDENCE FOR GS44-GS52 (IT SHOULD NOT BE SPLIT UP)

80. In women with positive aPL, with or without APS criteria, does treating with hydroxychloroquine during pregnancy versus not treating impact the maternal and pregnancy outcomes? **RELEVANCE GS44 BUT NO EVIDENCE**

No evidence

81. In women with positive aPL but not meeting clinical or laboratory criteria for APS, does treating with low-dose aspirin during pregnancy versus not treating impact the maternal and pregnancy outcomes? **EVIDENCE FOR GS45**

Summary: One direct observational study[1] addressed this PICO question. The result for Pregnancy Loss favored No LDA treatment, for Preterm Birth slightly favored LDA group, but with high imprecision for both outcomes.

Quality of Evidence across outcomes: Very low.

Outcomes	Author, year	Study type	Population Description	Treatment given to relevant population	Results
Pregnancy loss	2523, Del Ross 2013[1] Direct	Retrospective observational cohort	139 pregnancies of 114 APL positive women not fulfilling criteria for APLAS	**LDA** and **no LDA**	LDA 8/104 (7.7%), No LDA 1/35 (2.9%), OR=2.83 [0.34, 23.50]

Preterm birth	2523, Del Ross 2013[1] Direct	Retrospective observational cohort	139 pregnancies of 114 APL positive women not fulfilling criteria for APLAS	**LDA** and **no LDA**	Preterm birth: LDA 4/96 (4.2%), No LDA 2/34 (5.9%), OR= 0.70 [0.12, 3.98]

82**.** In women with positive aPL **meeting OB-APS criteria**, does treating with LDA during pregnancy versus not treating with LDA impact the maternal and pregnancy outcomes [listed]? **EVIDENCE FOR GS48**

Summary: This PICO question is addressed by one direct RCT[2], and three direct observational[3-5] studies. In a direct RCT the outcome results are mixed, some slightly favoring placebo patients, the others favoring LDA, but the results are highly imprecise due to small sample size. The following outcomes: *pregnancy loss, gestational hypertension, and congenital anomalies* slightly favor placebo over LDA therapy with OR=1.42 (0.27 to 7.34), 1.08 (0.18 to 6.32), and 1.07(0.06 to 18.62) respectively. Preterm birth mean value significantly favors placebo OR=6.03 (0.27 to 135.99), SGA significantly favors the LDA group OR= 0.22 (0.02 to 2.19) but the results are highly imprecise.

Quality of Evidence across outcomes: Low.

Table 1: RCT

LDA compared to no LDA- for pregnant women with aPL

Bibliography: . PICO 5A for pregnant women with aPL treated. [2]

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no LDA- APLA syndrome	**With LDA**		**Risk with no LDA- APLA syndrome**	**Risk difference with LDA**
Pregnancy loss											

40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/20 (15.0%)	4/20 (20.0%)	**OR 1.42** (0.27 to 7.34)	150 per 1,000	**50 more per 1,000** (105 fewer to 414 more)
Preterm birth											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	0/17 (0.0%)	2/16 (12.5%)	**OR 6.03** (0.27 to 135.99)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Gestational HTN											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/17 (17.6%)	3/16 (18.8%)	**OR 1.08** (0.18 to 6.32)	176 per 1,000	**11 more per 1,000** (139 fewer to 399 more)
SGA											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	4/17 (23.5%)	1/16 (6.3%)	**OR 0.22** (0.02 to 2.19)	235 per 1,000	**172 fewer per 1,000** (229 fewer to 167 more)
Congenital anomalies											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	1/17 (5.9%)	1/16 (6.3%)	**OR 1.07** (0.06 to 18.62)	59 per 1,000	**4 more per 1,000** (55 fewer to 479 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide CI crossing significant effect and no-effect lines

83. In women with positive aPL but not meeting clinical or laboratory criteria for APS, does treating with low-dose aspirin and prophylactic heparin during pregnancy versus low dose aspirin alone impact the maternal and pregnancy outcomes? **RELEVANCE GS47 BUT NO EVIDENCE**

No evidence

84. In women with positive aPL but not meeting criteria for OB/thrombotic-APS, does treating with low-dose aspirin during pregnancy versus not treating impact the maternal and pregnancy outcomes?

See evidence for question 82

85. In women with positive aPL but not meeting criteria for OB/thrombotic-APS, does treating with low-dose aspirin and prophylactic heparin during pregnancy versus low dose aspirin alone impact the maternal and pregnancy outcomes?

No evidence

86. In women with positive aPL meeting criteria for OB-APS, does treating with prophylactic Hep+LDA during pregnancy versus not treating impact the maternal and pregnancy outcomes? **EVIDENCE FOR GS48**

Summary: This PICO question is addressed by three direct RCTs[6-8], and five direct observational studies[9-13]. The outcomes provided by direct RCT trials show favorable effect of LMWH+LDA over LDA for pregnancy failures in women who were d-dimer positive, but findings for other outcomes were not statistically different and were imprecise (Table 1). The outcomes across direct observational studies favored LDA+LMWH use, except IUGR, which was similar in both groups (Table 2).

Quality of Evidence across outcomes: Moderate

Table 1: RCTs

LDA+LMWH compared to LDA in APS for pregnant women with aPL treated

Bibliography: . PICO 5A for pregnant women with aPL treated. [3925 Bao 2017; 11556 Farquharson 2002]

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With LDA in APS	**With LDA+LMWH**		**Risk with LDA in APS**	**Risk difference with LDA+LMWH**
Pregnancy failure by D-dimer positivity											
1015 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	155/518 (29.9%)	48/497 (9.7%)	**OR 0.26** (0.18 to 0.37)	299 per 1,000	**199 fewer per 1,000** (228 fewer to 163 fewer)
Pregnancy failure by D-dimer positivity - D-dimer negative											
406 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	32/197 (16.2%)	27/209 (12.9%)	**OR 0.76** (0.44 to 1.33)	162 per 1,000	**34 fewer per 1,000** (84 fewer to 43 more)
Pregnancy failure by D-dimer positivity - D-dimer positive											
609 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	123/321 (38.3%)	21/288 (7.3%)	**OR 0.13** (0.08 to 0.21)	383 per 1,000	**308 fewer per 1,000** (336 fewer to 268 fewer)
Pregnancy loss											

LDA+LMWH compared to LDA in APS for pregnant women with aPL treated

Bibliography: . PICO 5A for pregnant women with aPL treated. [3925 Bao 2017; 11556 Farquharson 2002]

Certainty assessment							Summary of findings				
130 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⊕⊕⊕◯ MODERATE	13/67 (19.4%)	13/63 (20.6%)	**OR 0.86** (0.15 to 4.83)	194 per 1,000	**23 fewer per 1,000** (from 159 fewer to 344 more)
Preterm birth											
130 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⊕⊕⊕◯ MODERATE	5/67 (7.5%)	6/63 (9.5%)	**OR 1.27** (0.35 to 4.66)	75 per 1,000	**18 more per 1,000** (from 47 fewer to 199 more)
SGA											
32 (1 RCT)	not serious	not serious	not serious	very serious [a]	none	⊕⊕◯◯ LOW	3/16 (18.8%)	3/16 (18.8%)	**OR 1.00** (0.17 to 5.90)	188 per 1,000	**0 fewer per 1,000** (150 fewer to 389 more)
Hypertensive Disorder											
32 (1 RCT)	not serious	not serious	not serious	very serious [a]	none	⊕⊕◯◯ LOW	2/16 (12.5%)	0/16 (0.0%)	**OR 0.18** (0.01 to 3.97)	125 per 1,000	**100 fewer per 1,000** (124 fewer to 237 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide CI crossing significant effect and no-effect lines

References: 3925 Bao 2017; 11556 Farquharson; **2394 van Hoorn 2016**

Table 2: Observational studies

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Preterm delivery	2626 Naru 2010[9] Direct	retrospective cohort study		64 women with OB-APS	hep 5000 units + LDA 75 mg daily vs LDA 75 mg daily	Preterm delivery: Hep+LDA 12/35 (34%), LDA 9/29 (31%), OR=1.16 [0.41, 3.32]
	7339 Clark 2007[13] Direct	Retrospective chart review and collected demographic, clinical, and obstetric outcome data on patients whose pregnancies had progressed to at least 27 weeks	5-years	aPL positive women had a history of RPL and were positive for aCL IgG and/or LAC on at least 2 occasions, 6 weeks apart, but negative for anatomic, hormonal, or genetic investigations, and an index pregnancy that progressed to at least 27 weeks' gestation n=87 aPL-positive women Mean age: 33.3 years	Prophylactic anticoagulation therapy was given during pregnancy to 71/87 aPL-positive patients: • Prophylactic doses of low molecular weight heparin (LMWH; 5000 IU once daily or a weight-adjusted equivalent) with low-dose aspirin (LDA, 81 mg/day): 44 • LDA only: 27 women; No treatment: 16 women	Preterm Delivery (<37 weeks) • LDA: 13 (48.1%) • LMWH/LDA: 7 (15.9%)
	3311, Goel 2006[10]	prospective observational cohort direct	Patients were followed until delivery	622 pregnant women with and elevated ACL IgG	Aspirin 80mg versus aspirin + heparin 5000 q12h	Preterm birth: LDA 4/19 (21%) LDA+Heparin 8/32 (25%) OR=0.80 [0.20, 3.13]
SGA	2626 Naru 2010[9] Direct	retrospective cohort study		64 women with OB-APS	hep 5000 units + LDA 75 mg daily vs LDA 75 mg daily	Small for gestational age: Hep+LDA 8/35 (23%), 6/29 (21%), OR=1.14 [0.34, 3.75]
Gestational hypertension	2626 Naru 2010[9]	retrospective cohort study		64 women with OB-APS	hep 5000 units + LDA 75 mg daily vs LDA 75 mg daily	Gestational hypertension: Hep+LDA 10/35 (29%), LDA 9/29 (31%), OR=0.89 [0.30, 2.61]
Neonatal death	2626 Naru 2010[9] Direct	retrospective cohort study		64 women with OB-APS	hep 5000 units + LDA 75 mg daily vs LDA 75 mg daily	Neonatal death: Hep+LDA 3/35 (9%), LDA 6/29 (21%), OR=0.36 [0.08, 1.59]

Pregnancy loss	3311, Goel 2006[10]	prospective observational cohort direct	Patients were followed until delivery	622 pregnant women with and elevated ACL IgG	Aspirin 80mg versus aspirin + heparin 5000 q12h	Pregnancy loss: LDA 26/45 (58%) LDA+Heparin 13/45 (29%), OR= 3.37 [1.40, 8.08]
	7169 Cohn, 2010[12]	Observational Direct	1987-2006	171 women with APS	LDA + Heparin vs. LDA	**LDA** First trimester miscarriage 38/104 (37%) **LDA + Heparin** First trimester miscarriage 11/67 (16%)
Live birth	7169 Cohn, 2010[12]	Observational	1987-2006	171 women with APS	LDA + Heparin vs. LDA	**LDA** 64/104 (62%) live births **LDA + Heparin** 53/67 (79%) live births
IUGR	4583 Brewster, 1999[11] Direct	Observational	1992 - 1997	62 infants born 55 women with OB APS	LDA alone LDA + LMWH	LDA: 6/23 (26%) had IUGR LDA + LMWH: 7/26 (27%) had IUGR

87. In women with positive aPL meeting criteria for OB-APS, does treating with full-dose Hep+LDA during pregnancy versus not treating impact the maternal and pregnancy outcomes?

No evidence

88. In women with positive aPL meeting criteria for OB-APS and having failed standard heparin + low dose aspirin (Hep+LDA), does treating with prophylactic Hep+LDA and IVIG during pregnancy versus not adding IVIG impact the maternal and pregnancy outcomes? **EVIDENCE FOR GS50**

Summary: This PICO question is addressed by one direct RCT[14], one indirect RCT[15], and five direct observational studies[16-20].

In a direct RCT some outcomes were in favor of Hep+LDA, while others were in favor of Hep+LDA+IVIG or had similar effects. Due to small sample size all outcome results have high imprecision. The outcome of preterm birth has a statistically strong association between Hep+LDA+IVIG use [OR=27.86 (1.20 to 646.08)]. Preeclampsia, however, has a less strong association with IVIG use [OR 6.00 (0.46 to 77.75)]. Other outcomes such as IUGR, fetal distress, infant RDS, NICU admission have slightly more favorable effect from Hep+LDA+IVIG, but the results are imprecise [OR=0.33 (0.03 to 4.19); OR=0.12 (0.01 to 2.87); OR=0.38 (0.01 to 10.74); OR=0.21 (0.02 to 2.52)]. Oligohydramnios had similar effect from either treatment [OR=1.40 (0.14 to 13.57)].

The indirect RCT that compared Hep+LDA to IVIG only, had consistent results for some outcomes with the direct RCT.[15] IVIG increased the likelihood of preterm delivery but the rates of preterm delivery were low [OR=2.85 (0.11 to 74.34)], while gestational hypertension and PROM were slightly favorable to IVIG use [OR=0.46(0.08 to 2.63); OR=0.29 (0.01 to 7.47)]. Pregnancy loss had similar results in both treatments [OR=1.07(0.39 to 2.94)]. Due to small sample size all outcome results have high imprecision.

The observational studies compare LDA+LMWH with IVIG+ LDA+LMWH. In the direct observational study[18] the results were slightly favorable towards use of IVIG+ LDA+LMWH: **Pregnancy loss**: Group A 2/20, Group B 3/20, OR= 0.63 [0.09, 4.24]; **Preterm birth** >34 <37: Group A 2/20, Group B 4/20, OR= 0.44 [0.07, 2.76]; **Gestational hypertension**: Group A 0/20, Group B 3/20,OR= 0.12 [0.01, 2.53]; **Stillbirth**: Group A 0/20, Group B 1/20, OR=0.32 [0.01, 8.26]; **PROM**: Group A 2/20, Group B 2/20, OR= 1.00 [0.13, 7.89]; **Antenatal hemorrhage**: Group A 0/20, Group B 1/20, OR= 0.32 [0.01, 8.26]; **SGA**: Group A 2/20, 3/20, OR= 0.63 [0.09, 4.24], but all results are very imprecise. In Deguchi 2017[16] study comparing IVIG+ LDA+LMWH and LDA+LMWH all outcomes results were favorable to LDA+LMWH [**Pregnancy loss**: 4 (7.4%), **Live Birth**: 50 (92.6%), **Median gestational age** (range): 36 (24-41) vs in IVIG+ LDA+LMWH **Pregnancy loss**: 3 (25%); **Live Birth**: 9 (75%); **Median gestational age** (range): 34 (26-39)]. In Ruffatti 2014[19] study **Live births** rate for LMWH+LDA = 81/104 (77.9%) was less favorable than in LDA+Heparin+IVIG 18/21 (85.7%). In Diejomaoh 2002[17] study the outcomes on **spontaneous abortions, preterm birth, and perinatal loss** were better for IVIG group, but the results are very imprecise due to small sample size.

Quality of Evidence across outcomes: Low.

IVIG + LMWH + LDA compared to LMWH + LDA for pregnant women with aPL

Bibliography: PICO 5A for pregnant women with aPL treated. 7486 Branch 2000

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With LMWH + LDA	With IVIG + LMWH + LDA		Risk with LMWH + LDA	Risk difference with IVIG + LMWH + LDA
Preterm delivery											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/9 (33.3%)	7/7 (100.0%)	**OR 27.86** (1.20 to 646.08)	333 per 1,000	**600 more per 1,000** (42 more to 664 more)
Pre-eclampsia											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	1/9 (11.1%)	3/7 (42.9%)	**OR 6.00** (0.46 to 77.75)	111 per 1,000	**317 more per 1,000** (57 fewer to 796 more)
IUGR											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/9 (33.3%)	1/7 (14.3%)	**OR 0.33** (0.03 to 4.19)	333 per 1,000	**192 fewer per 1,000** (319 fewer to 344 more)
Oligohydramnios											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/9 (22.2%)	2/7 (28.6%)	**OR 1.40** (0.14 to 13.57)	222 per 1,000	**63 more per 1,000** (184 fewer to 573 more)

IVIG + LMWH + LDA compared to LMWH + LDA for pregnant women with aPL

Bibliography: PICO 5A for pregnant women with aPL treated. 7486 Branch 2000

Certainty assessment							Summary of findings				
Fetal distress											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/9 (33.3%)	0/7 (0.0%)	**OR 0.12** (0.01 to 2.87)	333 per 1,000	**277 fewer per 1,000** (328 fewer to 256 more)
Infant RDS											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	1/9 (11.1%)	0/7 (0.0%)	**OR 0.38** (0.01 to 10.74)	111 per 1,000	**66 fewer per 1,000** (110 fewer to 462 more)
NICU admission											
16 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	4/9 (44.4%)	1/7 (14.3%)	**OR 0.21** (0.02 to 2.52)	444 per 1,000	**301 fewer per 1,000** (429 fewer to 224 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Wide CI crossing both significant effect and no-effect lines

References: 7486 Branch 2000

Table 2: Observational studies

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	3381 Deguchi 2017[16] Direct	Clinical data were retrospectively collected from medical records	2008-2013	**APS** according to the clinical and laboratory criteria of the updated Sydney classification criteria n=81 pregnancies in 69 women Mean maternal age: 31.4 (SD: 4) years Primary APS: 45 (55.6%)	LDA + Heparin: n=54 LDA + Heparin + IVIG: n=12	LDA + Heparin • Pregnancy loss: 4 (7.4%) ○ All 4 with normal chromosomes LDA + Heparin+IVIG • Pregnancy loss: 3 (25%) ○ 2 with normal chromosome, 1 with abnormal chromosome A multiple logistic regression analysis demonstrated that LDA + heparin therapy decreased the risk of pregnancy loss (OR 0.13, 95%CI 0.03–0.62), and that a history of pregnancy loss despite LDA + heparin therapy increased the risk of pregnancy loss (OR 8.74, 95% CI 1.69–45.2). LDA therapy prior to pregnancy decreased the risk of premature delivery (OR 0.14, 95% CI 0.03–0.69).
	2852 Diejomaoh 2002[17] Direct	Prospective observational		43 patients with APS. 3 subgroups (primary and secondary recurrent spontaneous miscarriage) SLE and history of previous thromboembolic disorder were absent in all patients.	LDA and heparin (5000 I. U 12 hourly) in primary recurrent arm (n=18). LDA, heparin and IVIG in the secondary recurrent spontaneous arm (n=25);	Perinatal loss: IVIG 2/7, no IVIG 0/18, OR= 3.94 [0.18, 87.10]
	2852 Diejomaoh 2002[17] Direct	Prospective observational		43 patients with APS. 3 subgroups (primary and secondary recurrent spontaneous miscarriage) SLE and history of previous thromboembolic disorder were absent in all patients.	LDA and heparin (5000 I. U 12 hourly) in primary recurrent arm (n=18). LDA, heparin and IVIG in the secondary recurrent spontaneous arm (n=25);	Spontaneous abortions: IVIG 0/7, no IVIG 4/18, OR= 0.21 [0.01, 4.54]
	2840 Triolo 2003[15]	RCT		16 patients OB-APS	Compared Hep+LDA to IVIG only	Pregnancy loss: Similar results in both treatments [OR=1.07(0.39 to 2.94)]

Preterm birth	2779, Jeremic 2005[18]	prospective observational study Direct	Perinatal period	40 patients with aPL and APAS	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	Preterm birth >34 <37: Group A 2/20, Group B 4/20, OR= 0.44 [0.07, 2.76]
	2852 Diejomaoh 2002[17] Direct	Prospective observational		43 patients with APS. 3 subgroups (primary and secondary recurrent spontaneous miscarriage) SLE and history of previous thromboembolic disorder were absent in all patients.	LDA and heparin (5000 I. U 12 hourly) in primary recurrent arm (n=18). LDA, heparin and IVIG in the secondary recurrent spontaneous arm (n=25);	Preterm birth: IVIG 0/7, no IVIG 1/18, OR= 0.78 [0.03, 21.36]
	2840 Triolo 2003[15]	RCT		16 patients OB-APS	Compared Hep+LDA to IVIG only	Preterm delivery: Stronger association with IVIG use [OR=2.85 (0.11 to 74.34)]
Stillbirth	2779, Jeremic 2005[18]	prospective observational study Direct	Perinatal period	40 patients with aPL and APAS	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	Stillbirth: Group A 0/20, Group B 1/ 20, OR= 0.32 [0.01, 8.26]
Live Birth	2458 Ruffatti, 2014[19] Direct	Observational		156 women with APS with 196 pregnancies	LDA Prophylactic Heparin w/ LDA Therapeutic Heparin w/ LDA LDA + Heparin + IVIG and/or prednisone	**Live births** LDA = 11/16 (68.8%) Prophylactic Heparin w/ LDA = 81/104 (77.9%) Therapeutic Heparin w/ LDA = 39/55 (70.9%) LDA + Heparin + IVIG and/or prednisone = 18/21 (85.7%)
	3381 Deguchi 2017[16] Direct	Clinical data were retrospectively collected from medical records	2008-2013	**APS** according to the clinical and laboratory criteria of the updated Sydney classification criteria n=81 pregnancies in 69 women	Hep/LDA/IVIG/pred vs. Hep/LDA LDA + Heparin: n=54 LDA + Heparin + IVIG: n=12	LDA + Heparin • Live Birth: 50 (92.6%) LDA + Heparin+IVIG • Live Birth: 9 (75%)

				Mean maternal age: 31.4 (SD: 4) years Primary APS: 45 (55.6%)		
PROM	2779, Jeremic 2005[18] Direct	prospective observational study	Perinatal period	40 patients with aPL and APAS	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	PROM: Group A 2/20, Group B 2/20, OR= 1.00 [0.13, 7.89]
	2840 Triolo 2003[15]	RCT		16 patients OB-APS	Compared Hep+LDA to IVIG only	PROM were slightly favorable to IVIG use OR=0.29 (0.01 to 7.47)
Antenatal hemorrhage	2779, Jeremic 2005[18]	prospective observational study Direct	Perinatal period	40 patients with aPL and APAS	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	Antenatal hemorrhage: Group A 0/ 20, Group B 1/20, OR= 0.32 [0.01, 8.26]
SGA	2779, Jeremic 2005[18]	prospective observational study Direct	Perinatal period	40 patients with aPL and APAS	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	SGA: Group A 2/20, 3/20, OR= 0.63 [0.09, 4.24]
	6674 Ye 2017[20] Direct	Prospective cohort study	Perinatal period	atypical and typical APS with h/o recurrent spont abortion, 267 pts	Group A: prednisone (10 mg/d) + HCQ (0.2 g bid) + LDA (75 mg/d) + LMWH vs Group B: LDA + LMWH	Small for gestational age: Group A 8/126, Group B 20/141, OR=0.41 [0.17, 0.97]
Median gestational age	3381 Deguchi 2017[16] Direct	Clinical data were retrospectively collected from medical records	2008-2013	**APS** according to the clinical and laboratory criteria of the updated Sydney classification criteria n=81 pregnancies in 69 women Mean maternal age: 31.4 (SD: 4) years Primary APS: 45 (55.6%)	Hep/LDA/IVIG/pred vs. Hep/LDA LDA + Heparin: n=54 LDA + Heparin + IVIG: n=12	LDA + Heparin • Median gestational age (range): 36 (24-41) LDA + Heparin+IVIG • Median gestational age (range): 34 (26-39)

Hypertension/ preeclampsia	2779, Jeremic 2005[18]	prospective observational study Direct	Perinatal period	40 patients with aPL	Group A: IVIG+LMWH+LDA vs Group B: LMWH+LDA	Gestational hypertension: Group A 0/20, Group B 3/20,OR= 0.12 [0.01, 2.53]
	2840 Triolo 2003[15]	RCT		16 patients OB-APS	Compared Hep+LDA to IVIG only	Gestational hypertension: OR=0.46 (0.08 to 2.63)

89. In women with positive aPL meeting criteria for OB-APS and having failed standard heparin + low dose aspirin (Hep+LDA), does treating with prophylactic Hep+LDA and prednisone during pregnancy versus not adding prednisone impact the maternal and pregnancy outcomes? *This refers to positive aPL and pregnancy complications* **EVIDENCE FOR GS51**

Summary: This PICO question is addressed by three direct observational studies[16,19,21] and one indirect observational study[20].

In Ruffatti, 2014[19] study the l**ive birth** rate in LDA group was 68.8% and in LDA + Heparin +IVIG was 75%. In Deguchi 2017 study,[16] prednisolone was identified as a risk factor for hypertensive disorders (OR 6.93, 95%CI 1.30–37.0), thrombocytopenia (OR= 5.5, 95%CI 1.44–21.0); had a weak positive association with preterm delivery (OR= 1.31 (0.38–4.52), and weak negative association with pregnancy loss (OR= 0.86 (0.27–2.73).

The Ye 2017[20] study compared Prednisone + HCQ+LDA+LMWH with LDA+LMWH. The outcomes favored Prednisone + HCQ+LDA+LMWH for **Pregnancy loss**: 14/126 vs 32/141 (OR=0.43 [0.22, 0.84]) and **Small for gestational age**: 8/126, vs 20/141 (OR=0.41 [0.17, 0.97]). **Preterm delivery** was similar in each group: 18/126 vs 20/141, OR=1.01 [0.51, 2.01].

Quality of Evidence across outcomes: Low.

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	6674 Ye 2017[20]	Prospective cohort study	Perinatal period	atypical and typical APS with h/o recurrent spont abortion, 267 pts	Group A: **prednisone** (10 mg/d) + HCQ (0.2 g bid) + LDA (75 mg/d) + LMWH vs Group B: LDA + LMWH	Pregnancy loss: Group A 14/126, Group B 32/141, OR=0.43 [0.22, 0.84]
Preterm delivery	6674 Ye 2017 Direct[20]	Prospective cohort study	Perinatal period	atypical and typical APS with h/o recurrent spont abortion, 267 pts	Group A: **prednisone** (10 mg/d) + HCQ (0.2 g bid) + LDA (75 mg/d) + LMWH vs Group B: LDA + LMWH	Preterm delivery: Group A 18/126, Group B 20/141, OR=1.01 [0.51, 2.01]
Live births	2458 Ruffatti, 2014[19]	Observational		156 women with APS with 196 pregnancies	LDA Prophylactic Heparin w/ LDA Therapeutic Heparin w/ LDA LDA + Heparin + IVIG and/or prednisone	**Live births** LDA = 11/16 (68.8%) Prophylactic Heparin w/ LDA = 81/104 (77.9%) Therapeutic Heparin w/ LDA = 39/55 (70.9%) LDA + Heparin + IVIG and/or prednisone = 18/21 (85.7%)
	3381 Deguchi 2017[16] Direct	Clinical data were retrospectively collected from medical records	2008-2013	**APS** according to the clinical and laboratory criteria of the updated Sydney classification criteria n=81 pregnancies in 69 women Mean maternal age: 31.4 (SD: 4) years Primary APS: 45 (55.6%)	LDA + Heparin: n=54 LDA + Heparin + IVIG: n=12 Prednisolone was taken by patients across different treatment regimens	• Prednisolone was identified as a risk factor for hypertensive disorders (OR 6.93, 95%CI 1.30–37.0), thrombocytopenia ((OR= 5.5, 95%CI 1.44–21.0); and no association with pregnancy loss (OR= 0.86 (0.27–2.73)

90. In women with thrombotic APS, does treating with full dose Hep+LDA during pregnancy versus not treating impact the maternal and pregnancy outcomes?

No evidence

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5B.

5B. In women with RD who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy [listed] versus having active disease prior to pregnancy on maternal and pregnancy outcomes [listed]?

Population: Women with RD who are considering pregnancy

Interventions:
Quiescent or stable low activity disease for one-three months
Quiescent or stable low activity disease for six months
Scleroderma: Stable for 2 years

Comparator (varies with outcome):
Similar patients with active disease

Outcomes:
Pregnancy loss: spontaneous abortion, stillbirth
MBD
Gestational hypertensive disease including preeclampsia
Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
Induced labor
Premature rupture of membranes
Small for gestational age infants (SGA)
Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
Long-term offspring effects
Flare of RD
Damage from RD
Maternal morbidity (infection, thrombosis)
Maternal mortality

91. In women with SLE, vasculitis, or myositis who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy for one-three months versus having active disease prior to pregnancy on maternal and pregnancy outcomes? **EVIDENCE FOR GS53**

Summary: This PICO was addressed by 10 observational studies with direct evidence[1-10]. All of these observational studies assessed pregnancy and maternal outcomes in patients with SLE with active versus inactive disease at the time of conception. One study[1] prospectively followed 24 SLE pregnancies; another followed 26 patients observationally[2]; another followed 60 patients prospectively[3]; another followed 36 SLE pregnancies retrospectively[8]; another prospectively followed 40 SLE pregnancies[9]. In another study[4] all singleton births from the Medical Birth Registry of Norway from 2006-2015 among mothers with SLE were included (n=180). Another larger observational study[5], reviewed outcomes retrospectively of 140 pregnancies in women with SLE; another retrospective series[7] reviewed 213 pregnancies among patients with SLE. Another study[6] retrospectively analyzed 55 pregnancies in patients with pre-existing lupus nephritis. In a retrospective cohort study[10] 147 pregnancies among patients with SLE were reviewed. These patients were followed for organ-specific activity during pregnancy (hematologic, nephritis, skin disease, arthritis, and serositis).

Evidence was supplemented by 11 additional observational studies with indirect evidence[3,11-20]. One study[11] included patients with both SLE and RA. In this retrospective cross-sectional study, 210 patients were followed for 2 years; pregnancy outcomes were reported (but not stratified by disease activity). One study[19] reported outcomes of 22 pregnancies in 14 women with ANCA-associated vasculitis. In this observational study, pre-eclampsia complicated 2 pregnancies; 1 newborn was born with a cleft palate; 8 women experienced relapse of their disease at a mean of 21 months after conception. All other studies (9 in total) reported outcomes of pregnancies among patients with SLE (not stratified by disease activity at conception).

Quality of evidence across outcomes: Very low

Active SLE v non-active SLE during pregnancy (disease activity assessed either prior to conception or in first trimester) impact on pregnancy and maternal outcomes

Bibliography:

PICO 5b impact of disease activity levels on pregnancy outcome/RD

Bibliography: 11742 Tozman 1980; 2316 Kothari 2016; 3343 Carmona 1999; 3377 Skorpen 2017; 3384 Phansenee 2017; 3706 Rahman 205; 3866 Bobrie 1987; 3890 Jungers 1982; 7570 Gaballa 2012

Certainty assessment							Summary of findings		
№ of participants	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty	Study event rates (%)		Anticipated absolute effects

Active SLE v non-active SLE during pregnancy (disease activity assessed either prior to conception or in first trimester) impact on pregnancy and maternal outcomes

Bibliography:

PICO 5b impact of disease activity levels on pregnancy outcome/RD

Bibliography: 11742 Tozman 1980; 2316 Kothari 2016; 3343 Carmona 1999; 3377 Skorpen 2017; 3384 Phansenee 2017; 3706 Rahman 205; 3866 Bobrie 1987; 3890 Jungers 1982; 7570 Gaballa 2012

Certainty assessment							Summary of findings				
(studies) Follow-up						**of evidence**	**Non-active SLE during pregnancy**	**Active SLE during pregnancy**	**Relative effect (95% CI)**	**Risk with placebo**	**Risk difference with Active SLE v non-active SLE during pregnancy (either noted at onset or first trimester) for pregnancy and maternal outcomes**
Fetal Growth Restriction											
180 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	22/121 (18.2%)	19/59 (32.2%)	**OR 2.14** (1.04 to 4.40)	182 per 1,000	140 more per 1,000 (6 more to 313 more)
Low Birth Weight											
140 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	42/94 (44.7%)	31/46 (67.4%)	**OR 2.56** (1.22 to 5.35)	447 per 1,000	227 more per 1,000 (50 more to 365 more)

Active SLE v non-active SLE during pregnancy (disease activity assessed either prior to conception or in first trimester) impact on pregnancy and maternal outcomes

Bibliography:

PICO 5b impact of disease activity levels on pregnancy outcome/RD

Bibliography: 11742 Tozman 1980; 2316 Kothari 2016; 3343 Carmona 1999; 3377 Skorpen 2017; 3384 Phansenee 2017; 3706 Rahman 205; 3866 Bobrie 1987; 3890 Jungers 1982; 7570 Gaballa 2012

Certainty assessment							Summary of findings				
Preterm Birth											
431 (6 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	63/255 (24.7%)	58/176 (33.0%)	**OR 2.11** (1.32 to 3.37)	247 per 1,000	162 more per 1,000 (55 more to 278 more)
Fetal loss											
314 (6 observational studies)	serious [a]	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	24/185 (13.0%)	28/129 (21.7%)	**OR 1.74** (0.87 to 3.48)	130 per 1,000	76 more per 1,000 (15 fewer to 212 more)
Preeclampsia											
312 (3 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	17/190 (8.9%)	24/122 (19.7%)	**OR 2.89** (1.45 to 5.76)	89 per 1,000	132 more per 1,000 (35 more to 272 more)
Flare											

Active SLE v non-active SLE during pregnancy (disease activity assessed either prior to conception or in first trimester) impact on pregnancy and maternal outcomes

Bibliography:

PICO 5b impact of disease activity levels on pregnancy outcome/RD

Bibliography: 11742 Tozman 1980; 2316 Kothari 2016; 3343 Carmona 1999; 3377 Skorpen 2017; 3384 Phansenee 2017; 3706 Rahman 205; 3866 Bobrie 1987; 3890 Jungers 1982; 7570 Gaballa 2012

Certainty assessment							Summary of findings				
265 (4 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	35/157 (22.3%)	55/108 (50.9%)	**OR 3.40** (1.92 to 6.03)	223 per 1,000	271 more per 1,000 (132 more to 411 more)
Maternal death											
55 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	0/36 (0.0%)	2/19 (10.5%)	**OR 10.43** (0.47 to 229.05)	0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
PROM											
40 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	2/27 (7.4%)	0/13 (0.0%)	**OR 0.38** (0.02 to 8.45)	74 per 1,000	45 fewer per 1,000 (72 fewer to 329 more)
Pregnancy induced HTN											

Active SLE v non-active SLE during pregnancy (disease activity assessed either prior to conception or in first trimester) impact on pregnancy and maternal outcomes

Bibliography:

PICO 5b impact of disease activity levels on pregnancy outcome/RD

Bibliography: 11742 Tozman 1980; 2316 Kothari 2016; 3343 Carmona 1999; 3377 Skorpen 2017; 3384 Phansenee 2017; 3706 Rahman 205; 3866 Bobrie 1987; 3890 Jungers 1982; 7570 Gaballa 2012

Certainty assessment							Summary of findings				
40 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	5/27 (18.5%)	6/13 (46.2%)	**OR 3.77** (0.88 to 16.24)	185 per 1,000	276 more per 1,000 (19 fewer to 602 more)
MBD											
24 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	1/11 (9.1%)	0/13 (0.0%)	**OR 0.26** (0.01 to 7.03)	91 per 1,000	66 fewer per 1,000 (90 fewer to 322 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

b. wide CI, crosses 1; small sample size

Active disease v inactive disease 6 mo prior to conception, impact on risk of organ-system specific flare

Bibliography: Tedeschi SK, Massarotti E, Guan H, Fine A, Bermas BL, Costenbader KH. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. Lupus. 2015;24(12):1283-1292.

PICO 5b impact of having quiescent/low activity disease prior to pregnancy versus having active disease prior to pregnancy on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no active dz	**With active dz 6 mo prior**		**Risk with no active dz**	**Risk difference with active dz 6 mo prior**
Hematologic Activity											
147 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	11/130 (8.5%)	12/17 (70.6%)	**OR 25.96** (7.72 to 87.28)	85 per 1,000	621 more per 1,000 (332 more to 805 more)
Nephritis											
147 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	8/138 (5.8%)	6/9 (66.7%)	**OR 32.50** (6.84 to 154.51)	58 per 1,000	609 more per 1,000 (238 more to 847 more)
Skin Disease											

Active disease v inactive disease 6 mo prior to conception, impact on risk of organ-system specific flare

Bibliography: Tedeschi SK, Massarotti E, Guan H, Fine A, Bermas BL, Costenbader KH. Specific systemic lupus erythematosus disease manifestations in the six months prior to conception are associated with similar disease manifestations during pregnancy. Lupus. 2015;24(12):1283-1292.

PICO 5b impact of having quiescent/low activity disease prior to pregnancy versus having active disease prior to pregnancy on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
147 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	6/132 (4.5%)	6/15 (40.0%)	**OR 14.00** (3.75 to 52.32)	45 per 1,000	355 more per 1,000 (106 more to 668 more)
Arthritis											
147 (1 observational study)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	5/134 (3.7%)	3/13 (23.1%)	**OR 7.74** (1.61 to 37.18)	37 per 1,000	193 more per 1,000 (21 more to 553 more)

Explanations

a. Retrospective observational study

Additional studies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy Loss	Gupta, 2010[11]	Observational; retrospective cross-sectional	2 years	210 female patients with SLE and RA	Various treatments were given. Adverse outcomes = complicated live birth and any form of pregnancy loss	424 pregnancies in SLE patients (303 before disease onset and 151 after) and 590 pregnancies in RA patients (544 before and 46 after onset of disease). Normal live births, pregnancy loss, complicated live birth (IUGR, low birth weight, preterm labor).

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Included a sub-analysis to evaluate effect of Cytoxan on menstrual cycles in patients with SLE. 60 SLE pts had received Cytoxan.	PICO question is indirectly addressed, but the paper does report reproductive outcomes between patients before disease onset and after disease onset: Among SLE patients before disease onset, 221 (73%) had normal live births, 25 (8%) had complicated but live births, and 57 (19%) had pregnancy loss. Among RA patients before disease onset, 439 (81%) had normal live births, 29 (5%) had complicated but live births, and 76 (14%) had pregnancy loss. Among SLE patients after disease onset, 27 (22%) had normal live births, 30 (25%) had complicated but live births, and 64 (53%) had pregnancy loss. Among RA patients after disease onset, 32 (70%) had normal live births, 3 (7%) had complicated but live births, and 11 (24%) had pregnancy loss.
Pregnancy loss	Mintz 1986[14]	Observational prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients Control group: 123 pregnancies in 124 healthy women seen in the same High Risk Clinic (but were not high-risk patients; were house physicians or	Various	10 pregnancies occurred when SLE was active. 92 pregnancies occurred when SLE was inactive, but 55 (59.7%) of pregnancies were complicated by maternal flare either during pregnancy, postpartum, or postabortion. Over ½ of these flares began in 1st trimester and 20% during puerperium. <u>Pregnancy outcomes:</u> Among control pregnancies (n=123) -7 abortions (5.7%) -11 premature (8.9%) -105 term births (78%) Among all SLE pregnancies (n=102) -17 abortions (16%), p<0.009 compared to control -50 premature (49%), p<0.0001 -35 term births (34%), p<0.0001

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				wives of physicians)		Among active SLE pregnancies (at time of conception) (n=51) -7 abortions (14%), p<0.05 compared to control -30 premature (59%), p<0.0001 -14 term births (27%), p<0.001 Among inactive SLE pregnancies (at time of conception) (n=51) -10 abortions (20%), p<0.01 compared to control -20 premature (39%), p<0.001 -21 term births (41%), p<0.0001 Z test for modified proportions used for statistical analysis. Spontaneous abortions occurred in 16% of pregnancies with no difference between mothers with active or inactive disease. 5 stillbirths and one neonatal death also occurred. Note: Low numbers in some of the outcomes and predictor variables may have prevented comparisons
Pregnancy loss	Lockshin 1989[12]	Observational prospective study	Unclear. It is mentioned that they tracked 58% of the patients in followup from 6 months to 4 years postpartum, and that the remaining women were followed for up to 2 months postpartum	80 pregnancies among 80 pregnant women with SLE	Various. Women who used prednisone (n=53) were also separately analyzed	For women who had active disease, there were 5 deaths/21 pregnancies For women with inactive disease, there were 14 deaths/51 pregnancies For patients who were not treated with steroids and who had active disease: 3 fetal deaths/11 pregnancies For patients who were not treated with steroids and who had inactive disease: 12 fetal deaths/42 pregnancies Fetal death was therefore not related to disease activity among total group and among women who were not treated with steroids (NS)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						Note: “the frequencies of abnormalities in the 80 pregnancies was low, even when excluding prednisone-treated patients”; but specific fetal abnormalities were not addressed
Pregnancy loss	Carmona, 1999[3]	Prospective cohort study	11 years	46 SLE patients in Spain with 60 pregnancies Inactive disease in 56 pregnancies and active disease in 4 pregnancies	Inactive disease	Outcomes: 1. Pregnancy loss: Three women miscarried during the first trimester (5%of pregnancies). All of them had inactive disease at conception. 2. Neonatal birthweight: No differences found between patients with active disease at conception versus inactive disease (2363 +/- 900 versus 2842 +/-888 grams in inactive disease). Other outcomes not discussed in relation to disease activity
Pregnancy loss	Ku, 2016[15]	Retrospective cohort study	10 years	109 pregnancies from 83 SLE patients; assessed Disease activity at time of conception (SLEDAI-2K)	Various	Outcomes: 1. Pregnancy loss: Mean SLEDAI-2K, SD: 14.9 +/- 7.8 in fetal loss pregnancies versus 8.1 +/- 5.5 in live births, p <0.0001, OR 0.002) 2. SLE onset: Mean SLEDAI-2K, SD: 15.4±7.4 in new onset SLE versus 8.4±5.9 in pre-existing SLE; p <0.001
Pregnancy loss	Mankee, 2015[18]	Observational, from Hopkins Lupus Cohort	Pregnancy	202 pregnancies from 175 different women after excluding twin pregnancies and pregnancies for which did not have a first trimester assessment of lupus	Not specified	Pregnancy loss rates by characteristics of the patients: - 22/202 (11%) pregnancy loss - LAC+ first trimester 6/16 (38%) loss, LAC- first trimester 16/186 (9%) loss (p= 0.0035) - Low complement first trimester 13/83 (16%) loss, normal complement first trimester 8/118 (7%) loss (p=0.049) - Mean prednisone dose during first trimester 10+ 9/55 (16%) loss, <10 12/146 (8%) loss (p=0.093) PGA > 2 during pregnancy 6/21 (29%) loss, <=2 15/180 (8%) loss (p=0.0046)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				anticoagulant; determined the percentage of women who had a pregnancy loss in groups defined by potential risk factors		
Pregnancy loss	Whitelaw, 2008[20]	Retrospective observational study	Pregnancy; data available for most patients in 6 mo prior to conception	47 pregnancies in 31 patients, South Africa	"majority had inactive disease as a result of our policy of planned pregnancy and use of antimalarials"	36 (77%) live births, 8 SABs, 2 TABs, 1 still birth.
Pregnancy loss	Le Thi Huong 1994[13]	Observational prospective study	1987-1992, France	117 cases of SLE and pregnancy	Various treatments	Of 117 pregnancies, 103 were analyzed. Pregnancy outcome: 28 full-term births, 48 premature births, 18 fetal losses (13 early, 2 late, 3 stillbirth), 5 therapeutic abortions, 4 elective abortions. Lupus was active at pregnancy onset in 28 patients. 20 patients were taking prednisone ranging from 5-50 mg/d (mean 25+/- 15 mg/g—I think "g" in denominator is a typo and meant to be /day). Disease activity was moderate except in 2 cases with renal involvement that led to spontaneous abortion and fetal loss. Fetal loss was correlated with history of proteinuria and absence of SSA+, not with SLE activity at pregnancy onset Note: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables.
Pregnancy loss	Mokbel, 2013[17]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies);	Remission (excluded 5 patients with active disease)	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				35% hypertensive, 43.2% with nephritis		
Pregnancy loss	Hussein Aly, 2016[16]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	Various	Fetal death: 7 (8%) Spontaneous abortion: 9 (10%)
Pregnancy complication (pre-eclampsia, IUGR)	Whitelaw, 2008[20]	Retrospective observational study	Pregnancy; data available for most patients in 6 mo prior to conception	47 pregnancies in 31 patients, South Africa	"majority had inactive disease as a result of our policy of planned pregnancy and use of antimalarials"	12/47 (26%) developed preeclampsia of which one experienced intrauterine death. 14 (39%) of live births were premature, 5 (14%) experienced IUGR
Pregnancy complication (IUGR, low birth weight, preterm labor)	Gupta, 2010[11]	Observational; retrospective cross-sectional	2 years	210 female patients with SLE and RA	Various treatments were given. Adverse outcomes = complicated live birth and any form of pregnancy loss Included a sub-analysis to evaluate effect of Cytoxan on menstrual cycles in patients with SLE. 60 SLE pts had received Cytoxan.	424 pregnancies in SLE patients (303 before disease onset and 151 after) and 590 pregnancies in RA patients (544 before and 46 after onset of disease). Normal live births, pregnancy loss, complicated live birth (IUGR, low birth weight, preterm labor). PICO question is indirectly addressed, but the paper does report reproductive outcomes between patients before disease onset and after disease onset: Among SLE patients before disease onset, 221 (73%) had normal live births, 25 (8%) had complicated but live births, and 57 (19%) had pregnancy loss. Among RA patients before disease onset, 439 (81%) had normal live births, 29 (5%) had complicated but live births, and 76 (14%) had pregnancy loss. Among SLE patients after disease onset, 27 (22%) had normal live births, 30 (25%) had complicated but live births, and 64 (53%) had pregnancy loss. Among RA patients after disease onset, 32 (70%) had normal live births, 3 (7%) had complicated but live births, and 11 (24%) had pregnancy loss.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy complication (pre-term birth)	Le Thi Huong 1994[13]	Observational prospective study	1987-1992, France	117 cases of SLE and pregnancy	Various treatments	Of 117 pregnancies, 103 were analyzed. Pregnancy outcome: 28 full-term births, 48 premature births, 18 fetal losses (13 early, 2 late, 3 stillbirth), 5 therapeutic abortions, 4 elective abortions. Prematurity was related to history of fetal loss**,** active SLE at pregnancy onset (n=16, 33%)**,** hypertension, and prednisone doses of 20 mg qd or greater during pregnancy IUGR correlated with pregnancy of short duration, low C3/4, hypertension, and absence of SSA+ 3 of 22 newborns whose mothers had SSA+ developed neonatal lupus: 2 with cutaneous and 1 with complete AV block Note: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables.
Pregnancy complication (preterm birth, SGA)	Mintz 1986[14]	Observational prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients Control group: 123 pregnancies in 124 healthy women seen in the same High Risk Clinic (but were not high-risk patients; were house physicians or wives of physicians)	Various	10 pregnancies occurred when SLE was active. 92 pregnancies occurred when SLE was inactive, but 55 (59.7%) of pregnancies were complicated by maternal flare either during pregnancy, postpartum, or postabortion. Over ½ of these flares began in 1st trimester and 20% during puerperium. <u>Pregnancy outcomes:</u> Among control pregnancies (n=123) -7 abortions (5.7%) -11 premature (8.9%) -105 term births (78%) Among all SLE pregnancies (n=102) -17 abortions (16%), p<0.009 compared to control -50 premature (49%), p<0.0001 -35 term births (34%), p<0.0001 Among active SLE pregnancies (at time of conception) (n=51) -7 abortions (14%), p<0.05 compared to control

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						-30 premature (59%), p<0.0001 -14 term births (27%), p<0.001 Among inactive SLE pregnancies (at time of conception) (n=51) -10 abortions (20%), p<0.01 compared to control -20 premature (39%), p<0.001 -21 term births (41%), p<0.0001 Z test for modified proportions used for statistical analysis. --- 49% premature newborns in the entire group, and 59% among mothers with active SLE 23% of newborns were small for gestational age in the entire group, which increased to 65% (n=13) in mothers with active SLE versus 35% in the inactive SLE group (n=7). Among controls, 113 of 118 newborns were adequate weight for gestational age (AGA). Among SLE, 66 of 86 newborns were AGA (77%). P<0.0001 compared to control. Among controls, 5 of the 118 newborns were small for gestational age (SGA). Among SLE, 20 of 68 newborns were SGA. P<0.0001. Spontaneous abortions occurred in 16% of pregnancies with no difference between mothers with active or inactive disease. 5 stillbirths and one neonatal death also occurred. Note: Low numbers in some of the outcomes and predictor variables may have prevented comparisons
Pregnancy complication(preeclampsia, preterm birth)	Hussein Aly, 2016[16]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	Various	Preeclampsia: 12 (13%) Preterm birth: 12 (13%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy complication (preterm birth, preeclampsia)	Tuin, 2012[19]	Observational	Pregnancy, median followup after the last conception was 98 months	22 pregnancies in 14 women with AAV; median age at dx = 25 years, ENT involvement in 71%, renal involvement in 50%. All women in remission at conception.	None, CS, CsA, AZA, cotrimazole	Median gestational age = 39+4 weeks, including 2 preterm deliveries; median birthweight 3400 gm; hypothyroidism occurred in 1 newborn; cleft palate in 1 newborn of a twin pregnancy; pre-eclampsia in 2 pregnancies; c/s in 2 pregnancies
Pregnancy complication (preeclampsia, preterm birth)	Mokbel, 2013[17]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis	Remission (excluded 5 patients with active disease)	Preeclampsia: 8/37 (19.4%) Preterm birth: 12/37 (32.4%) PROM: 9/37 (24%)
Disease flare	Tuin, 2012[19]	Observational	Pregnancy, median followup after the last conception was 98 months	22 pregnancies in 14 women with AAV; median age at dx = 25 years, ENT involvement in 71%, renal involvement in 50%. All women in remission at conception.	None, CS, CsA, AZA, cotrimazole	8 women experiences relapse mean 21 months (range 7-62 months) after conception—1 during pregnancy, 7 after delivery
SLE flare	Hussein Aly, 2016[16]	Prospective	October 2010 to January 2015, Cairo	84 pregnant SLE patients	Various	Antenatal SLE flare: 40 (44%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		observational	University Hospitals	(91 pregnancies)		
SLE flare	Mokbel, 2013[17]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis	Remission (excluded 5 patients with active disease)	Flare: 21/32 (65%)
SLE flare	Whitelaw, 2008[20]	Retrospective observational study	Pregnancy; data available for most patients in 6 mo prior to conception	47 pregnancies in 31 patients, South Africa	"majority had inactive disease as a result of our policy of planned pregnancy and use of antimalarials"	6/47 (13%) had flares all mild
SLE flare	Le Thi Huong 1994[13]	Observational prospective study	1987-1992, France	117 cases of SLE and pregnancy	Various treatments	Of 117 pregnancies, 103 were analyzed. 2 patients died (both had severe nephrotic syndrome, used AZA, and died from infection) Lupus was active at pregnancy onset in 28 patients. 20 patients were taking prednisone ranging from 5-50 mg/d (mean 25+/- 15 mg/g—I think "g" in denominator is a typo and meant to be /day). Disease activity was moderate except in 2 cases with renal involvement that led to spontaneous abortion and fetal loss. Of 75 patients with inactive SLE at conception, 27 flared during pregnancy and 7 postpartum. 6 pregnancies were c/b hypertension (3 with associated proteinuria). Of 48 patients with inactive SLE both at onset and during course of pregnancy, 7 relapsed in postpartum period. Note: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables.

92. In women with SLE, vasculitis, or myositis who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy for six months versus having active disease prior to pregnancy on maternal and pregnancy outcomes?

See above; studies generally did not specify inactive disease for 1-3 months versus 6 months. **GS53**

93. In women with inflammatory arthritis who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy for one-three months versus having active disease prior to pregnancy on maternal and pregnancy outcomes?
No evidence

94. In women with inflammatory arthritis who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy for six months versus having active disease prior to pregnancy on maternal and pregnancy outcomes?
No evidence

95. In women with scleroderma who are considering pregnancy, what is the impact of having quiescent / low activity disease prior to pregnancy for 2 years versus having active disease prior to pregnancy on maternal and pregnancy outcomes?
No evidence

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5C.

5C. In women with RD with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy [listed] versus no immunosuppressive therapy on maternal and pregnancy outcomes?

Population: Women with RD that is currently active and that would require immunosuppressive therapy in a non-pregnant state including those with …

- Active SLE without nephritis
- SLE nephritis
- Myositis
- Scleroderma
- Inflammatory arthritis (RA, PsA, AS)

Intervention: immunosuppressive therapy (such as sDMARD or bDMARD) compatible with pregnancy (as determined by the analysis in the medication section)

Comparator:

- No treatment for the active RD
- Prednisone in addition to compatible DMARD for the active RD
- Prednisone alone for the active RD

Outcomes:
Pregnancy loss: spontaneous abortion, stillbirth
MBD
Gestational hypertensive disease including preeclampsia
Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
Induced labor
Premature rupture of membranes
Small for gestational age infants (SGA)
Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
Long-term offspring effects
Flare of RD
Damage from RD
Maternal morbidity (infection, thrombosis)
Maternal mortality

96. In women with active SLE without nephritis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy on maternal and pregnancy outcomes? **EVIDENCE FOR GS54**

Only one study directly addressed compared long-term offspring outcomes in 47 SLE pregnancies exposed to azathioprine vs. 12 pregnancies not exposed to azathioprine[1]. Use of special education services in offspring < age 2 was increased with azathioprine exposure during pregnancy (OR 5.25) as well as use of special education services in offspring ≥ age 2 (OR 6.62). Use of speech therapy services ≥ age 2 was also increased with pregnancy exposure to azathioprine (OR 7.2). All other offspring outcomes (hearing impairment, gross and fine motor deficits, speech delay, ADHD) were not significantly increased (CI included 1).

In terms of congenital malformations, one study directly addressed exposure to HCQ during the first trimester vs. no immunosuppression in pregnant patients with SLE. No increase in was seen in congenital malformation (CI includes 1)[2].

For pregnancy loss, one study directly addressed exposure to HCQ during the first trimester vs. no immunosuppression in pregnant patients with SLE. No increase in was seen in fetal death (CI includes 1)[2]. An indirect study of pregnancies exposed to HCQ vs no pregnancy exposure showed similar rates of stillbirth[3]. Other indirect evidence includes one study of severe SLE with increased odds of fetal loss with exposure to azathioprine vs. no treatment (OR 3.2) as well as increased odds of fetal loss with cyclophosphamide exposure vs. no cyclophosphamide (OR 2.9)[4].

For preterm birth, one study directly addressed exposure to HCQ during the first trimester vs. no immunosuppression in pregnant patients with SLE[2]. No increase was seen in preterm birth (CI includes 1). Indirect evidence from two other studies (one case-control[5] and one observational[3]) showed similar rates of preterm birth with exposure to HCQ during pregnancy.

In terms of gestational hypertension, one case-control study of SLE pregnancy exposed to HCQ vs no exposure showed lower rates of hypertension (24% vs 38%) and of pre-eclampsia (3% vs 38%), but differences were not significant[5].

Two studies indirectly addressed SGA: one case-control study[5] showed non-significantly decreased rates of IUGR in HCQ-exposed vs non-HCQ-exposed pregnancies (18% vs 41%) and one observational study[3] showed similar rates of SGA between HCQ and non-HCQ-exposed infants.

For labor induction, one case-control study showed similar rates of labor induction between HCQ and non-HCQ-exposed pregnancies (61% vs 59%)[5].

For SLE flare, one case-control study showed similar rates of flare between HCQ and non-HCQ-exposed pregnancies (62% vs 58%)[5]. One observational study showed higher rate of SLE flare in women who stopped HCQ during pregnancy (55%) vs continued HCQ (30%) or never took it (36%) (p=0.05)[3].

For renal flare, one case-control study showed similar rates between HCQ and non-HCQ-exposed pregnancies (12% vs 11%)[5].

For thrombosis, one case-control study showed similar rates of between HCQ and non-HCQ-exposed pregnancies (3% vs 4%)[5].

Quality of Evidence across outcomes is very low due to indirect evidence, observational studies and imprecision.

Azathioprine compared to no azathioprine for offspring developmental delays for active RD on maternal and pregnancy outcomes

Bibliography: . PICO 5c impact of immunosuppression for active RD on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no azathioprine for offspring developmental delays	With azathioprine		Risk with no azathioprine for offspring developmental delays	Risk difference with azathioprine
Use of special education services age <2											
60 (1 observational study)	serious [a]	not serious	serious [b]	not serious	none	⨁◯◯◯ VERY LOW	5/47 (10.6%)	5/13 (38.5%)	**OR 5.25** (1.23 to 22.43)	106 per 1,000	**278 more per 1,000** (21 more to 621 more)
Hearing impairment age <2											

Azathioprine compared to no azathioprine for offspring developmental delays for active RD on maternal and pregnancy outcomes

Bibliography: . PICO 5c impact of immunosuppression for active RD on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
60 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	strong association	⨁◯◯◯ VERY LOW	0/47 (0.0%)	1/13 (7.7%)	**OR 11.40** (0.44 to 297.17)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Fine motor deficit age <2											
60 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	1/47 (2.1%)	1/13 (7.7%)	**OR 3.83** (0.22 to 65.85)	21 per 1,000	**56 more per 1,000** (17 fewer to 567 more)
Gross motor deficit age <2											
60 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	strong association	⨁◯◯◯ VERY LOW	0/47 (0.0%)	1/13 (7.7%)	**OR 11.40** (0.44 to 297.17)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

Azathioprine compared to no azathioprine for offspring developmental delays for active RD on maternal and pregnancy outcomes

Bibliography: . PICO 5c impact of immunosuppression for active RD on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
Speech delay age <2											
60 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	none	⨁◯◯◯ VERY LOW	2/47 (4.3%)	1/13 (7.7%)	**OR 1.88** (0.16 to 22.47)	43 per 1,000	**35 more per 1,000** (35 fewer to 457 more)
Use of special educational services age ≥2											
60 (1 observational study)	serious [a]	not serious	serious [b]	not serious	strong association	⨁◯◯◯ VERY LOW	7/47 (14.9%)	7/13 (53.8%)	**OR 6.67** (1.72 to 25.82)	149 per 1,000	**390 more per 1,000** (82 more to 670 more)
Use of speech therapy age ≥2											

Azathioprine compared to no azathioprine for offspring developmental delays for active RD on maternal and pregnancy outcomes

Bibliography: . PICO 5c impact of immunosuppression for active RD on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
60 (1 observational study)	serious [a]	not serious	serious [b]	not serious	strong association	⨁◯◯◯ VERY LOW	5/47 (10.6%)	6/13 (46.2%)	**OR 7.20** (1.72 to 30.13)	106 per 1,000	**355 more per 1,000** (64 more to 676 more)
ADHD age ≥2											
60 (1 observational study)	serious [a]	not serious	serious [b]	serious [c]	strong association	⨁◯◯◯ VERY LOW	1/47 (2.1%)	2/13 (15.4%)	**OR 8.36** (0.69 to 100.77)	21 per 1,000	**133 more per 1,000** (6 fewer to 665 more)

ADHD: Attention-deficit hyperactivity disorder **CI:** Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

b. no assessment of disease activity

c. crosses 1

References:

2532 Marder 2013

HCQ exposure during first trimester compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No immunosuppression during pregnancy	With HCQ exposure during first trimester		Risk with No immunosuppression during pregnancy	Risk difference with HCQ exposure during first trimester
Congenital malformations											
365 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	13/194 (6.7%)	**OR 3.00** (0.96 to 9.38)	23 per 1,000	**44 more per 1,000** (1 fewer to 160 more)
Fetal Deaths											
365 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	2/194 (1.0%)	**OR 0.43** (0.08 to 2.40)	23 per 1,000	**13 fewer per 1,000** (21 fewer to 31 more)
Preterm Birth											

HCQ exposure during first trimester compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
365 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	6/171 (3.5%)	10/194 (5.2%)	**OR 1.49** (0.53 to 4.20)	35 per 1,000	**16 more per 1,000** (16 fewer to 97 more)
Any adverse fetal outcome											
365 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	15/171 (8.8%)	25/194 (12.9%)	**OR 1.54** (0.78 to 3.02)	88 per 1,000	**41 more per 1,000** (18 fewer to 137 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References: 2486 Cooper 2014

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	2746 Clowse 2006[3]	Observational	Pregnancy (data available pre-pregnancy)	Prospective study of pregnancies in women with SLE evaluated between 1987 and 2002 from the Hopkins Lupus Cohort.	3 groups: no HCQ exposure during pregnancy (163 pregnancies), continuous use of HCQ during pregnancy (56 pregnancies), or cessation of HCQ treatment either in the 3 months prior to or during the first trimester of pregnancy (38 pregnancies).	Outcomes reported by HCQ group, not by Prednisone and AZA use. In group 1 (no HCQ), 21 (13%) were on AZA; in Group 2 (HCQ continued), 8 (14%) were on AZA; in Group 3 (HCQ stopped), 2 (5%) were on AZA. In group 1, 66 (40%) were on high-dose pred (>= 20 mg/day or pulse). In group 2, 15 (27%) were on high-dose pred. In group 3, 17 (45%) were on high-dose pred. In group 1, 109 (67%) took some dose of Prednisone during pregnancy. In group 2, 35 (63%). In group 3, 34 (89%). P=0.0025 More patients in group 3 (stopped HCQ during pregnancy) took prednisone in pregnancy Stillbirths (pregnancy loss after 20 weeks) 13 (8) 3 (6) 3 (9) p = 0.85
Pregnancy loss	2984, Martinez-Rueda, 1996[4]	Case control	Pregnancies from 1968 to 1991 (cases were fetal wastage, controls were live births)	46 pregnant SLE patients; 39 with renal disease (73 pregnancies)	Azathioprine cyclophosphamide	AZA (during any period) was significantly associated with greater odds of fetal loss (OR 3.2, 95% Confidence Interval 1.01 to 10.3; p=0.04) CYC was associated with higher odds of fetal loss (OR 2.9 CI 1.9-4.3, p=0.04)
Pregnancy loss	6696, Mokbel, 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti	Azathioprine (67%)	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%)

				SSB/La antibodies); 35% hypertensive, 43.2% with nephritis		Neonatal deaths: 4/30 (13%) **Outcomes not reported by exposure**
Prematurity	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Fetal outcomes: Prematurity : HCQ group 17 (55%), control 21 (48%)
Preterm	2746 Clowse 2006[3]	Observational	Pregnancy (data available pre-pregnancy)	Prospective study of pregnancies in women with SLE evaluated between 1987 and 2002 from the Hopkins Lupus Cohort.	The pregnancies were divided into 3 groups: no HCQ exposure during pregnancy (163 pregnancies), continuous use of HCQ during pregnancy (56 pregnancies), or cessation of HCQ treatment either in the 3 months prior to or during the first trimester of pregnancy (38 pregnancies).	Outcomes reported by HCQ group, not by Prednisone and AZA use. In group 1 (no HCQ), 21 (13%) were on AZA; in Group 2 (HCQ continued), 8 (14%) were on AZA; in Group 3 (HCQ stopped), 2 (5%) were on AZA. In group 1, 66 (40%) were on high-dose pred (>= 20 mg/day or pulse). In group 2, 15 (27%) were on high-dose pred. In group 3, 17 (45%) were on high-dose pred. In group 1, 109 (67%) took some dose of Prednisone during pregnancy. In group 2, 35 (63%). In group 3, 34 (89%). P=0.0025 More patients in group 3 (stopped HCQ during pregnancy) took prednisone in pregnancy

						Extreme preterm (20–27.9 weeks) 15 (10) 6 (12) 2 (6) p=0.83 Preterm (28–36.9 weeks) 49 (31) 13 (27) 16 (47) p=0.87
Preterm birth	6696, Mokbel, 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis	Azathioprine (67%)	Preterm birth: 12/37 (32.4%) **Outcomes not reported by exposure**
Gestational HTN	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Maternal outcomes: Hypertension: HCQ group 8 (24%), control 20 (38%), Pre-eclampsia: HCQ group 1 (3%), control 20 (38%)
Pre-eclampsia	6696, Mokbel, 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La	Azathioprine (67%)	Preeclampsia: 8/37 (19.4%) **Outcomes not reported by exposure**

				antibodies); 35% hypertensive, 43.2% with nephritis		
IUGR	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Fetal outcomes: IUGR: HCQ group 6 (19%), control 18 (41%)
SGA	2746 Clowse 2006[3]	Observational	Pregnancy (data available pre-pregnancy)	Prospective study of pregnancies in women with SLE evaluated between 1987 and 2002 from the Hopkins Lupus Cohort.	3 groups: no HCQ exposure during pregnancy (163 pregnancies), continuous use of HCQ during pregnancy (56 pregnancies), or cessation of HCQ treatment either in the 3 months prior to or during the first trimester of pregnancy (38 pregnancies).	Outcomes reported by HCQ group, not by Prednisone and AZA use. In group 1 (no HCQ), 21 (13%) were on AZA; in Group 2 (HCQ continued), 8 (14%) were on AZA; in Group 3 (HCQ stopped), 2 (5%) were on AZA. In group 1, 66 (40%) were on high-dose pred (>= 20 mg/day or pulse). In group 2, 15 (27%) were on high-dose pred. In group 3, 17 (45%) were on high-dose pred. In group 1, 109 (67%) took some dose of Prednisone during pregnancy. In group 2, 35 (63%). In group 3, 34 (89%). P=0.0025 More patients in group 3 (stopped HCQ during pregnancy) took prednisone in pregnancy

						Small for gestational age (<10th percentile for age) among live births 29 (20) 11 (24) 7 (23) 0.93
PROM	6696, Mokbel, 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis	Azathioprine (67%)	PROM: 9/37 (24%) **Outcomes not reported by exposure**
Labor induction	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Fetal outcomes: Induction of delivery: HCQ group 19 (61%), control 26 (59%)
Flares	2746 Clowse 2006[3]	Observational	Pregnancy (data available pre-pregnancy)	Prospective study of pregnancies in women with SLE evaluated between 1987 and 2002 from	3 groups: no HCQ exposure during pregnancy (163 pregnancies), continuous use of HCQ during pregnancy (56 pregnancies), or	Outcomes reported by HCQ group, not by Prednisone and AZA use. In group 1 (no HCQ), 21 (13%) were on AZA; in Group 2 (HCQ continued), 8 (14%) were on AZA; in Group 3 (HCQ stopped), 2 (5%) were on AZA. In group 1, 66 (40%) were on high-dose pred (>= 20 mg/day or pulse). In group 2, 15 (27%) were on high-dose pred. In group 3, 17 (45%) were on high-dose pred. In group 1, 109 (67%) took

				the Hopkins Lupus Cohort.	cessation of HCQ treatment either in the 3 months prior to or during the first trimester of pregnancy (38 pregnancies).	some dose of Prednisone during pregnancy. In group 2, 35 (63%). In group 3, 34 (89%). P=0.0025 More patients in group 3 (stopped HCQ during pregnancy) took prednisone in pregnancy Flare rate 59 (36) 17 (30) 21 (55) 0.053
Flares	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Maternal outcomes: Total number of flares: HCQ group 21 (62%), 31 (58%)
Flares	6696, Mokbel, 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis	Azathioprine (67%)	Flare: 21/32 (65%) **Outcomes not reported by exposure**

Renal flare	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Maternal outcomes: Renal flare only: HCQ group 4 (12%), control 6 (11%)
thrombosis	2978, Buchanan 1996[5]	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day Prednisolone and azathioprine were used on clinical grounds to control disease activity.	Steroid sparing effect of HCQ: maximum mean dose of prednisolone received during pregnancy HCQ 13.84 (14.29)mg Control 16.13 (13.43) mg, NS Maternal outcomes: Thrombosis: HCQ group 1 (3%), control 2 (4%)
	2560 Saavedra 2012[7]	Retrospective cohort	Pregnancy outcomes	Women with SLE—with and without history of lupus nephritis	95 pregnancies in 92 SLE women -88/95=93% prednisone -70/95=74% antimalarials -45/95=47% azathioprine	95 pregnancies in 92 SLE women -60/95=63% without h/o nephritis -35/95=37% with h/o lupus nephritis Preeclampsia -8/35=23% with h/o nephritis -8/60=13.3% without h/o nephritis

					Outcomes not broken down by therapy	Maternal flare -19/35=54% h/o nephritis -15/60=25% without h/o nephritis Live birth -28/35=80% h/o nephritis -54/60=90% without h/o nephritis Preterm birth -17/35=48.5% h/o nephritis -24/60=40% without h/o nephritis
	3690, Clowse 2005[8]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	APS. 62% of women with low-activity lupus and 95% of women with high-activity lupus took prednisone. More women with high-activity lupus took high doses of prednisone (20 mg per day) during pregnancy (72% versus 22% of women with low-activity lupus). In 1/3 of the pregnancies, the women were	Perinatal deaths - 20% with APS versus 6% without APS. Gestational age infants – 39% if diagnosed with lupus during pregnancy versus 20% if diagnosed prior to pregnancy. Maternal mortality - 3 out of 267 pregnancies (0.011%, or 11 per 1,000 pregnancies) Live births - 83% of pregnancies in women without any active lupus and 90% of pregnancies in those with mild lupus activity. Full-term deliveries - 60% of pregnancies in women without lupus activity and in 61% in those with mild lupus activity. Neither age of the mother, nor duration of SLE prior to the pregnancy, nor the presence of APS had an impact on the incidence of high-activity lupus.

					treated with hydroxychloroquine. The first-line therapy for high-activity lupus was high-dose prednisone, which was taken in 72% of cases. Azathioprine was also administered, with one-quarter of the women with high-activity lupus taking the drug. Nine of these 14 women started treatment with azathioprine during pregnancy. Cyclophosphamide was administered for severe lupus in 1 patient, and another patient had inadvertant exposure to it in the week following conception.	**Outcomes by disease activity: Study did not test association between medications use and outcomes** Live births: High 44 (77%), Low 185 (88%), RR= 0.88 [0.75, 1.02] Perinatal mortality: High 9 (16%), Low 10 (5%), RR= 3.32 [1.41, 7.77] Miscarriage: High 4 (7%), Low 15 (7%), RR= 0.98 [0.34, 2.85] Extreme prematurity: High 10 (17%), 13 (6%), RR= 2.83 [1.31, 6.12] Prematurity: High 28 (49%), Low 55 (26%), RR= 1.88 [1.32, 2.66] Full-term births: High 15 (26%), 127 (61%), RR= 0.44 [0.28, 0.68] Small for gestational age baby: High 13/44 (30%), Low 38/183 (21%), RR= 1.42 [0.83, 2.43]

97. In women with active SLE without nephritis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus prednisone therapy on maternal and pregnancy outcomes? **GS54**

All evidence is indirect.

For fetal loss, one retrospective observational study of SLE pregnancies looked at azathioprine plus prednisolone vs prednisolone alone, and no significant difference in spontaneous abortion (8% vs 6.6%), stillbirth (6.9% vs 2.2%), or neonatal death (2.3% vs 4.4%) was seen between groups[9]. Another retrospective study[10] found all fetal death to be 22% with any prednisone exposure, 5.5% 1st trimester spontaneous abortion, and 3.6% 2nd trimester IUFD, but DMARD use was not analyzed in this group. A third observational study found only one stillbirth out of 39 patients with prednisone exposure (2.6%)[11].

In terms of preterm birth, one retrospective observational study of SLE pregnancies treated with azathioprine plus prednisolone vs prednisolone alone found preterm delivery to be similar in both groups (39% vs 40.5%)[9]. Two retrospective studies looked at preterm birth with any prednisone exposure: the rate was 44% in one[12] and 21% in the other[10].

Only one study addressed PROM: a retrospective observational study with data about prednisolone exposure and rate of PROM of 14% without mention of other DMARD treatment[10].

Only one study addressed gestational HTN and found pre-eclampsia in 31% of pregnancies with any prednisone exposure[11].

One retrospective study looked at small-for-dates pregnancies with any prednisone exposure and found a rate of 23% in SLE pregnancies[10].

Two studies addressed NLE with prednisone exposure. One retrospective study found a rate of 11.6% with any prednisone exposure[10]. Another observational study found 1 case of congenital heart block in SLE pregnancies exposed to prednisone (2.6%)[11].

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal loss	2424, Saavedra 2015[9]	Retrospective observational	January 2005 to April 2013 Outpatient clinic, Mexico City, Mexico	172 women with SLE (178 pregnancies)	Prednisolone and Azathioprine (n=87) vs Prednisone alone (n=91)	Spontaneous abortions: 7 (8%) vs 6 (6.6%) Stillbirth: 6 (6.9%) vs 2 (2.2%) All fetal loss: 13 (14.9%) vs 9 (9.9%) Neonatal death: 2 (2.3%) vs 4 (4.4%)
Fetal loss	3765, Kobayishi 1999[10]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26	fetal loss with any prednisone exposure therapeutic abortion 7 1st trim spontaneous abortion 3 second trim IUFD 2 live birth 43 Study does not mention what DMARDs these patients were taking

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	
Fetal loss	3035 TambyRaja 1993[11]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28 patients had known SLE, 2 were diagnosed	In 13 (25%) of patients disease was in remission during pregnancy and no meds required. In 39 (75%) pregnancies the mother received	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy - In 17 (44%) additional therapy needed 1 stillbirth due to hypoxia

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				during pregnancy	prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation occurred despite prednisolone (44%) and more than one drug had to be added.	
Preterm	2424, Saavedra 2015[9]	Retrospective observational	January 2005 to April 2013 Outpatient clinic, Mexico City, Mexico	172 women with SLE (178 pregnancies)	Prednisolone and Azathioprine (n=87) vs Prednisone alone (n=91)	Preterm delivery: 34 (39%) vs Preterm delivery: 32 (40.5%)
Preterm	3715 Clark 2003[12]	Observational	1999-2001	72 pregnancies	Variable.	Of 72 pregnancies, 28 pregnancies (38.9%) resulted in preterm delivery.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		retrospective		in women with SLE	43 women used prednisone. 24 women used prednisone ≥10 mg daily.	24 women (53.3%) who had term deliveries used prednisone, and 19 (67.9%) who had preterm deliveries used prednisone (p=NS). Any prednisone exposure 19/43 preterm (44%) 24/43 term (56%) More women in preterm group (50%) used prednisone ≥10 mg daily during pregnancy than did women in term group (22%) (p=0.028). Mean dose of prednisone: in preterm group 24.8 mg, and 16.7 mg in the term group (p=0.047).
Preterm	3765, Kobayishi 1999[10]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in	Preterm births: Nine of 11 premature deliveries were treated with PSL. Three of five pregnancies, in which the patients received more than 15 mg/day of PSL, resulted in premature deliveries. The frequency of premature delivery in these patients (60%) was significantly *(P* < 0.05) high when compared with that in patients who received 0-15 mg/day of PSL (13.1%, eight out of 61 cases).

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	Any prednisone exposure premature delivery 9 (21%) Study does not mention what DMARDs these patients were taking

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
PROM	3765, Kobayishi 1999[10]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted	Any prednisone exposure preterm PROM 6 (14%) Study does not mention what DMARDs these patients were taking

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	
Gestational HTN	3035 TambyRaja 1993[11]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28 patients had known SLE, 2 were diagnosed during pregnancy	In 13 (25%) of patients disease was in remission during pregnancy and no meds required. In 39 (75%) pregnancies the mother received prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy - In 17 (44%) additional therapy needed Pre-eclampsia in 12 pregnancies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation occurred despite prednisolone (44%) and more than one drug had to be added.	
SFD	3765, Kobayishi 1999[10]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26	prednisone exposure SFD 10 (23%) Study does not mention what DMARDs these patients were taking

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	
NLE	3765, Kobayishi 1999[10]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone	Any prednisone exposure NLE 5 (11.6%) Study does not mention what DMARDs these patients were taking

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					[PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a	

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	
NLE	3035 TambyRaja 1993[11]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28 patients had known SLE, 2 were diagnosed during pregnancy	In 13 (25%) of patients disease was in remission during pregnancy and no meds required. In 39 (75%) pregnancies the mother received prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy - In 17 (44%) additional therapy needed CHB observed in 1 baby

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					occurred despite prednisolone (44%) and more than one drug had to be added.	
	3846 Lockshin 1989[13]	Observational, prospective	Unclear. It is mentioned that they tracked 58% of the patients in followup from 6 months to 4 years postpartum, and that the remaining women were followed for up to 2 months postpartum	80 pregnancies among 80 pregnant women with SLE	Various. Women who used prednisone (n=53) were also separately analyzed. * "the frequencies of abnormalities in the 80 pregnancies was low, even when excluding prednisone-treated patients"; specific abnormalities were not addressed	For women who had active disease, there were 5 deaths/21 pregnancies, For women with inactive disease, there were 14 deaths/51 pregnancies For patients who were not treated with steroids and who had active disease: 3 fetal deaths/11 pregnancies. For patients who were not treated with steroids and who had inactive disease: 12 fetal deaths/42 pregnancies. Fetal death was therefore not related to disease activity among total group and among women who were not treated with steroids (NS) **Other medications not assessed. Active SLE rather than SLE flare was assessed in prednisone-exposed group.**
	7640, Rezk, 2017[14]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	Prednisolone and Azathioprine Prednisolone: retrospective 204 (86.4), prospective 188 (87.8%)	**Outcomes not reported by treatment during pregnancy, but instead prospective vs retrospective** <u>Retrospective arm (2005 to 2010)</u> Lupus flare: 19 (8.1%) Maternal mortality: 6 (2.5%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Azathioprine: retrospective 44 (18.6%), prospective 38 (17.7%)	Neonatal death: 9 (3.8%) Preeclampsia: 68 (28.8%) Preterm birth: 96 (40.7%) Spontaneous abortion: 47 (19.9%) VTE: 38 (16.1%) Worsening of renal functions: 65 (27.5%) <u>Prospective arm (2010 to 2015)</u> Lupus flare: 7 (3.3%) Maternal mortality: 1 (0.46%) Neonatal death: 1 (0.46%) Preeclampsia: 60 (28.1%) Preterm birth: 46 (21.5%) Spontaneous abortion: 18 (8.4%) VTE: 12 (5.6%) Worsening of renal functions: 34 (15.8%)
	3377 Skorpen 2017[15]	Observational	Through pregnancy	Data from the medical birth registry of Norway linked with	Prednisolone AZA	Outcomes = birth weight, pre-eclampsia, preterm birth in cases with inactive disease v active disease v population controls. **Outcomes were not reported by exposure to immunosuppression or prednisone**

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				data from RevNatus, a nationwide observational register recruiting women with inflammatory rheumatic disease; included singleton births in women with SLE from 2006-2015. N=180 cases. Disease activity assessed using LAI P.	HCQ	Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%).
	2746 Clowse 2006[3]	Observational	Pregnancy (data available pre-pregnancy)	Prospective study of pregnancies in women with SLE evaluated between 1987 and 2002 from the Hopkins Lupus Cohort.	3 groups: no HCQ exposure during pregnancy (163 pregnancies), continuous use of HCQ during pregnancy (56 pregnancies), or cessation of HCQ treatment either in the 3 months prior to or during the first trimester of pregnancy (38	**Outcomes reported by HCQ group, not by Prednisone and AZA use.** More patients in group 3 (stopped HCQ during pregnancy) took prednisone in pregnancy (statistically significant, see column to left). In group 1 (no HCQ), 21 (13%) were on AZA; in Group 2 (HCQ continued), 8 (14%) were on AZA; in Group 3 (HCQ stopped), 2 (5%) were on AZA. In group 1, 66 (40%) were on high-dose pred (>= 20 mg/day or pulse). In group 2, 15 (27%) were on high-dose pred. In group 3, 17 (45%) were on high-dose pred. In group 1, 109 (67%) took

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					pregnancies). The pregnancy outcomes, fetal outcomes, and lupus activity during pregnancy were compared among these groups	some dose of Prednisone during pregnancy. In group 2, 35 (63%). In group 3, 34 (89%). P=0.0025
	3369 Nicklin 1991[16]	Retrospective observational	Pregnancy and delivery	SLE patients	18/42 pregnancies treated with immunosuppressive medications 12/42 pred alone	42 pregnancies, various treatments **(outcomes not listed by treatment)** - 4/42=9.5% IUGR 14/42=33.3% pregnancy induced hypertension

98. In women with SLE nephritis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy on maternal and pregnancy outcomes?

No evidence available as outcomes of one prospective cohort study were not reported separately associated with immunosuppression during pregnancy[17].

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2346 Moroni 2016[17]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians)	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%) • Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%) • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%) **Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%) • Small for gestational age: 12 (16.4%) • Mean birth weight (SD): 2753 (683) g • Neonatal cutaneous lupus: 0 (0%) • Congenital heart-block: 0 (0%) The probability of having a baby which was small for gestational age was 85% reduced in patients who received hydroxychloroquine during pregnancy (OR: 0.15; 95% CI: 0.03, 0.77) *__note: results not stratified by patients who did and did not taking immunosuppressive therapy during pregnancy__

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months		

99. In women with SLE nephritis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus prednisone therapy on maternal and pregnancy outcomes? **GS54**

No evidence available as outcomes of one prospective cohort study were not reported separately associated with immunosuppression during pregnancy[17].
Quality of evidence: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2346 Moroni 2016[17]	Prospective cohort study of women with	October 2016 – December 2013	Women prospectively followed after receiving a counselling	No prednisone/ immunosuppressive therapy: 13 (18.3%)	***note: results not stratified by patients who did and did not taking immunosuppressive therapy during pregnancy**

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		lupus nephritis		visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years	Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%) • Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%) • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%) **Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%) • Small for gestational age: 12 (16.4%) • Mean birth weight (SD): 2753 (683) g • Neonatal cutaneous lupus: 0 (0%) • Congenital heart-block: 0 (0%) The probability of having a baby which was small for gestational age was 85% reduced in patients who received hydroxychloroquine during pregnancy (OR: 0.15; 95% CI: 0.03, 0.77)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months		

100. In women with Myositis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy on maternal and pregnancy outcomes?

No evidence

101. In women with Myositis with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus prednisone therapy on maternal and pregnancy outcomes?

No evidence

102. In women with Scleroderma with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy on maternal and pregnancy outcomes?

No evidence

103. In women with Scleroderma with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus prednisone therapy on maternal and pregnancy outcomes?

No evidence

104. In women with Inflammatory arthritis (RA, PsA, AS) with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy on maternal and pregnancy outcomes? **GS54**

Two observational studies directly addressed immunosuppression in patients with inflammatory arthritis compared to no immunosuppression. The remainder of evidence is indirect.

With respect to spontaneous abortion, one observational study directly compared exposure to methotrexate pre-conception to no methotrexate exposure and found no significant difference (OR 0.91, CI includes 1)[18]. However, methotrexate exposure post-conception in the same study was associated with a higher risk of spontaneous abortion (OR 2.47, CI 1.54 to 3.95). Another observational study of leflunomide-exposed pregnancies found the rate of spontaneous abortion to be 15%[19]. An observational study of certolizumab exposure during pregnancy[20] found a miscarriage rate of 20% (52/372 known outcomes), 625 exposed.

With respect to stillbirth, one observational study directly compared exposure to methotrexate pre-conception to no methotrexate exposure and found no significant difference (OR 1.67, CI includes 1)[18]. Methotrexate exposure post-conception in the same study had an OR of 2.46 compared to no MTX exposure but CI included 1. The same study looked at methotrexate exposure in the first trimester vs. no immunosuppression and found OR 3.98 but CI included 1. An observational study of 1st trimester methotrexate exposure showed 4 miscarriages/28 pregnancies (14%)[21]. Another study of certolizumab exposure[20] found 1 stillbirth out of 372 known outcomes (0.3%), 625 exposed.

With respect to fetal death, one observational study directly compared MTX exposure in the first trimester to no MTX exposure during pregnancy and found no significant difference in risk (OR 3.98, CI includes 1)[2]. Similarly, the same study found TNFi exposure (etanercept, infliximab, and adalimumab) in the first trimester to have no difference in risk (OR 0.33, CI includes 1). Exposure to other immunosuppression (gold, SSZ, leflunomide, minocycline, azathioprine) in the first trimester also had no difference in risk compared to no immunosuppression in the same study (OR 0.66, CI includes 1). Another observational study of leflunomide-exposed pregnancies found the rate of all fetal death to be 43%[19]. A second study of leflunomide exposure during 1st trimester had no fetal deaths[22], while in the same study, exposure prior to conception resulted in 7% fetal loss.

In evaluation of major birth defects, one observational study directly compared exposure to methotrexate pre-conception to no methotrexate exposure and found no significant difference (OR 0.98, CI includes 1)[2]. Similarly, methotrexate exposure post-conception in the same study was not associated with a higher risk of spontaneous abortion (OR 1.91, CI included 1). Another prospective cohort study of pregnant women with RA/JRA[23] found no significant difference in major birth defects with leflunomide exposure (followed by cholestryramine washout) in the first trimester vs no leflunomide. Several studies provided indirect data on major birth defects. One registry study looked at exposure to DMARDs and anti-TNF (8 methotrexate, 2 leflunomide, 58 HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab)[24]. The OR for major malformation was 1.05 (CI includes 1) and no children exposed to MTX, LEF, ETAN, or ADA had any major malformation. Two other studies looked at leflunomide-exposed pregnancies. One registry study reported only 1 major birth defect out of 65 pregnancies exposed (1.5%)[19]. The second study of leflunomide exposure during first trimester or pre-conception found no major birth defects[22].

With respect to minor abnormalities, three studies provide indirect evidence. One database study of 65 leflunomide-exposed pregnancies found minor anomalies to be 4.6%[19]. Another study of leflunomide-exposed pregnancies found 14/16 exposed in the first trimester with minor structural anomalies, and 21/29 exposed pre-conception with minor structural anomalies, without unifying features[22]. Another observational study of 28 pregnancies with MTX exposure (including 22 RA, Takayasu 2, PsA 2, DM 1, AS 1 found only 1 child with minor abnormalities (3.6%)[21].

In evaluation of congenital malformation, one observational study directly compared exposure to MTX in the first trimester to no MTX exposure and found no significant difference (OR 1.90, CI includes 1)[2]. The same study compared exposure to TNFi (etanercept, infliximab, and adalimumab) vs no TNF exposure and found no significant difference (OR 1.55, CI includes 1). Exposure to other immunosuppression (gold, SSZ, leflunomide, minocycline, azathioprine) in the first trimester also had no difference in risk compared to no immunosuppression in the same study (OR 1.6, CI includes 1). Indirect evidence comes from an observational study of certolizumab exposure during pregnancy[20]: 12 cases of congenital malformation were seen in 372 pregnancies with known outcome (625 exposed).

With respect to preterm birth, one observational study directly compared MTX exposure in the first trimester to no MTX exposure during pregnancy and found no difference in risk (OR 0.54, CI includes 1)[2]. Similarly, the same study found TNFi exposure (etanercept, infliximab, and adalimumab) in the first trimester to have no difference in risk (OR 1.56, CI includes 1). Exposure to other immunosuppression (gold, SSZ, leflunomide, minocycline, azathioprine) in the first trimester also had no difference in risk compared to no immunosuppression in the same study (OR 0.88, CI includes 1).

With respect to any adverse fetal outcome, one observational study directly compared MTX exposure in the first trimester to no MTX exposure during pregnancy and found no difference in risk (OR 1.54, CI includes 1)[2]. Similarly, the same study found TNFi exposure (etanercept, infliximab, and adalimumab) in the first trimester to have no difference in risk (OR 1.56, CI includes 1). Exposure to other immunosuppression (gold, SSZ, leflunomide, minocycline, azathioprine) in the first trimester also had no difference in risk compared to no immunosuppression in the same study (OR 1.56, CI includes 1)—no events were seen in either group.

Quality of Evidence across outcomes: Very low

MTX exposure pre-conception in pregnant women with RD compared to no MTX exposure in pregnant women with RD

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no MTX exposure in pregnant women with RD	With MTX exposure pre-conception in pregnant women with RD		Risk with no MTX exposure in pregnant women with RD	Risk difference with MTX exposure pre-conception in pregnant women with RD
Spontaneous Abortion											
595 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	44/459 (9.6%)	12/136 (8.8%)	**OR 0.91** (0.47 to 1.78)	96 per 1,000	**8 fewer per 1,000** (48 fewer to 63 more)
Stillbirth											

MTX exposure pre-conception in pregnant women with RD compared to no MTX exposure in pregnant women with RD

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
595 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	2/459 (0.4%)	1/136 (0.7%)	**OR 1.69** (0.15 to 18.81)	4 per 1,000	**3 more per 1,000** (4 fewer to 72 more)
Elective Terminations											
595 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	33/459 (7.2%)	13/136 (9.6%)	**OR 1.36** (0.70 to 2.67)	72 per 1,000	**23 more per 1,000** (20 fewer to 99 more)
Live Births											

MTX exposure pre-conception in pregnant women with RD compared to no MTX exposure in pregnant women with RD
Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
595 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	380/459 (82.8%)	110/136 (80.9%)	**OR 0.88** (0.54 to 1.44)	828 per 1,000	**19 fewer per 1,000** (106 fewer to 46 more)
Major birth defects											
507 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	14/393 (3.6%)	4/114 (3.5%)	**OR 0.98** (0.32 to 3.05)	36 per 1,000	**1 fewer per 1,000** (24 fewer to 66 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

b. crosses 1

References:

2487 Weber-Shoendorfer, 2014

MTX exposure post-conception in pregnant women with RD compared to no MTX exposure post-conception in pregnant women with RD

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no MTX exposure post-conception in pregnant women with RD	**With MTX exposure post-conception in pregnant women with RD**		**Risk with no MTX exposure post-conception in pregnant women with RD**	**Risk difference with MTX exposure post-conception in pregnant women with RD**
Spontaneous abortion											
647 (1 observational study)	not serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	44/459 (9.6%)	39/188 (20.7%)	**OR 2.47** (1.54 to 3.95)	96 per 1,000	**112 more per 1,000** (44 more to 199 more)
Stillbirth											

MTX exposure post-conception in pregnant women with RD compared to no MTX exposure post-conception in pregnant women with RD
Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
647 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	2/459 (0.4%)	2/188 (1.1%)	**OR 2.46** (0.34 to 17.57)	4 per 1,000	**6 more per 1,000** (3 fewer to 67 more)
Elective Terminations											
647 (1 observational study)	not serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	33/459 (7.2%)	49/188 (26.1%)	**OR 4.55** (2.81 to 7.36)	72 per 1,000	**189 more per 1,000** (107 more to 291 more)
Live Births											

MTX exposure post-conception in pregnant women with RD compared to no MTX exposure post-conception in pregnant women with RD
Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
647 (1 observational study)	not serious [a]	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	380/459 (82.8%)	99/188 (52.7%)	**OR 0.23** (0.16 to 0.34)	828 per 1,000	**303 fewer per 1,000** (393 fewer to 207 fewer)
Major birth defects											
499 (1 observational study)	not serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	14/393 (3.6%)	7/106 (6.6%)	**OR 1.91** (0.75 to 4.87)	36 per 1,000	**30 more per 1,000** (9 fewer to 117 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

b. crosses 1

References: 2487 Weber-Shoendorfer, 2014

First trimester MTX exposure compared to No use of immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With No use of immunosuppression during pregnancy	With First trimester MTX exposure		Risk with No use of immunosuppression during pregnancy	Risk difference with First trimester MTX exposure
Congenital Malformations											
194 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	1/23 (4.3%)	**OR 1.90** (0.20 to 17.75)	23 per 1,000	**20 more per 1,000** (19 fewer to 275 more)
Fetal Deaths											
194 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	2/23 (8.7%)	**OR 3.98** (0.69 to 23.04)	23 per 1,000	**64 more per 1,000** (7 fewer to 332 more)
Preterm Birth											
194 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	6/171 (3.5%)	0/23 (0.0%)	**OR 0.54** (0.03 to 9.93)	35 per 1,000	**16 fewer per 1,000** (34 fewer to 230 more)

First trimester MTX exposure compared to No use of immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
Any Adverse Fetal Outcome											
194 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	15/171 (8.8%)	3/23 (13.0%)	**OR 1.56** (0.42 to 5.86)	88 per 1,000	**43 more per 1,000** (49 fewer to 273 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References: 2486 Cooper 2014

First trimester TNF exposure compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With No immunosuppression during pregnancy	**With First trimester TNF exposure**		**Risk with No immunosuppression during pregnancy**	**Risk difference with First trimester TNF exposure**
Congenital Malformations											

First trimester TNF exposure compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
227 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	2/56 (3.6%)	**OR 1.55** (0.28 to 8.68)	23 per 1,000	**12 more per 1,000** (17 fewer to 149 more)
Fetal Deaths											
227 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	0/56 (0.0%)	**OR 0.33** (0.02 to 6.21)	23 per 1,000	**16 fewer per 1,000** (23 fewer to 106 more)
Preterm Births											
227 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	6/171 (3.5%)	3/56 (5.4%)	**OR 1.56** (0.38 to 6.44)	35 per 1,000	**19 more per 1,000** (21 fewer to 155 more)
Any Adverse Fetal Outcome											
194 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	15/171 (8.8%)	3/23 (13.0%)	**OR 1.56** (0.42 to 5.86)	88 per 1,000	**43 more per 1,000** (49 fewer to 273 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References: 2486 Cooper 2014

Other Immunosuppression exposure (Gold, SSZ, Leflunomide, Minocycline, Azathioprine) during first trimester compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With No immunosuppression during pregnancy	**With Other Immunosuppression exposure (Gold, SSZ, Leflunomide, Minocycline, Azathioprine) during first trimester**		**Risk with No immunosuppression during pregnancy**	**Risk difference with Other Immunosuppression exposure (Gold, SSZ, Leflunomide, Minocycline, Azathioprine) during first trimester**
Congenital Malformations											
300 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	4/129 (3.1%)	**OR 1.34** (0.33 to 5.45)	23 per 1,000	**8 more per 1,000** (16 fewer to 92 more)
Fetal Deaths											

Other Immunosuppression exposure (Gold, SSZ, Leflunomide, Minocycline, Azathioprine) during first trimester compared to No immunosuppression during pregnancy

Bibliography: Barbhaiya M. PICO 5C. In women with RD with active disease, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus no immunosuppressive therapy. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
300 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	4/171 (2.3%)	2/129 (1.6%)	**OR 0.66** (0.12 to 3.65)	23 per 1,000	**8 fewer per 1,000** (21 fewer to 57 more)
Preterm Births											
300 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	6/171 (3.5%)	4/129 (3.1%)	**OR 0.88** (0.24 to 3.19)	35 per 1,000	**4 fewer per 1,000** (26 fewer to 69 more)
Any adverse fetal outcome											
0 cases 0 controls (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	0 cases 0 controls		**OR 1.56** (0.42 to 5.86)	**Low**	
										0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References 2486, Cooper, 2014

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	6663 Weber-Schoendorfer 2017[19]	German pharmacovigilance database — leflunomide exposed pregnancies. Prospective data collection	Pregnancy outcomes And MBD	Women with RA (54) Psoriatic arthritis (6) Other diseases (4)	Leflunomide-exposed pregnancies 47 with 1st trimester exposure 18 with pre-conception exposure	65 pregnancies with complete data -19/65=29% elective termination -10/65=15% spontaneous abortion -37/65=57% live birth all fetal death 28/65 = 43%
Fetal loss	2403 Clowse 2015[20]	Observational	Prospective and retrospective cohort	All pregnancies were CZP-exposed for a total of 625 pregnancies. Paternal exposures n=33, maternal exposures n=339.	Certolizumab pegol	Gestational age at birth, birthweight, Cesarean delivery, multiple gestation, congenital malformations were assessed. Also assessed CDAI at baseline/visit prior to pregnancy/change from baseline, DAS28, concomitant medications, maternal age, trimester of CZP exposure 625 pregnancies with 372 known outcomes. Maternal exposed pregnancies: 254 live births, 52 miscarriages, 32 induced abortions, 1 stillbirth, 1 neonatal death. Almost all had exposure in 1st trimester.
Fetal loss	2558 Cassina 2012[22]	Observational	Patients exposed to LEF b/w 1999 and 2009, who	45 women exposed to LEF. 16 exposed during 1st trimand 29 were exposed preconception	All pregnancies were exposed to leflunomide	All 16 pregnancies exposed to LEF during 1st trimester resulted in live births. 27 (93%) of the pregnancies with exposure prior to conception resulted in live births.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			contacted OTIS.			
Fetal loss	2798 Lewden 2004[21]	Observational	28 cases evaluated from 1993-2001	28 cases of women treated with low-dose methotrexate during 1st trimester	Methotrexate Mean dose: 10.5 mg/wk 2 patients received folic acid before pregnancy (folic acid data available only for 4 patients) Highest dose was 50 mg qwk Mean cumulative dose of mtx since the beginning of pregnancy: 30.7 +/2 23.3 mg 19 patients also took steroids and/or NSAIDs.	Diseases: RA 22 patients, Takayasu arteritis 1 patient (2 pregnancies), PsA in 2, DM 1, AS 1 16 patients dc'd methotrexate during 1st 4 weeks gestation, 10 stopped 5-8 weeks gestation, and 1 stopped after gestational week 8. 19 live births (3 premature), 4 miscarriages, 5 elective terminations in the group.
MBD	2650 Chambers 2010[23]	Prospective observational cohort	Patients enrolled btw 1999 and 2009	Pregnant women with diagnosis of RA or JRA exposed to at least 1 dose of	Leflunomide versus none Note: Enrollment was completed prior	Gestational timing of the last dose of leflunomide was on average 3.1 weeks after conception, with the latest exposure ending at 8.6 weeks after conception.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				LEF during 1st trimester vs disease-matched group that didn't take LEF vs comparison group of healthy women 250 participants from the US and Canada were enrolled in the cohort study: 64 in the leflunomide-exposed group, 108 in the disease-matched comparison group, and 78 in the normal healthy comparison group	to 21st week of gestation and before known outcomes of the pregnancy or major structural defects were diagnosed prenatally in order to minimize bias	Nearly all women in the leflunomide group (95.3%) underwent at least one course of the cholestyramine washout procedure early in pregnancy immediately following discontinuation of leflunomide, and 12 women (18.8%) reported receiving >1 course of cholestyramine (range 2–6 courses). No sig differences in rate of major structural defects in exposed group relative to either comparison group; rates were similar overall to the 3-4% expected in general population. The overall proportion of major structural anomalies did not differ significantly between disease-matched groups (P = 0.13 among live births, P = 0.73 excluding lost to follow-up.).
MBD	6663 Weber-Schoendorfer 2017[19]	German pharmacovigilance database — leflunomide exposed pregnancies. Prospecti	Pregnancy outcomes And MBD	Women with RA (54) Psoriatic arthritis (6) Other diseases (4)	Leflunomide-exposed pregnancies 47 with 1st trimester exposure 18 with pre-conception exposure	65 pregnancies with complete data -1/65=1.5% MBD (cholestyramine washout)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		ve data coll.				
MBD	2558 Cassina 2012[22]	Observational	Patients exposed to LEF between 1999 and 2009, who contacted OTIS.	45 women exposed to LEF. 16 were exposed during 1st trimester and 29 were exposed preconception	All pregnancies were exposed to leflunomide	2 structural defects among women exposed to LEF during pregnancy (major; 1 with aplasia cutis congenita (twin of this baby died), No major structural defects among women exposed prior to conception
MBD	6168 Viktil 2012[24]	Observational	2004-2007	Pregnancies in Norway over 3 years Maternal and fetal exposures to anti-rheumatic drugs.	Patients treated with any of the following: NSAIDs, CS, SSZ, AZA, HCQ, ETAN, MTX, LEF, ADA.	154,976 expectant pregnancies. 1461 mothers and 1198 fathers were given anti-rheumatic drugs at least once during the study period.Exposures: 8 methotrexate, 2 leflunomide, 58 HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab. No major malformations of mtx, leflunomide, etanercept, or adalimumab. OR for malformations in children with mothers who had been exposed to any drug: 1.06 (0.85-1.32), and for men: 1.19 (0.93-1.51) OR for major malformation in children with mothers who had been exposed: 1.05 (0.79-1.40), and for men: 1.26 (0.93-1.71) No children born to mothers exposed to MTX, LEF, ETAN, ADA had major malformations.
Congenital malformations	2403 Clowse 2015[20]	Observational	Prospective and retrospective cohort	All pregnancies were CZP-exposed for a total of 625 pregnancies. Paternal exposures n=33, maternal	Certolizumab pegol	Gestational age at birth, birthweight, Cesarean delivery, multiple gestation, congenital malformations were assessed. Also assessed CDAI at baseline/visit prior to pregnancy/change from baseline, DAS28, concomitant medications, maternal age, trimester of CZP exposure 625 pregnancies with 372 known outcomes.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				exposures n=339.		12 cases of congenital malformations
Minor anomalies	6663 Weber-Schoendorfer 2017[19]	German pharmacovigilance database — leflunomide exposed pregnancies. Prospective data collection	Pregnancy outcomes And MBD	Women with RA (54) Psoriatic arthritis (6) Other diseases (4)	Leflunomide-exposed pregnancies 47 with 1st trimester exposure 18 with pre-conception exposure	65 pregnancies with complete data -3/65%=4.6% minor anomalies
Minor anomalies	2798 Lewden 2004[21]	Observational descriptive study	28 cases evaluated from 1993-2001	28 cases of women treated with low-dose methotrexate during 1st trimester	Methotrexate Mean dose: 10.5 mg/wk 2 patients received folic acid before pregnancy (folic acid data available only for 4 patients) Highest dose was 50 mg qwk Mean cumulative dose of mtx since the beginning of	Diseases: RA 22 patients, Takayasu arteritis 1 patient (2 pregnancies), PsA in 2, DM 1, AS 1 16 patients dc'd methotrexate during 1st 4 weeks gestation, 10 stopped 5-8 weeks gestation, and 1 stopped after gestational week 8. 1 child exposed until 8.5 weeks gestation had minor anomalies.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					pregnancy: 30.7 +/2 23.3 mg 19 patients also took steroids and/or NSAIDs.	
Minor anomalies	2558 Cassina 2012[22]	Observational	Patients exposed to LEF between 1999 and 2009, who contacted OTIS.	45 women exposed to LEF. 16 exposed during 1st trim and 29 exposed preconception	All pregnancies were exposed to leflunomide	defects among women exposed to LEF during pregnancy : Minor anomalies observed in 14. These included short nose, flat nasal bridge, and long philtrum. Minor structural anomalies observed in 21 without a unifying anomaly.

105. In women with Inflammatory arthritis (RA, PsA, AS) with currently active disease that would require immunosuppressive therapy in a non-pregnant state, what is the impact of treatment with immunosuppressive therapy compatible with pregnancy versus prednisone therapy on maternal and pregnancy outcomes? **GS54**
Two studies provide direct evidence on impact of immunosuppression vs steroid during pregnancy on maternal outcomes.

With respect to infectious risk in women with RA, PsA, AS, and IBD, one study[25] comparing non-biologic exposure with steroid exposure found the serious infection incidence rate/100 person years to be similar with OR 0.63 (CI includes 1); including SLE pregnancies the OR was 0.67 (CI includes 1). The same study reported similar results with anti-TNF exposure, with OR 0.61 (CI includes 1).

With respect to pre-eclampsia, a database study of women with autoimmune disease (RA, PsA, SLE)[26] found the risk for pre-eclampsia with DMARD use to be 3.03 (CI 1.36-6.72) vs corticosteroid use 1.24 (CI 0.8-1.92). With adjustment for pre-eclampsia risk factors including autoimmune disease and renal disease, aRR were 2.29 for DMARD (CI 0.81-6.44) vs 0.89 for steroid use (CI 0.51-1.56).

Quality of evidence across outcomes: Very low

Non-biologic compared to steroid impact on maternal morbidity (infection) in patients with RA, PsA, AS, or IBD in Patients with Active RD

Bibliography: . PICO 5c: Impact of Immunosuppressive Therapy on Maternal and Fetal Outcomes in Patients with Active RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With steroid	With non-biologic		Risk with steroid or IBD	Risk difference with non-biologic
Serious infectious event incidence rate/100 person years											
1365 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	29/856 (3.4%)	11/509 (2.2%)	**OR 0.63** (0.31 to 1.27)	34 per 1,000	**12 fewer per 1,000** (23 fewer to 9 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References: 2322 Desai 2017

Anti-TNF compared to steroid impact on maternal morbidity (infection) in patients with RA, PsA, AS, or IBD in Patients with Active RD
Bibliography: . PICO 5c: Impact of Immunosuppressive Therapy on Maternal and Fetal Outcomes in Patients with Active RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With steroid or IBD	With anti-TNF		Risk with steroid	Risk difference with anti-TNF
Serious infectious event incidence rate/100 person years											
1378 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	29/856 (3.4%)	11/522 (2.1%)	**OR 0.61** (0.30 to 1.24)	34 per 1,000	**13 fewer per 1,000** (23 fewer to 8 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational

b. crosses 1

References: 2322 Desai 2017

Non-biologic compared to steroid impact on maternal morbidity (infection) in patients with SLE, RA, AS, IBD, or PsA in Patients with Active RD

Bibliography: . PICO 5c: Impact of Immunosuppressive Therapy on Maternal and Fetal Outcomes in Patients with Active RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With steroid impact on maternal morbidity (infection) in patients with SLE, RA, AS, IBD, or PsA	With non-biologic		Risk with steroid impact on maternal morbidity (infection) in patients with SLE, RA, AS, IBD, or PsA	Risk difference with non-biologic
Serious infectious event incidence rate/100 person years											
2153 (1 observational study)	serious [a]	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	40/1162 (3.4%)	23/991 (2.3%)	**OR 0.67** (0.40 to 1.12)	34 per 1,000	**11 fewer per 1,000** (20 fewer to 4 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. observational study

b. crosses 1

References: 2322 Desai 2017

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pre-eclampsia	2534 Palmsten 2012[26]	Observational	Patients with AI disease exposed to DMARDs, CS, NSAIDs. Outcome of interest was preeclampsia. British Columbia database 1997-2006	414 women had a DMARD dispensed during pregnancy.	NSAID exposure in 36,284 pregnancies CS exposure in 7282 pregnancies DMARD exposure in 1220 pregnancies Adjustment: Preeclampsia risk factor adjustment + asthma, renal disease, RA/Psoriasis, SLE, IBD, joint radiograph, ≥2 rheumatology visits, platelet count, physician visits (0–8, 9–14, 15–24, ≥25), number of non-study drugs (0–1, 2–3, ≥4), baseline days supply of DMARDs (linear term), baseline days supply of corticosteroids (0, 1 to 6, 7–89, ≥90), and baseline days supply of NSAIDs (0, 1 to 6, 7–89, ≥90).	Risk for preeclampsia: If DMARD RR 3.03 (1.36-6.72), aRR: 2.29 (0.81-6.44) If CS: RR 1.24 (0.8-1.92), aRR 0.89 (0.51-1.56) If NSAID: RR 0.86 (0.66-1.14), aRR: (0.84-1.10) Incidence of preeclampsia: 2.3% for past DMARD users, 2.7% for past CS users, 2.9% for past NSAID users. RA/psoriasis n=869, 3.1% developed preeclampsia SLE n=196, 5.1% developed preeclampsia IBD n=513, 2.3% developed preeclampsia Among women without AI diseases (n=286220), 2.4% developed preeclampsia

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3398 Polachek 2017[27]	Observational	Pregnancy and first year post-partum	Women with PsA who were pregnant 1990-2015 identified from Toronto PsA database; 29 PsA women with 42 pregnancies identified	During 28 (66.7%) pregnancies, patients were treated with medications: 17 (40.5%) NSAIDS (3 as a sole therapy), 2 (4.8%) prednisone, 15 (35.7%) DMARDS (sulfasalazine, azathioprine, and hydroxychloroquine), and 11 (26.2%) biologic drugs (10 anti-TNF α and 1 Ustekinumab). Intra-articular steroid injections were used during 4 pregnancies (9.5%).	Of the 42 pregnancies, 40 (95%) resulted in normal live birth. Arthritis improved or was stable low activity in 24 (58.5%) of pregnancies. During the postpartum period, 21 (52.5%) had either improvement or stable low PsA activity, whereas 16 (40%) had either worsening or stable high disease activity. Among the pregnancies with favorable course, the majority (58.3%) used either DMARDS, biologic drugs, or both during pregnancy, while 41.7% used NSAIDS alone or no treatment at all In the unfavorable course group, more than half (53.9%) used either DMARDS, biologic drugs, or both. **Outcomes not reported as flare (maternal outcome)**

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5D. No evidence

5D. In women who are pregnant with scleroderma renal crisis, what is the impact of treatment with ACE-inhibitor or ARB therapy versus similar women not treated with ACE-inhibitor and/or ARB therapy on maternal and pregnancy outcomes [listed]?

Population:
- Women with scleroderma in renal crisis

Intervention:
- Treatment with an ACE-inhibitor or ARB in pregnancy

Comparator:
- No treatment with an ACE-inhibitor or ARB in pregnancy

Outcomes:
- Infant renal function/structure
- Maternal renal function
- Pregnancy loss (spontaneous abortion, stillbirth)
- Maternal death

RELEVANCE GS55 BUT NO EVIDENCE

5E.

5E. In women with RD [listed] who are pregnant [variables listed], what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

Population:

- Women with RD who are considering pregnancy
    - Any woman with a RD and
        - Renal disease
        - Hypertension
        - aPL(+) but not meeting modified Sapporo APS criteria
    - SLE
    - Systemic sclerosis
    - RA and other inflammatory arthritis
    - Vasculitis
    - Myositis
    - Sjogren's

Intervention:

- Low-dose aspirin

Comparator:

- Similar patients who are not treated with low-dose aspirin

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease, including preeclampsia
- Preterm birth: preterm birth < 34 weeks, preterm birth > 34 and < 37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Damage from RD
- Maternal morbidity (including loss of renal function)
- Maternal mortality

106. In women with RD who are considering pregnancy and have renal disease, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes? **EVIDENCE FOR GS56**

Summary: This PICO question for the women with RD who are considering pregnancy and have renal disease is addressed by three indirect observational studies.[1-3]. In all studies patients had lupus nephritis.

In two studies[1,2], all patients had lupus nephritis and all of them received aspirin. In a third study[3] out of 40 SLE patients, 9 patients had LN, 6 patients had hypertension, and 77%% did not receive aspirin. None of studies had control groups, so the outcomes can't be compared within studies. Between studies, the rate of fetal loss among patients receiving LDA was 6/71 (8.2%), among patients with renal disease not receiving LDA was 1 out of 9 (11%); Preeclampsia: 6 (8.4%) and 8/37 (19.4%) respectively. Renal flares was 13 (19.7%) among pregnant patients receiving LDA[1] with a predictor of renal flare relative risk ratio 0.81[2]. Poor fetal outcome: 8 out of 9 (89%) in patients with renal disease not receiving LDA[3]. It is unclear though how many exactly patients with renal disease were non-pregnant and how many of them did not receive LDA in a third study[3].

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	All patients received aspirin during pregnancy and 4 were given low molecular weight heparin	**Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%) • Small for gestational age: 12 (16.4%) • Mean birth weight (SD): 2753 (683) g • Neonatal cutaneous lupus: 0 (0%) • Congenital heart-block: 0 (0%)
	7570, Gaballa, 2012[3]	Prospective observational	March 28 to October 2010	40 SLE pregnant women (group A) versus 35 non-pregnant SLE patients (group B). Patients with renal disease (n=9). It's unclear	No LDA (only 27% received)	Pregnancy loss: 1 out of 9 (11%) with renal disease Poor fetal outcome: 8 out of 9 (89%) with renal disease.

				from study how many patients with renal disease were in either group.		
Maternal outcomes	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	All patients received aspirin during pregnancy and 4 were given low molecular weight heparin	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%) • Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%) • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%)
	3413 Moroni, 2016[2]	Cohort study		37 lupus nephritis patients	Aspirin n=37	**<u>Aspirin</u>** **Predictor Renal flare** Relative risk ratio 0.81 95% CI 0.244 – 0.2668 P 0.72
	7570, Gaballa, 2012[3]	Prospective observational	March 28 to October 2010	40 SLE pregnant women (group A) versus 35 non-pregnant SLE patients (group B). Patients with renal disease (n=9). It's unclear from study how many patients with renal disease were in either group.	No LDA (only 27% received)	Antenatal SLE flare up during pregnancy: 21/32 (65%) of all patients Pre-eclampsia: 8/37 (19.4%) of all patients Postpartum flare: 8/37 (35.5%) of all patients
	3635 Imbasciati 2009[4]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN	Various LDA used during 68 pregnancies (60%)	Note: 27/74 women had LAC or ACL Ab+ (36%) Predictors of adverse fetal and maternal outcomes: LDA during pregnancy: adj RR 0.11 (0.03-0.38), p=0.003—protective This was seen in univariate and adjusted models (univariate RR not presented, but p=0.006).

107. In women with RD who are considering pregnancy and have hypertension, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

Summary: This PICO question is indirectly addressed by two observational studies[3,5]; having pregnant women with hypertension (35%) in first study who mostly received LDA, and non-pregnant women in second study who mostly did not take LDA. In pregnant patients taking LDA the rate of fetal loss was 24%, in non-hypertensive women not receiving LDA the rate was 17%. It is unclear though how many exactly patients with fetal loss had hypertension in the first study, while it is also unclear how many exactly patients with hypertension were not taking LDA in a second study. For other outcomes there is not enough information from a second study on how many patients with hypertension had other outcomes. Patients with hypertension not taking LDA had strong association with poor maternal (6/6, 100%) and fetal outcomes (4/6, 67%), while pregnant patients receiving LDA had Antenatal SLE flare up during pregnancy 21/32 (65%), Pre-eclampsia 8/37 (19.4%), Postpartum flare 8/37 (35.5%).

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis Secondary APS: 54.1% ACL (IgM): 40.5% ACL (IgG): 48.6% LAC: 24.3%	LDA (89.2%)	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%) Preterm birth: 12/37 (32.4%) PROM: 9/37 (24%)
	7570, Gaballa, 2012[3]	Prospective observational	March 28 to October 2010	40 SLE pregnant women, 6 of them with gestational hypertension.	No LDA (only 27% received)	Congenital heart block: 1 Pregnancy loss: 1 out of 6 patients with hypertension (17%) Preterm birth: 10
Maternal outcomes	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertensive, 43.2% with nephritis Secondary APS: 54.1% ACL (IgM): 40.5% ACL (IgG): 48.6% LAC: 24.3%	LDA (89.2%)	Pre-eclampsia: 8/37 (19.4%)

	7570, Gaballa, 2012[3]	Prospective observational	March 28 to October 2010	40 SLE pregnant women, 6 of them with gestational hypertension.	No LDA (only 27% received)	Antenatal SLE flare up during pregnancy: 21/32 (65%) of all patients Pre-eclampsia: 8/37 (19.4%) of all patients Postpartum flare: 8/37 (35.5%) of all patients

108. In women with RD who are considering pregnancy and aPL(+) but not meeting modified Sapporo APS criteria, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

Summary: This PICO question is addressed by one direct RCT[6], one direct observational[7] and two indirect RCTs[8,9] and one indirect observational study[10]. In a direct RCT the outcome results are mixed, some slightly favoring placebo patients, the others favoring LDA, but the results are highly imprecise due to small sample size. The following outcomes: *pregnancy loss, gestational hypertension, and congenital anomalies* slightly favor placebo over LDA therapy with OR=1.42 (0.27 to 7.34), 1.08 (0.18 to 6.32), and 1.07(0.06 to 18.62) respectively. Preterm birth mean value significantly favors placebo OR=6.03 (0.27 to 135.99), SGA significantly favors the LDA group OR= 0.22 (0.02 to 2.19) but the results are highly imprecise.

In a direct observational study[7] the rates of Pregnancy loss were similar in LDA group 4/19 (21.1%) and in no-LDA group 6/29 (20.7%), the rate of Hypertensive disease was higher in LDA group 5/19 (26.3%) compared to no-LDA group 3/29 (10.3%).
In the Rai 1997 study[8] the rate of miscarriages in LDA group was 26/45 (58%), in Goel 2006[9] the rate of pregnancy loss was 38.5%, preterm delivery (before 37 wga) 2/39 (5%). 2 had preeclampsia (5%). There was no control group that didn't receive LDA.
Another study[10] compared rates of pregnancy loss between aPL(+) patients treated with LDA, which was 0, to patients with aPL(-) which was 5%.

Quality of Evidence across outcomes: Low.

Table 1: RCT

LDA compared to no LDA- for pregnant women with aPL
Bibliography: PICO 5e for pregnant women with aPL treated.

Certainty assessment							Summary of findings		
№ of participants	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**		**Study event rates (%)**		**Anticipated absolute effects**

(studies) Follow-up						Overall certainty of evidence	With no LDA- APL syndrome	With LDA	Relative effect (95% CI)	Risk with no LDA-APL syndrome	Risk difference with LDA
Pregnancy loss											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/20 (15.0%)	4/20 (20.0%)	OR 1.42 (0.27 to 7.34)	150 per 1,000	**50 more per 1,000** (105 fewer to 414 more)
Preterm birth											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	0/17 (0.0%)	2/16 (12.5%)	OR 6.03 (0.27 to 135.99)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Gestational HTN											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	3/17 (17.6%)	3/16 (18.8%)	OR 1.08 (0.18 to 6.32)	176 per 1,000	**11 more per 1,000** (139 fewer to 399 more)
SGA											
33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	4/17 (23.5%)	1/16 (6.3%)	OR 0.22 (0.02 to 2.19)	235 per 1,000	**172 fewer per 1,000** (229 fewer to 167 more)
Congenital anomalies											

33 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	1/17 (5.9%)	1/16 (6.3%)	OR 1.07 (0.06 to 18.62)	59 per 1,000	**4 more per 1,000** (55 fewer to 479 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

b. Wide CI crossing significant effect and no-effect lines

References: 2897 Pattison 2000

Table 2: Observational studies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	4746 Out, 1992[7]	Observational **Direct**		aPL n=48	LDA vs. No LDA In the LDA group 3 were treated with heparin instead of LDA	**LDA n=19** Pregnancy loss: 4/19 (21.1%) **No LDA n=29** Pregnancy loss: 6/29 (20.7%)
	3343, Carmona 1999[10]	Prospective Cohort study Indirect	11 years	46 SLE patients in Spain with 60 pregnancies, of whom 16 were SLE patients with aPL	All 16 patients with aPL+ received LDA from 1 month before attempting conception and throughout pregnancy	Outcome assessed: Pregnancy loss (spontaneous abortion, stillbirth) • 0 patients in aPL+ group had miscarriage (all treated with LDA) • 5% spontaneous abortion rate (<20 weeks) among aPL- group (not treated with LDA)
	2967 Rai 1997[8]	RCT Indirect	2 years	90 women with history of recurrent miscarriage (>/=3) and persistently positive APL antibodies	LDA vs. LDA+5,000 U heparin BID	26/45 (58%) miscarriages in LDA group

	3311 Goel 2006[9]	RCT Indirect	Patients were followed until delivery	450 pregnant women with h/o 2 or more SAB, 100 women had h/o 1 or more live births and no h/o abortion (controls). 72 patients in the study group had positive ACL IGG	The 72 women with +ACL were randomized to receive aspirin 80mg versus aspirin + heparin 5000 q12h	Of the 39 patients who received LDA, 24 (61.5%) had a live birth. 38.5% pregnancy loss. 2 babies were delivered preterm (before 37 wga). 2 had preeclampsia. There was no control group that didn't receive LDA. Additionally, some of these patients may have met criteria for APS(mean number of previous miscarriages was 2.85+/-1.16), which is not part of this PICO
Maternal outcomes	4746 Out, 1992[7]	Observational **Direct**		aPL n=48	LDA vs. No LDA In the LDA group 3 were treated with heparin instead of LDA	**LDA n=19** Hypertensive disease: 5/19 (26.3%) **No LDA n=29** Hypertensive disease: 3/29 (10.3%)

109. In women with SLE who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes? **GS56**

Summary: This PICO question is addressed by one direct[11] and three indirect observational studies[1,3,4]. In a direct observational study[11], the outcomes for patients receiving LDA have less beneficial effects across all outcomes except SGA that favors LDA group (Hypertensive disorders: LDA 23% vs no-LDA 9% (RR=2.55); Preterm birth: LDA 43% vs no-LDA 16.7% (RR=2.57); IUFD: LDA 6.7% vs no-LDA 1.5% (RR=4.47); SGA: 6.7% vs 18% (RR=0.37)). Two indirect studies did not have comparisons, all patients in Moroni 2016 study[1] received LDA, while most of patients in another study[3] did not receive LDA. Comparing the outcomes between those two studies, the outcomes that favored LDA group were: the rate of pregnancy loss in patients receiving LDA was 12 (16.4%) vs in patients not receiving LDA was 8/40 (20%), RR=0.82; preeclampsia: 6 (8.4%) vs 8/37 (19.4%), RR=0.43; total flares 24% and 35.5%, RR=0.68; the outcomes that favored no-LDA group: preterm births in LDA group 30.0% vs in no-LDA 10/40 (25%), RR=1.2, but the quality of evidence for those comparisons is very low. In another indirect study[4] patients receiving LDA during pregnancy had pregnancy loss adj RR 0.11 (0.03-0.38), p=0.003, which has a protective effect. Given all this information, the LDA is likely to have a protective effect on pregnancy loss, SGA, pre-eclampsia, total flares, and a harmful effect on Hypertensive disorders, preterm birth, and IUFD.

Quality of Evidence across outcomes: Very low.

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	2358, Abheiden, 2007[11]	Cohort study **Direct**		SLE without aPL n=88 SLE with aPL n=8	LDA vs. No LDA	**LDA n=30** Hypertensive disorders n=7 (23%) Preterm birth n=13 (43%) IUFD n=2 (6.7%) SGA n=2 (6.7%) **No LDA n=66** Hypertensive disorders n=6 (9%) Preterm birth n=11 (16.7%) IUFD n=1 (1.5%) SGA n=12 (18%)
	2346 Moroni 2016[1] Indirect	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	All patients received aspirin during pregnancy and 4 were given low molecular weight heparin	**Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%) • Small for gestational age: 12 (16.4%) • Mean birth weight (SD): 2753 (683) g • Neonatal cutaneous lupus: 0 (0%) • Congenital heart-block: 0 (0%)
	3635 Imbasciati 2009[4] Indirect	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN	Various LDA used during 68 pregnancies (60%)	Note: 27/74 women had LAC or ACL Ab+ (36%) Predictors of adverse fetal and maternal outcomes: LDA during pregnancy – pregnancy loss: adj RR 0.11 (0.03-0.38), p=0.003—protective

						This was seen in univariate and adjusted models (univariate RR not presented, but p=0.006).
	7570, Gaballa, 2012[3] Indirect	Prospective observational	March 28 to October 2010	40 SLE pregnant women with renal disease (n=9) and gestational hypertension (n=6)	No LDA (only 27% received)	Congenital heart block: 1 Pregnancy loss: 8 (3 spontaneous abortion, 5 stillbirth) Preterm birth: 10
Maternal outcomes	2346 Moroni 2016[1] Indirect	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	All patients received aspirin during pregnancy and 4 were given low molecular weight heparin	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%) • Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%) • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%)
	7570, Gaballa, 2012[3] Indirect	Prospective observational	March 28 to October 2010	40 SLE pregnant women with renal disease (n=9) and gestational hypertension (n=6)	No LDA (only 27% received)	Antenatal SLE flare up during pregnancy: 21/32 (65%) of all patients Pre-eclampsia: 8/37 (19.4%) of all patients Postpartum flare: 8/37 (35.5%) of all patients

110. In women with Systemic sclerosis who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

No evidence.

111. In women with RA and other inflammatory arthritis who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

No evidence.

112. In women with Vasculitis who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

No evidence.

113. In women with myositis who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

No evidence.

114. In women with Sjogren's disease who are pregnant, what is the impact of treatment with low-dose aspirin (LDA) versus no LDA on maternal and pregnancy outcomes?

No evidence.

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5F.

5F. In women with SLE who are considering pregnancy or are pregnant [variables listed], what is the impact of treatment with HCQ throughout pregnancy versus no such treatment with HCQ on maternal and pregnancy outcomes [listed]?

Population: Women with SLE who are considering pregnancy or are pregnant
SLE without renal disease or aPL
SLE with renal disease
SLE with aPL

Intervention: HCQ

Comparator: Similar patients who are not treated with HCQ

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of SLE

- Damage from SLE
- Maternal morbidity
- Maternal mortality

115. In women with SLE without renal disease or aPL who are considering pregnancy or are pregnant, what is the impact of treatment with HCQ throughout pregnancy versus no treatment with HCQ on maternal and pregnancy outcomes? **EVIDENCE FOR GS57**

This PICO is addressed by evidence from observational studies only. There were a total of 21 studies included.

- Pregnancy loss: spontaneous abortion, stillbirth (15 studies)[1-15]
- Gestational hypertensive disease including preeclampsia (9 studies)[1,5,6,8,9,11,14,16,17]
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks (14 studies)[1-8,10-12,14,16,17]
- Induced labor (2 studies)[9,16]
- Premature rupture of membranes (4 studies) [1,6,9,11]
- Small for gestational age infants (SGA) (2 studies)[2,7]
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG) (8 studies) [3,8-11,15,17,18]
- Flare of SLE (12 studies)[1,2,5,8-11,14,16,17,19,20]
- Damage from SLE (2 studies)[1,17]
- Maternal morbidity (2 studies)[16,17]
- Maternal mortality (4 studies)[1,7,12,17]

Three observational studies found that rates of SLE flare were significantly lower in patients taking HCQ relative to those not taking HCQ (OR=0.58; 95% CI: 0.37 to 0.91) [1-3] Similarly, one observational study found that rates of SLE Flare were significantly lower in patients continuing HCQ relative to those not stopping HCQ during pregnancy (OR=0.37; 95% CI:0.15 to 0.88).[2] One

observational study found lower rates of intrauterine growth restriction (IUGR) in patients taking HCQ relative to those not taking HCQ (OR=0.14; 95% CI: 0.05 to 0.44)[1] However, one observational study reported higher rates of live births in patients not taking HCQ relative to those who were (OR=0.26; 95% CI: 0.13 to 0.50),[3] and two observational studies found lower rates of miscarriage in patients not taking HCQ relative to those who were (OR=2.38; 95% CI: 1.33 to 4.26).[1,3] The authors suggest, however, that these differences may be related to maternal illness rather than HCQ intake.

For the remainder of outcomes, no statistically significant statements can be made regarding whether use of HCQ vs. no HCQ throughout pregnancy is beneficial or harmful.

Quality of evidence across outcomes: Low to Very low

HCQ compared to no HCQ for women with SLE on maternal and pregnancy outcomes

Bibliography: PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no HCQ	**With HCQ**		**Risk with no HCQ**	**Risk difference with HCQ**
Preterm birth <32 wks											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	2/77 (2.6%)	0/41 (0.0%)	**OR 0.36** (0.02 to 7.76)	26 per 1,000	**16 fewer per 1,000** (25 fewer to 145 more)
Preterm birth <37 wks											
346 (2 observational studies)	not serious	serious [b]	not serious	not serious	none	⨁◯◯◯ VERY LOW	116/253 (45.8%)	25/93 (26.9%)	**OR 0.46** (0.27 to 0.77)	458 per 1,000	**178 fewer per 1,000** (272 fewer to 64 fewer)
Preterm delivery											

HCQ compared to no HCQ for women with SLE on maternal and pregnancy outcomes

Bibliography: PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
508 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	33/413 (8.0%)	27/95 (28.4%)	**OR 4.57** (2.58 to 8.09)	80 per 1,000	**204 more per 1,000** (103 more to 333 more)
Fetal death											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	3/77 (3.9%)	3/41 (7.3%)	**OR 1.95** (0.37 to 10.11)	39 per 1,000	**34 more per 1,000** (24 fewer to 252 more)
Live births											
569 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	434/455 (95.4%)	96/114 (84.2%)	**OR 0.26** (0.13 to 0.50) Favors no-HCQ	954 per 1,000	**111 fewer per 1,000** (225 fewer to 42 fewer)
Miscarriage											
798 (2 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	34/631 (5.4%)	20/167 (12.0%)	**OR 2.38** (1.33 to 4.26) Favors no-HCQ	54 per 1,000	**65 more per 1,000** (17 more to 141 more)
Stillbirth											

HCQ compared to no HCQ for women with SLE on maternal and pregnancy outcomes

Bibliography: PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
798 (2 observational studies)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	20/631 (3.2%)	4/167 (2.4%)	**OR 0.68** (0.23 to 2.06)	32 per 1,000	**10 fewer per 1,000** (24 fewer to 31 more)
IUGR											
118 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	33/77 (42.9%)	4/41 (9.8%)	**OR 0.14** (0.05 to 0.44) Favors HCQ	429 per 1,000	**334 fewer per 1,000** (392 fewer to 180 fewer)
Gestational HTN including pre-eclampsia											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	14/77 (18.2%)	3/41 (7.3%)	**OR 0.36** (0.10 to 1.32)	182 per 1,000	**108 fewer per 1,000** (160 fewer to 45 more)
PROM											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	12/77 (15.6%)	4/41 (9.8%)	**OR 0.59** (0.18 to 1.95)	156 per 1,000	**58 fewer per 1,000** (124 fewer to 109 more)
SLE flare											
448 (3 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	129/304 (42.4%)	46/144 (31.9%)	**OR 0.58** (0.37 to 0.91) Favors HCQ	424 per 1,000	**125 fewer per 1,000** (210 fewer to 23 fewer)

HCQ compared to no HCQ for women with SLE on maternal and pregnancy outcomes

Bibliography: PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes.

Certainty assessment							Summary of findings				
SLE damage - renal											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	5/77 (6.5%)	7/41 (17.1%)	**OR 2.96** (0.88 to 10.02)	65 per 1,000	**106 more per 1,000** (7 fewer to 345 more)
Maternal mortality											
118 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	0/77 (0.0%)	0/41 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Major anomalies											
537 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	15/440 (3.4%)	7/97 (7.2%)	**OR 2.20** (0.87 to 5.56)	34 per 1,000	**38 more per 1,000** (4 fewer to 130 more)
SGA											
228 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	36/176 (20.5%)	11/52 (21.2%)	**OR 1.04** (0.49 to 2.23)	205 per 1,000	**6 more per 1,000** (93 fewer to 160 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

b. High I square

References: 2423 Leroux 2015; 2746 Clowse 2006; 2515 Diav-Citrin 2013; 7642 Hwang 2017

HCQ continued vs stopped impact on pregnancy and maternal outcomes for women with SLE

Bibliography: . PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With HCQ stopped	With HCQ continued		Risk with HCQ stopped	Risk difference with HCQ continued
Miscarriage											
89 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	4/37 (10.8%)	7/52 (13.5%)	**OR 1.28** (0.35 to 4.75)	108 per 1,000	**26 more per 1,000** (67 fewer to 257 more)
Stillbirth											
89 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	3/37 (8.1%)	3/52 (5.8%)	**OR 0.69** (0.13 to 3.65)	81 per 1,000	**24 fewer per 1,000** (70 fewer to 163 more)
Preterm birth											
89 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	18/37 (48.6%)	19/52 (36.5%)	**OR 0.61** (0.26 to 1.43)	486 per 1,000	**120 fewer per 1,000** (289 fewer to 89 more)
SGA											

HCQ continued vs stopped impact on pregnancy and maternal outcomes for women with SLE

Bibliography: . PICO 5f impact of HCQ treatment throughout pregnancy for women with SLE on maternal and pregnancy outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
89 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	7/37 (18.9%)	11/52 (21.2%)	**OR 1.15** (0.40 to 3.31)	189 per 1,000	**22 more per 1,000** (104 fewer to 247 more)
SLE flare											
89 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	21/37 (56.8%)	17/52 (32.7%)	**OR 0.37** (0.15 to 0.88) Favors continued HCQ	568 per 1,000	**241 fewer per 1,000** (403 fewer to 32 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

References: 2746 Clowse 2006

Direct

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy Loss	2903, Georgiou 2000[4]	Case-control	Perinatal period	47 pregnant SLE patients with 57 pregnancies compared with 59 non-pregnant control SLE patients	8 pregnant and 16 non-pregnant patients treated with HCQ (200mg/day). Other treatments included: prednisone – 26, azathioprine – 1.	**These outcomes are not associated with the HCQ or any other medication use, since just a small number of patients used HCQ and in both groups** **Therapeutic abortions**: pregnant with SLE – 3 (6%), 3 with active SLE; healthy pregnant women – 2 (3%) **Spontaneous abortions**: pregnant with SLE – 9 (19%), among them 2 with active SLE, 7 with non-active SLE); healthy pregnant women – 2 (3%) **Stillbirths**: pregnant with SLE – 1 (2%), 1 with active SLE; healthy pregnant women – 8 (19%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						Total fetal loss: pregnant with SLE – 13 (28%), 6 with active SLE, 7 with non-active SLE); healthy pregnant women – 3 (5%)
	5342 Chakravarty 2005[5]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used Plaquenil versus none (fetal outcomes): No events reported for fetal loss or 5-minute Agpar<7 Small numbers in Plaquenil group. Surprising that Plaquenil was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe. Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%).
Pre-term birth	2903, Georgiou 2000[4]	Case-control	Perinatal period	47 pregnant SLE patients with 57 pregnancies compared with 59 non-pregnant control SLE patients	8 pregnant and 16 non-pregnant patients treated with HCQ (200mg/day). Other treatments included: prednisone – 26, azathioprine – 1.	**Premature deliveries**: pregnant with SLE – 3 (6%), 1 with active SLE, 3 with non-active SLE); healthy pregnant women – 8 (19%)
	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day	**Fetal outcomes**: Prematurity : HCQ group 17 (55%), control 21 (48%)
	5342 Chakravarty 2005[5]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used Plaquenil versus none (fetal outcomes): Prematurity RR 1.1 (0.6-2.0) Small numbers in Plaquenil group. Surprising that Plaquenil was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%).
IUGR	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day	IUGR: HCQ group 6 (19%), control 18 (41%)
Gestational hypertensive disease including preeclampsia	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day	Hypertension: HCQ group 8 (24%), control 20 (38%) Pre-eclampsia: HCQ group 1 (3%), control 20 (38%)
	5342 Chakravarty 2005[5]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used Plaquenil versus none: Preeclampsia RR 1.2 (0.4-3.7) So Plaquenil use was not associated with adverse maternal outcomes. Small numbers in Plaquenil group. Surprising that Plaquenil was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe. Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%).
Induced labor	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with	HCQ 200 mg/day	Induction of delivery: HCQ group 19 (61%), control 26 (59%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				HCQ , and 53 controls		
Flare of SLE	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day	Total number of flares: HCQ group 21 (62%), 31 (58%) Renal flare only: HCQ group 4 (12%), control 6 (11%)
	5342 Chakravarty 2005[5]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used Plaquenil versus none: Risk of flare RR 1.1 (0.8-1.7) Risk of severe flare RR 0.7 (0.2-2.8) So Plaquenil use was not associated with adverse maternal outcomes. Small numbers in Plaquenil group. Surprising that Plaquenil was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe. Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%).
Maternal Morbidity	2978, Buchanan 1996[16],	Case-control	Perinatal period	33 SLE patients with 36 pregnancies treated with HCQ , and 53 controls	HCQ 200 mg/day	Thrombosis: HCQ group 1 (3%), control 2 (4%)

Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy Loss	2684 Teh 2009[6]	observational	Pregnancy	17 pregnancies in 16 patients with SLE at Sarawak General Hospital in Sarawak, Malaysia, between 2006-2007	75% received HCQ	3/17 fetal loss Outcomes not stratified by use of HCQ
	3690, Clowse 2005[7]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	In 1/3 of the pregnancies, the women were treated with hydroxychloroquine.	Outcomes by disease activity: Live births: High 44 (77%), Low 185 (88%), RR= 0.88 [0.75, 1.02] Perinatal mortality: High 9 (16%), Low 10 (5%), RR= 3.32 [1.41, 7.77] Miscarriage: High 4 (7%), Low 15 (7%), RR= 0.98 [0.34, 2.85]
	2790, Molad, 2005[8]	Prospective observational	1987 to 2002, Lupus Clinic of Rabin Medical Center, Petah Tiqva, Israel	20 pregnant women with SLE (29 pregnancies)	No HCQ (25.9%), no subgroup data	Spontaneous abortion: 6 (20.7%)
	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	Intrauterine death: 5 Spontaneous abortion: 7 (37%)
	7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	No HCQ (46%); no subgroup data	Fetal death: 7 (8%) Spontaneous abortion: 9 (10%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Spontaneous abortion: 47 (19.9%) <u>Prospective arm (2010 to 2015)</u> Spontaneous abortion: 18 (8.4%)
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%)
	5608 Le Thi Huong 1994[12]	Observational, prospective	1987-1992, France	117 pregnancies among SLE mothers	Various treatments. 11 patients were pregnant while using HCQ (200-400 mg qd)	Of 117 cases, 103 were analyzed. Pregnancy outcome: 28 full-term births, 18 fetal losses (13 early, 2 late, 3 stillbirth), 5 therapeutic abortions, 4 elective abortions. **HCQ was maintained in only 2 pregnancies (no ocular or vestibular problems in infants). Except in the case of induced abortion, HCQ was stopped because prednisone was started at a dosage of 10 mg/d upon diagnosis of pregnancy among all other patients.** **<u>Note</u>**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables. No correlates of maternal or pregnancy outcomes were assessed for HCQ as almost all women stopped taking HCQ during the course of their pregnancies.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2711 Silva 2008[13]	observational	Pregnancy	315 patients with juvenile SLE followed in 12 Brazilian pediatric rheumatology centers; total of 24 unplanned pregnancies occurred	Inadvertently given IVCYC Prednisone AZA Antimalarial	24 unplanned pregnancies: 5 early fetal losses 18 live births 1 fetal death due to preeclampsia and premature birth Antimalarials: 3/5 (60%), 12/18 (67%)
	3376 Kroese 2017[14]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All	HCQ use during pregnancy: n=54	In 54 pregnancies, HCQ was used. Comparing the treatment before and after 2008, the use of HCQ during pregnancy increased: 16% received HCQ before 2008 and 58% after 2008 ($p < 0.01$). IUFD ($p = 0.20$) did not differ before and after 2008. **Note: No data on differences in pregnancy outcome by use of HCQ

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertension was scored by a gynecologist. <u>Mild hypertensive disease</u>: hypertensive disorders of pregnancy including pregnancy induced hypertension <u>Severe hypertensive disease</u>: hypertensive disorders of pregnancy including preeclampsi		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				a, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome) n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				• 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years Non-Caucasian: 16.5% Chronic hypertension: 14.1% Diabetes: 3.5%) History of thrombosis: 16.0%) History of nephritis: 39.6%		
	3049 Buchanan 1992[15]	Consecutive patients seen at a lupus pregnancy clinic	4-year period	n=76 patients with 100 pregnancies: 66 with SLE (ACR criteria), 7 with “lupus-like illness,” and 3 with primary APS	n=8 treated with HCQ during pregnancy	• 100% had disease activity during pregnancy • Fetal loss: 1 (12.5%) • Live births: 7 (87.5%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Median age of 8 patients taking HCQ: 30 (range: 22-35) years		
Pre-term birth	2684 Teh 2009[6]	observational	Prengnacy	17 pregnancies in 16 patients with SLE at Sarawak General Hospital in Sarawak, Malaysia, between 2006-2007	75% received HCQ	2/17 preterm birth Outcomes not stratified by use of HCQ
	3690, Clowse 2005[7]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	In 1/3 of the pregnancies, the women were treated with hydroxychloroquine.	Extreme prematurity: High 10 (17%), 13 (6%), RR= 2.83 [1.31, 6.12] Prematurity: High 28 (49%), Low 55 (26%), RR= 1.88 [1.32, 2.66]
	2790, Molad, 2005[8]	Prospective observational	1987 to 2002, Lupus Clinic of Rabin Medical Center, Petah Tiqva, Israel	20 pregnant women with SLE (29 pregnancies)	No HCQ (25.9%), no subgroup data	Preterm birth: 4 (17.4%)
	7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	No HCQ (46%); no subgroup data	Preterm birth: 12 (13%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Preterm birth: 96 (40.7%) <u>Prospective arm (2010 to 2015)</u> Preterm birth: 46 (21.5%)
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	Preterm birth: 12/37 (32.4%)
	5608 Le Thi Huong 1994[12]	Observational, prospective	1987-1992, France	117 pregnancies among SLE mothers	Various treatments. 11 patients were pregnant while using HCQ (200-400 mg qd)	Of 117 cases, 103 were analyzed. Pregnancy outcome: 48 premature births, **HCQ was maintained in only 2 pregnancies (no ocular or vestibular problems in infants). Except in the case of induced abortion, HCQ was stopped because prednisone was started at a dosage of 10 mg/d upon diagnosis of pregnancy among all other patients.** **<u>Note</u>**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables. No correlates of maternal or pregnancy outcomes were assessed for HCQ as almost all women stopped taking HCQ during the course of their pregnancies.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3376 Kroese 2017[14]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertensio	HCQ use during pregnancy: n=54	In 54 pregnancies, HCQ was used. Comparing the treatment before and after 2008, the use of HCQ during pregnancy increased: 16% received HCQ before 2008 and 58% after 2008 ($p < 0.01$). Preterm birth < 37 weeks ($p = 0.75$) did not differ before and after 2008. **Note: No data on differences in pregnancy outcome by use of HCQ

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n was scored by a gynecologist. Mild hypertensive disease: hypertensive disorders of pregnancy including pregnancy induced hypertension Severe hypertensive disease: hypertensive disorders of pregnancy including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome)		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies • 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Non-Caucasian: 16.5% Chronic hypertension: 14.1% Diabetes: 3.5%) History of thrombosis: 16.0%) History of nephritis: 39.6%		
IUGR	2684 Teh 2009[6]	observational	Prengnacy	17 pregnancies in 16 patients with SLE at Sarawak General Hospital in Sarawak, Malaysia, between 2006-2007	75% received HCQ	5/17 IUGR Outcomes not stratified by use of HCQ
Gestational hypertensive disease including preeclampsia	2684 Teh 2009[6]	observational	Prengnacy	17 pregnancies in 16 patients with SLE at Sarawak General Hospital in Sarawak, Malaysia, between 2006-2007	75% received HCQ	4/17 preeclampsia 1/17 eclampsia Outcomes not stratified by use of HCQ

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	Preeclampsia: 4
	2790, Molad, 2005[8]	Prospective observational	1987 to 2002, Lupus Clinic of Rabin Medical Center, Petah Tiqva, Israel	20 pregnant women with SLE (29 pregnancies)	No HCQ (25.9%), no subgroup data	Gestational hypertension: 2 (8%) Preeclampsia: 1 (3.7%)
	7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	No HCQ (46%); no subgroup data	Pre-eclampsia: 12 (13%)
	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Preeclampsia: 68 (28.8%) <u>Prospective arm (2010 to 2015)</u> Preeclampsia: 60 (28.1%)
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	Preeclampsia: 8/37 (19.4%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3376 Kroese 2017[14]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertensio	HCQ use during pregnancy: n=54	In 54 pregnancies, HCQ was used. Comparing the treatment before and after 2008, the use of HCQ during pregnancy increased: 16% received HCQ before 2008 and 58% after 2008 ($p < 0.01$). Occurrence of severe HD ($p = 0.31$) did not differ before and after 2008. **Note: No data on differences in pregnancy outcome by use of HCQ

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n was scored by a gynecologist. Mild hypertensive disease: hypertensive disorders of pregnancy including pregnancy induced hypertension Severe hypertensive disease: hypertensive disorders of pregnancy including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome)		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies • 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Non-Caucasian: 16.5% Chronic hypertension: 14.1% Diabetes: 3.5%) History of thrombosis: 16.0%) History of nephritis: 39.6%		
Induced labor	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	Induced labor: 61 (68%)
PROM	2684 Teh 2009[6]	observational	Prengnacy	17 pregnancies in 16 patients with SLE at Sarawak General Hospital in Sarawak, Malaysia, between 2006-2007	75% received HCQ	1/17 premature labor Outcomes not stratified by use of HCQ
	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	PROM: 4 (7%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	PROM: 9/37 (24%)
SGA	3690, Clowse 2005[7]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	In 1/3 of the pregnancies, the women were treated with hydroxychloroquine.	Small for gestational age baby: High 13/44 (30%), Low 38/183 (21%), RR= 1.42 [0.83, 2.43]
Fetal/Neonatal effects	3360 Derksen 1994[18]	Observational	1987-1993	Women with **SLE** (1982 ARA criteria) Patients who followed at a Lupus Clinic for 6 months prior to conception were prospectively followed through pregnancy n=25 patients had 35 pregnancies	Antimalarials used at conception in 10 pregnancies (28.6%); discontinued at median 5 weeks pregnancy (range: 4-10 weeks)	None of the live born infants had signs of neonatal lupus or congenital heart block

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Median age: 30 years (range: 20-37) Median disease duration: 5 years (range: 0.5-16) History of lupus nephritis: 40% of patients and 40% of pregnancies		
	2790, Molad, 2005[8]	Prospective observational	1987 to 2002, Lupus Clinic of Rabin Medical Center, Petah Tiqva, Israel	20 pregnant women with SLE (29 pregnancies)	No HCQ (25.9%), no subgroup data	Neonatal death: 1 due to sepsis
	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	Complete heart block: 1 Complete heart block and rash: 1 Inflammatory myocardiopathy: 1 (child later died after undergoing heart transplant) Neonatal death: 4 (4.5%) of 89 successful pregnancies Neonatal lupus: 9 (8%) of 108 pregnancies Neonatal rash: 6
	7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	No HCQ (46%); no subgroup data	Complete heart block: 0 (0%) Neonatal death: 3 (3)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	Neonatal deaths: 4/30 (13%)
	3049 Buchanan 1992[15]	Consecutive patients seen at a lupus pregnancy clinic	4-year period	n=76 patients with 100 pregnancies: 66 with SLE (ACR criteria), 7 with "lupus-like illness," and 3 with primary APS Median age of 8 patients taking HCQ: 30 (range: 22-35) years	n=8 treated with HCQ during pregnancy	100% had disease activity during pregnancy Neonatal lupus: 2 (25%; one with cutaneous features and one with congenital heart block)
	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Neonatal death: 9 (3.8%) <u>Prospective arm (2010 to 2015)</u> Neonatal death: 1 (0.46%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Flare of SLE	3376 Kroese 2017[14]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertensio	HCQ use during pregnancy: n=54	In 54 pregnancies, HCQ was used. Comparing the treatment before and after 2008, the use of HCQ during pregnancy increased: 16% received HCQ before 2008 and 58% after 2008 ($p < 0.01$). Flare rate during pregnancy ($p = 0.09$)) did not differ before and after 2008. **Note: No data on differences in pregnancy outcome by use of HCQ

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n was scored by a gynecologist. Mild hypertensive disease: hypertensive disorders of pregnancy including pregnancy induced hypertension Severe hypertensive disease: hypertensive disorders of pregnancy including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome)		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies • 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Non-Caucasian: 16.5% Chronic hypertension: 14.1% Diabetes: 3.5%) History of thrombosis: 16.0%) History of nephritis: 39.6%		
	7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies)	No HCQ (46%); no subgroup data	Antenatal SLE flare: 40 (44%)
	2991, Ruiz-Irastorza 1996[20]	Case-control	Perinatal period	78 pregnancies in 68 SLE patients and a control group of 50 consecutive, non-pregnant, age-matched SLE patients.	18% of patients in pregnancy group and 48% of patients in control group were on HCQ treatment.	12 renal flares during pregnancy. 8 out of 9 patients (88%) who flared during the year prior to conception flared again during pregnancy. Rate of flares: Pregnancy group 66%, control group 42% The rates of flare per patient/month were 0.093 ± 0.006 during pregnancy and the puerperium, and 0.049 ± 0.0044 during the year after puerperium.
	2994, Lima, 1995[9]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	No HCQ (13%); no subgroup data	Flare: 62 (57%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2790, Molad, 2005[8]	Prospective observational	1987 to 2002, Lupus Clinic of Rabin Medical Center, Petah Tiqva, Israel	20 pregnant women with SLE (29 pregnancies)	No HCQ (25.9%), no subgroup data	Flare (post-gestational): 6 (20.6%)
	6696, Mokbel, 2013[11]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	HCQ	Flare: 21/32 (65%)
	hwang7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Lupus flare: 19 (8.1%) <u>Prospective arm (2010 to 2015)</u> Lupus flare: 7 (3.3%)
Damage from SLE	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> Worsening of renal functions: 65 (27.5%) <u>Prospective arm (2010 to 2015)</u> Worsening of renal functions: 34 (15.8%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Maternal morbidity	7640, Rezk, 2017[17]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	No HCQ (<30% received, no subgroup analysis) Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	<u>Retrospective arm (2005 to 2010)</u> VTE: 38 (16.1%) <u>Prospective arm (2010 to 2015)</u> VTE: 12 (5.6%)
Maternal Mortality	5608 Le Thi Huong 1994[12]	Observational, prospective	1987-1992, France	117 pregnancies among SLE mothers	Various treatments. 11 patients were pregnant while using HCQ (200-400 mg qd)	2 patients died (both had severe nephrotic syndrome, used AZA, and died from infection) **HCQ was maintained in only 2 pregnancies (no ocular or vestibular problems in infants). Except in the case of induced abortion, HCQ was stopped because prednisone was started at a dosage of 10 mg/d upon diagnosis of pregnancy among all other patients.** **<u>Note</u>**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables. No correlates of maternal or pregnancy outcomes were assessed for HCQ as almost all women stopped taking HCQ during the course of their pregnancies.
	3690, Clowse 2005[7]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	In 1/3 of the pregnancies, the women were treated with hydroxychloroquine.	**Maternal mortality** - 3 out of 267 pregnancies (0.011%, or 11 per 1,000 pregnancies)
	7640, Rezk, 2017[17]	Observational (1 retrospective	2005 to 2010 (retrospective)	460 pregnant SLE patients (	No HCQ (<30% received, no subgroup analysis)	<u>Retrospective arm (2005 to 2010)</u> Maternal mortality: 6 (2.5%) <u>Prospective arm (2010 to 2015)</u>

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		arm, 1 prospective arm)	2010 to 2015 (prospective)	236 retrospective, 214 prospective)	Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%)	Maternal mortality: 1 (0.46%)

31. In women with SLE with aPL who are considering pregnancy or are pregnant, what is the impact of treatment with HCQ throughout pregnancy versus no such treatment with HCQ on maternal and pregnancy outcomes? **GS57**

This PICO was addressed by one single arm study with limited power. There is no mention as to whether the APS patients were treated with HCQ or some other drug.[7]

Quality of evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy Loss	3690, Clowse 2005[7]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	In 1/3 of the pregnancies, the women were treated with hydroxychloroquine	**Perinatal deaths** - 20% with APS versus 6% without APS.

116. In women with SLE with renal disease who are considering pregnancy or are pregnant, what is the impact of treatment with HCQ throughout pregnancy versus no such treatment with HCQ on maternal and pregnancy outcomes? **GS57**

This PICO was addressed by 3 indirect observational studies.[21-23] Flare of SLE, pregnancy loss, preterm birth, SGA, and preeclampsia were the outcomes addressed by the studies. No statistically significant statements can be made regarding whether HCQ vs. no HCQ is beneficial or not.

Quality of evidence across outcomes: Very low

Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Flare of SLE	3413 Moroni, 2016[21]	Cohort study	Not mentioned	37 lupus nephritis patients taking HCQ	HCQ	**Predictor Renal flare** Relative risk ratio 0.98 95% CI 0.296 – 3.299 P 0.98
	2882, Huong 2001[23]	Retrospective study	Perinatal period	32 pregnancies in 22 women with past or present histologically proven SLE nephritis	11 patients on HCQ. Other treatments included prednisone (n=31), aspirin (n=22), heparin (n=12), and azathioprine (1)	1 woman a proliferative glomerulonephritis occurred while receiving hydroxychloroquine
Pregnancy Loss	2882, Huong 2001[23]	Retrospective study	Perinatal period	32 pregnancies in 22 women with past or present histologically proven SLE nephritis	11 patients on HCQ. Other treatments included prednisone (n=31), aspirin (n=22), heparin (n=12), and azathioprine (1)	The outcome of 6 non-planned pregnancies: 1 feto-maternal death, 1 embryonic loss, 1 fetal death, The outcome of the 25 planned pregnancies: 4 embryonic losses, 1 fetal death
Preterm birth	2882, Huong 2001[23]	Retrospective study	Perinatal period	32 pregnancies in 22 women with past or present histologically proven SLE nephritis	11 patients on HCQ. Other treatments included prednisone (n=31), aspirin (n=22), heparin (n=12), and azathioprine (1)	The outcome of 6 non-planned pregnancies: 4 premature births The outcome of the 25 planned pregnancies: 14 premature births (one twin),

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
SGA	2346 Moroni 2016[22]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians)	Hydroxychloroquine: 37 (54.4%)	The probability of having a baby which was small for gestational age (n=12; 16.4%) was 85% reduced in patients who received hydroxychloroquine during pregnancy (OR: 0.15; 95% CI: 0.03, 0.77) *note: results not stratified by patients who did and did not taking HCQ during pregnancy

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months		
Preeclampsia	3413 Moroni, 2016[21]	Cohort study	Not mentioned	37 lupus nephritis patients taking HCQ	HCQ	**Predictor of preeclampsia/HELLP** Relative risk ratio 0.29 95% CI 0.052 – 1.686 P 0.17

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5G. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of checking autoantibodies [listed] prior to or early in pregnancy versus not checking these antibodies on maternal and pregnancy outcomes?

Population: Women with SLE, PSS, SS, or RA who are considering pregnancy or are pregnant

Interventions: Checking autoantibodies
aPL (aCL IgG, IgM, antib2GPI IgG, IgM, LAC)
Anti-Ro/La

Comparator: Similar patients who do not have these autoantibodies checked

Outcomes:
Pregnancy loss: spontaneous abortion, stillbirth
MBD
Gestational hypertensive disease including preeclampsia
Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
Induced labor
Premature rupture of membranes
Small for gestational age infants (SGA)
Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
Long-term offspring effects
Maternal thrombotic event (aPL)
Maternal morbidity
Maternal mortality

- Neonatal lupus (anti-Ro/La)

5H. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of repeated checking of autoantibodies [listed] during pregnancy as compared to not rechecking these antibodies (i.e. checking only once before or early in pregnancy) on maternal and pregnancy outcomes?

- Population: Women with SLE, Sjogren's syndrome, systemic sclerosis, or RA who are pregnant

Interventions: Re-checking autoantibodies (more than the one time preparing for or early in pregnancy)
aPL (aCL IgG, IgM; antib2GPI IgG, IgM; LAC)
Anti-Ro/La

Comparator: Similar patients who do not have these autoantibodies repeated.

Outcomes:
Pregnancy loss: spontaneous abortion, stillbirth
MBD
Gestational hypertensive disease including preeclampsia
Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
Induced labor
Premature rupture of membranes
Small for gestational age infants (SGA)
Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
Long-term offspring effects
Maternal thrombotic event (aPL)
Neonatal lupus (anti-Ro/La)
Maternal mortality
Maternal morbidity

117. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of checking aPL (aCL IgG, IgM, antib2GPI IgG, IgM, LAC) autoantibodies prior to or early in pregnancy versus not checking these antibodies on maternal and pregnancy outcomes?

There are no studies that directly address this issue, as there are no studies that evaluate pregnancy outcomes in women with these diseases who do not have antibodies checked. There are some descriptive studies that compare pregnancy outcomes by antibody status, but all outcomes are reported in patients with known antibody status. Data is indirect at best. **EVIDENCE FOR GS59**

Quality of Evidence across outcomes: Very low

Table 1: APL/LAC antibodies: Indirect evidence

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	33 pregnancies tested for APL (LAC, aCLAb, aCLP2-GPIAb).	Twelve of 33 pregnancies (36.4%) pregnancies tested positive for aPL. All 12 had live births, including two premature deliveries [24, 36 weeks of gestation (GW)], two SGA

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					45 pregnancies tested for anti-SSA/SSB.	neonates, and one NLE neonate at term delivery. Twenty-eight of the 45 pregnancies (62.2%) tested positive for maternal anti-SS-A antibody. In the 28 anti-SS-A antibody-positive pregnancies, five (1 7.9%) presented with NLE, whereas NLE was not observed in the pregnancies with a negative test for anti-SS-A antibody. Six (15.0%) of the 40 pregnancies were positive for maternal anti-SS-B antibody, and two (33.3%) of six developed NLE. Four of five NLE cases had only lupus erythema, and the other one developed lupus erythema and CCAVB.
	4283, Kim and Lee, 2008[2]	Retrospective Case Control study	Duration unclear; Included women who delivered between 2000 to 2005	Lupus cohort: 28 neonates born to 27 pregnant women with lupus Control group: 66 neonates born to 66 age-and-sex matched pregnant women	aPL testing: VDRL, lupus anticoagulant, aCL testing	Among the lupus cohort: aPL positive neonates (n=6): 0 with SGA aPL negative neonates (n=22): 7 with SGA
	2324 Saccone 2017[3]	Multicenter retrospective cohort	Pregnancy and delivery	Primary APL syndrome	Checking apl antibodies (all patients treated with Heparin and ASA)	750 pregnancies -640/750=85.3% single positive antibody -362/640=34.8% live birth -110/750=14.7 >1 positive antibody -45/110=40.9% live birth
	3306 Mecacci 2009[4]	Retrospective cohort	Pregnancy and delivery	SLE complicated by APL antibodies	Checking apl antibodies in sle patients 57women, 7 had known aps syndrome 31/57=54% aPL neg-no treatment 20/57=35% aPL pos (treated with hep alone)	aPL pos pregnancies - 17/20=85% live birth - 5/20=25% preterm delivery - 3/20=15% low birth weight (<5%) aPL neg pregnancies: - 28/34=82.3% live birth - 8/34=23.5% preterm delivery - 5/34=14.7% low birth weight (<5%)
	3690, Clowse 2005[5]	Case-series	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	Antiphospholipid antibody syndrome (APS) was diagnosed prior to the studied	**Perinatal deaths** - 20% with APS versus 6% without APS.

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					pregnancy in 18 women with 27 pregnancies (10% of pregnancies).	**Gestational age infants** – 39% if diagnosed with lupus during pregnancy versus 20% if diagnosed prior to pregnancy. **Live births** - 83% of pregnancies in women without any active lupus and 90% of pregnancies in those with mild lupus activity. **Fullterm deliveries** - 60% of pregnancies in women without lupus activity and in 61% in those with mild lupus activity. Neither age of the mother, nor duration of SLE prior to the pregnancy, nor the presence of APS had an impact on the incidence of high-activity lupus. Outcomes by disease activity: Live births: High 44 (77%), Low 185 (88%), RR= 0.88 [0.75, 1.02] Perinatal mortality: High 9 (16%), Low 10 (5%), RR= 3.32 [1.41, 7.77] Miscarriage: High 4 (7%), Low 15 (7%), RR= 0.98 [0.34, 2.85] Extreme prematurity: High 10 (17%), 13 (6%), RR= 2.83 [1.31, 6.12] Prematurity: High 28 (49%), Low 55 (26%), RR= 1.88 [1.32, 2.66] Full-term births: High 15 (26%), 127 (61%), RR= 0.44 [0.28, 0.68] Small for gestational age baby: High 13/44 (30%), Low 38/183 (21%), RR= 1.42 [0.83, 2.43]
	3706 Rahman 2005[6]	observational	Pregnancy	55 pregnancies in 24 patients with pre-existing lupus nephritis	Prednisone, heparin, azathioprine	**APL abs positive in 7 (29%)** of patients. They had 13 pregnancies between them, of which 5 (39%) resulted in spontaneous abortions, compared to 10 (24%) of 42 pregnancies in the APL negative patients.
	4744 Ginsberg 1992[7]	Cross-sectional	March 1987-April 1988	42 women with SLE	APL and LAC	**History of pregnancy loss** LAC (+): >/= 1 loss n=10 LAC (+): 0 loss n=5 LAC (-): >/= 1 loss n=0 LAC (-): 0 loss n=19 APL (+): >/= 1 loss n=5 APL (+): 0 loss n=0

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						APL (-): >/= 1 loss n=13 APL (-): 0 loss n=24 LAC+ APL+: > 1 loss n=4, 1 loss n=1, 0 loss n=0 LAC+ APL-: >1 loss n=3, 1 loss, n=2, 0 loss n=5 LAC- APL+: n=0 LAC- APL -: >1 loss n=0, 1 loss n=8, 0 loss n=19
	3715 Clark 2003[8]	Retrospective Observational	1999-2001	72 pregnancies in women with SLE	Checking autoantibodies	28 births were preterm, 45 births were term -10/18(55.5%) preterm women +APL IgG vs. 6/31 (19.4%) term women (p=0.023) -5/16 (31.3%) preterm women + LAC vs.11/24 (45.8%) term women (p=0.56) -6/25 (24%) preterm women had prolonged PTT vs. 7/40 (17.5%) of term women (p=0.75)
	4498 Munoz-Rodriguez 2002[9]	observational	pregnancy	103 patients with SLE (97 females) and 103 normal volunteers (age-and sex-matched)	Prevalence of autoantibodies: LAC n=29 (28%) APL n=29 (29%) B2 Glycoprotein n=25 (24%) Prothrombin n=40 (39%)	65 women were previously pregnant among the 97 with SLE N=26 (40%) had history of pregnancy loss 56% spontaneous abortion among women with LAC/APL vs. 25% in women without LAC/APL (p=0.01, OR 3.7 95%CI 1.2-10.9)
	4875 Zhan 2017[10]	Observational	2001-2015 China	251 SLE patients with 263 pregnancies	Frequency of autoantibodies: APS: n=56 (24.9%)	Among 263 pregnancies, 75 were newly diagnosed with SLE during pregnancy, 188 previously diagnosed. Adverse pregnancy outcome: 38.5% APL+ vs. 5.4% APL – Pregnancy Loss: 38.8% with APL+ vs. 14.4% APL-
	5342 Chakravarty 2005[11]	observational	1991-2001	63 pregnancies in 48 SLE women	29 (47%) women h/o +LAC/APL 10 met criteria for APS	APL+ vs. APL- -prematurity RR 0.9 (0.5-1.4)
	5608 Le Thi Huong 1994[12]	Observational	1987-1992 France	117 pregnancies in SLE women	LAC present in 14 women	Fetal loss, prematurity, IUGR, not correlated with LAC

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3049 Buchanan 1992[13]	Consecutive patients seen at a lupus pregnancy clinic	4-year period	n=76 patients with 100 pregnancies: 66 with SLE (ACR criteria), 7 with "lupus-like illness," and 3 with primary APS	Patients with aCL IgG+ or LAC+ were started on aspirin 75 mg/day. Patients with a history of venous or arterial thromboembolism were given heparin 5000 units twice daily.	n=40 patients with LAC+ were treated Fetal loss: n=21 (52%)
	3582 Hendawy 2011[14]	Retrospective review of medical records + prospective follow-up of recent pregnancies	Unknown	n=48 **SLE** patients with 38 retrospective pregnancies and 21 prospective pregnancies aPL+: 30%	--	Correlation between aPL+ and spontaneous abortion: r=0.413; p<0.05
	6962 Madazli 2014[15]	Retrospective review of medical records	2002-2011	Women with **SLE** see at a referral center for SLE. SLE diagnosed according to ACR criteria n=65 Mean age (SD): 28.8 (4.3) years Nulliparity: 28 (43.1%) Lupus nephritis: 9 (13.8%) LAC+: 18 (27.6%) aCL IgG+: 10 (15.3%) aCL IgM+: 9 (13.8%)	47.7% received steroids alone 92.3% received steroids alone or in combination with other medications 7 women with APS had anticoagulant therapy + steroids	aPL antibodies (n=19): • Fetal loss: 2 (10.5%) • Fetal growth restriction and/or preeclampsia: 5 (26.3%) • Preterm birth: 4 (21.0%) APS (n=7): • Fetal loss: 1 (14.2%) • Fetal growth restriction and/or preeclampsia: 2 (28.5%) Preterm birth: 2 (28.5%)
Maternal outcomes	5342 Chakravarty 2005[11]	Observational	1991-2001	63 pregnancies in 48 SLE women	29 (47%) women h/o +LAC/APL 10 met criteria for APS	APL+ vs. APL- -prematurity RR 0.9 (0.5-1.4)
	3690, Clowse 2005[5]	Case-series	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	Antiphospholipid antibody syndrome (APS) was diagnosed prior to the studied pregnancy in 18 women	**Maternal mortality** - 3 out of 267 pregnancies (0.011%, or 11 per 1,000 pregnancies)

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					with 27 pregnancies (10% of pregnancies).	
	3306 Mecacci 2009[4]	Retrospective cohort	Pregnancy and delivery	SLE complicated by APL antibodies	Checking apl antibodies in sle patients 57women, 7 had known aps syndrome 31/57=54% aPL neg-no treatment 20/57=35% aPL pos (treated with hep alone)	aPL pos pregnancies - 15% preeclampsia aPL neg pregnancies: - 14.7% preeclampsia
	3376 Kroese 2017[16]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertension was scored by a gynecologist. <u>Mild hypertensive disease</u>: hypertensive disorders of pregnancy including pregnancy induced hypertension	Medication use at start of pregnancies: • Hydroxychloroquine: 51.1% • Azathioprine: 27.6% Prednisone: 52.9%	Mild hypertensive disease: • SLE, no aPL: 18 (15.4%) • SLE, +aPL: 1 (7.1%) • SLE + APS: 2 (15.4%) Severe hypertensive disease: • SLE, no aPL: 19 (16.2%) • SLE, +aPL: 3 (21.4%) • SLE + APS: 4 (30.8%) Preeclamsia: • SLE, no aPL: 18/113 (15.9%) • SLE, +aPL: 3 (21.4%) • SLE + APS: 3 (23.1%) Eclampsia: • SLE, no aPL: 1/112 (0.9%) • SLE, +aPL: 0 (0%) • SLE + APS: 0 (0%) HELLP: • SLE, no aPL: 3 (2.6%) • SLE, +aPL: 1 (7.1%) • SLE + APS: 3 (23.1%)

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Severe hypertensive disease: hypertensive disorders of pregnancy including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome) n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies • 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years Non-Caucasian: 16.5% Chronic hypertension: 14.1% History of nephritis: 39.6%		
	3582 Hendawy 2011[14]	Retrospective review of medical records + prospective follow-up of recent pregnancies	Unknown	n=48 **SLE** patients with 38 retrospective pregnancies and 21 prospective pregnancies aPL+: 30%	--	Correlation between aPL+ and preeclampsia: r=0.382; p<0.05

118. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, is there a benefit to re-checking aPL (aCL IgG, IgM, antib2GPI IgG, IgM, LAC) autoantibodies in mid-pregnancy versus not re-checking these antibodies on maternal and pregnancy outcomes? **RELEVANCE: GS61 BUT NO EVIDENCE**

No evidence

119. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, what is the impact of checking anti-Ro/La autoantibodies prior to or early in pregnancy versus not checking these antibodies on maternal and pregnancy outcomes? **EVIDENCE GS60**

There are no studies that address this issue as there are no studies that evaluate pregnancy outcomes in women with these diseases who do not have antibodies checked. There are some descriptive studies that compare pregnancy outcomes by antibody status, but all outcomes are reported in patients with known antibody status. Data is indirect at best.

Quality of Evidence across outcomes: Very low

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal/ offspring outcomes	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	33 pregnancies tested for APL (LAC, aCLAb, aCLP2-GPIAb). 45 pregnancies tested for anti-SSA/SSB.	Twelve of 33 pregnancies (36.4%) pregnancies tested positive for aPL. All 12 had live births, including two premature deliveries [24, 36 weeks of gestation (GW)], two SGA neonates, and one NLE neonate at term delivery. Twenty-eight of the 45 pregnancies (62.2%) tested positive for maternal anti-SS-A antibody. In the 28 anti-SS-A antibody-positive pregnancies, five (1 7.9%) presented with NLE, whereas NLE was not observed in the pregnancies with a negative test for anti-SS-A antibody. Six (15.0%) of the 40 pregnancies were positive for maternal anti-SS-B antibody, and two (33.3%) of six developed NLE. Four of five NLE cases had only lupus erythema, and the other one developed lupus erythema and CCAVB.
	4370,	Cohort study	Mean 60 months duration	12 SSA/SSB positive mothers with 13 offspring.	Exposure to SSA/SSB antibodies during pregnancy	Outcome: Risk of autoimmune disease in offspring • Out of the 12 SSA/SSB positive mothers, 6 women gave birth to 7 children with fetal or

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	Strandberg 2006[17]		(range 2-84 months)	• Maternal diagnoses : n=6 with SLE, n=5 with Sjogren's syndrome, n=1 with UCTD. 6 SSA/SSB negative mothers with 6 offspring • Maternal diagnoses : n=2 with aPL, n=1 with Sjogren's, n=2 with MCTD, n=1 with SLE		neonatal lupus. (4 children born to 3 mothers with Sjogren's, and 3 children born to 3 mothers with SLE diagnosis.) • Out of the 6 SSA/SSB negative mothers, all 6 of their offspring were healthy
	4435, Neri 2004[18]	Prospective cohort study	Study duration unclear	90 pregnancies from 71 SLE patients followed between 1984 and 2001; in 2002, 47 offspring from these pregnancies enrolled in the current study	Anti-SSA/SSB and aPL testing in mothers during pregnancies; offspring in study were administered neuropsychological testing	Outcome assessed: Neuropsychological testing in offspring of patients with SLE No association with maternal antibodies to Ro/SSA and/or La/SSB or aPL (aCL or anti b2 GPI and/or LA) and childrens' intelligence levels. All 3 children with low scores in specific neuropsychological tests, had aPL positive mothers (3/3 versus 2/11; P , 0.02 Fisher Exact Test). The presence of other autoantibodies (e.g., anti-Ro/SS-A, anti-La/SS-B), were not related to the occurrence of LD
	3478, Tian 2015[19]	Case-control	Perinatal period	922 SLE patients with 2026 pregnancies	Antigen A(SSA) and Anti-SSB, ACL, aPL, LAC	Fetal loss - 50 including Spontaneous abortions - 39 women with 49 pregnancies Stillbirths - 8 Neonatal deaths - 3

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						The overall fetal loss rate - 3.0% (60/2026) Stillbirth rate - 0.39% (8/2026). In 50 women with fetal loss compared to those with normal pregnancies the levels of: ACL - 8/26 (31%) vs 98/385 (26%), LA - 2/7 (29%) vs 8/72 (11%), b2GP - 1 8/19 (42%) vs 81/321(25%), aPL - 18/29 (62%) vs 167/404 (41%), Anti-SSA - 21 (42%) vs 210 (24%), Anti-SSB - 10 (20%) vs 126(14%)
	4723 Buyon 1993[20]	Observational		Women who had children with heart block or manifestations of neonatal lupus without heart block, SLE and related AI diseases (who gave birth to healthy children), and 30 with AI diseases whose pregnancies ended in fetal loss unrelated to neonatal lupus	4 groups of maternal sera: 1.n=57 women with children with congenital heart block 2.n=14 with no rheumatic disease but 12 had children with transient manifestations of neonatal lupus without cardiac abnormalities 3.n=152 women with spectrum of AI diseases who gave birth to healthy children. 4.n=30 women with AI diseases whos sera were obtained during a pregnancy that ended in miscarriage	Of 57 children with heart block, 53% of mothers were pregnant at the time of serum sampling Of 12 children with lupus, 42% of mothers were pregnant at the time of serum sampling. Of 152 healthy children, 88% of mothers were pregnant at the time of serum sampling. Of 30 fetuses that died, all mothers were pregnant at the time of serum sampling (pregnant =pregnant + up to 3 months post partum. Not clear when sera were checked during pregnancy) Ro/La + in 100% mothers of infants with heart block Maternal SSB+ in 76% of heart block infants, 73% cutaneous lupus infants, 7% fetal death, and 15% healthy infants Maternal SSA+ (high titer) in 37/54=69% mothers of children with heart block vs. 29/71=41% mothers of health children (p<0.004)
	4875 Zhan 2017[10]	Observational	2001-2015 China	251 SLE patients with 263 pregnancies	Frequencies of Autoabs: SSA n=102 (38.8%) SSB n=36 (13.7%)	Adverse pregnancy outcomes: -45.9% SSA+ vs. 27.9% SSA- -16.4% SSB+ vs. 9.6% SSB- Not clear when antibodies were checked
	5342 Chakravarty 2005[11]	Observational	1999-2001	63 pregnancies in 48 women with SLE	20 (38%) women were SSA/SSB +	Women SSA/SSB+ vs. negative -prematurity RR 0.8 (0.5-1.3) -no fetal losses

110. In women with SLE, Sjogren's syndrome, systemic sclerosis, or RA, is there a benefit of re-checking anti-Ro/La autoantibodies in mid-pregnancy versus not checking these antibodies on maternal and pregnancy outcomes? **EVIDENCE GS62**

There is a single study that looks at re-checking SSA/SSB antibodies in relation to IVIg administration during pregnancy. However, there is no comparative group of pregnancies that did not repeat antibody status during pregnancy. Indirect evidence at best

Quality of Evidence across outcomes: Very low

Outcomes	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	4211, Friedman 2010[21]	Case-series	Perinatal period	17 pregnant women with anti-SSA/Ro and/or anti-SSB/La antibodies	Antibody titers assessed before every IVIG infusion, and at 28 wks, 34 wks and delivery were compared with values obtained at baseline. Fetal echocardiograms were performed weekly between 16 and 26 weeks of gestation and every two weeks thereafter until 34 weeks in accord with the protocol of PRIDE. IVIG (400mg/kg) was given every 3 weeks from 12 to 24 weeks of gestation.	**anti-SSA/Ro, anti-SB/La anti-Ro52 antibodies** in 2 mothers. 1 of these mothers had 2 previous children with CHB. **Prior pregnancy complicated by CHB** – 2 **IVIG** did not significantly alter the titers of anti-SSA/Ro, antiRo52, or anti-SSB/La antibodies. **Advanced heart block** - 3 (18%). **Third degree block** with mild tricuspid regurgitation and no hydrops – 1. **2nd degree** Wenckebach with occasional dropped beats - 1 In a third case, the mother missed the 23 and 24 week fetal echocardiograms and third degree block was detected at 25 weeks of gestation.

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5i.

5I. In women with RD and serious disease-related damage [listed], what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

CORE TEAM DECISION TO SUMMARIZE THIS INFORMATION AND INCLUDE IN DISCUSSION BUT WILL NOT USE AS A VOTE-ABLE STATEMENT.

Population: Women with RD and severe disease manifestations/complications including:

- Severe hypertension, renal insufficiency or ESRD
- Pulmonary disease to include pulmonary hypertension, “shrinking lung”, interstitial fibrosis / restrictive lung disease
- Cardiac disease to include severe cardiac valve disease (Libman-Sacks), cardiomyopathy, CAD
- Diffuse brain disease (psychosis, dementia)
- Osteonecrosis (hip)
- Antiphospholipid syndrome with stroke or MI
- Severe deformities of any joint, including cervical spine (especially C1-C2) and hips
- Advanced skin disease that interferes with labor/delivery, vascular access, or nursing or childcare
- Diffuse muscle weakness including (respiratory and swallowing)
- Vascular damage – including stenosis and aneurysm- from vasculitis (especially Takayasu’s)
- Severe neuropathies

Intervention: Pregnancy

Comparator:

- No pregnancy
- Pregnancy termination

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth < 28 weeks, preterm birth≥28 and <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)

- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity
- Maternal death

111. In women with RD and severe hypertension, renal insufficiency, or ESRD, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

Summary: This PICO is addressed indirectly by multiple observational studies. There are no relevant studies that directly address this PICO.

Detailed synopsis

Eight observational studies indirectly assess the outcome of pregnancy loss[1-8]. There were no direct comparisons made to women who were not pregnant or did not continue pregnancy. There was a wide variation of the percentage of pregnancies that ended in pregnancy loss, ranging from 5.4%-24% across the 8 studies. Most of the studies specify that some of the patients have hypertension or lupus nephritis, but it is unclear whether the patients truly had *severe* hypertension or renal insufficiency and the outcomes are not reported based on disease severity. Overall the Quality of Evidence is very poor for this outcome. 1 study found that fetal loss was correlated with a history of proteinuria.[2] Another study found among women with nephritis history, the relative risk of fetal loss was RR=0.4 (0.1-3.0).[8]

Six observational studies indirectly assess the outcome of gestational hypertensive disease including preeclampsia[2,4,5,7-9]. The rates of preeclampsia varied widely across studies, ranging from 2.9-19.4%. Most of the studies specify that some of the patients have hypertension or lupus nephritis, but it is unclear whether the patients truly had *severe* hypertension or renal insufficiency and the outcomes are not reported based on disease severity. One study reported a RR of 1.3(0.5-3.4) for developing preeclampsia amongst women who had nephritis history[8].

One observational study[9] of 77 pregnant SLE patients (92 deliveries), 46.7% of whom had renal disease (severity not specified), indirectly assessed the outcome of induced labor, reporting a rate of 20.6%. The study does not separate the patients who had renal disease from those who did not when reporting the outcome of induced labor.

One observational study[5] of 34 women with SLE/37 pregnancies reports the outcome of premature rupture of membranes at 24%. In that study, 35% of the patients had hypertension (severity not specified) and 43.2% had nephritis (renal insufficiency or ESRD not specified). The outcome of PROM is reported only overall for all patients in the study and is not broken down further into subgroups for the patients with HTN or nephritis.

Nine observational studies indirectly report the outcome of preterm birth[1-5,7-10].

The rates of pre-term birth ranged from 27.4%-35.8% across 4 studies[1,4,5,9], however 1 small observational study of women with SLE (61% whom had renal disease, severity not specified)[7] reported a rate of pre-term birth of only 8.3% (2 pregnancies out of 18 studied). 1 observational study[3] of 55 pregnancies in 24 patients with pre-existing lupus nephritis reported a subgroup of 10 patients with HTN (6 pregnancies with chronic HTN and superimposed pregnancy induced HTN in 2 of those, 4 pregnancies with severe pregnancy induced HTN). Of the 10 pregnancies complicated by HTN, 7 resulted in pre-term birth (3 spontaneous premature deliveries, 4 required preterm delivery by c-section). 1 observational

study[10] of 73 pregnancies in women with SLE found that a maternal history of renal disease was present in 9 out of 28 (32.1%) of pregnancies with preterm deliveries compared to 13/45 (28.8%) of term deliveries (p=0.978). The study gives no information about whether renal disease was active. An observational study[2] of 103 SLE pregnancies reported 28 full-term births, 48 premature births and found prematurity was related to hypertension and prednisone doses of 20 mg qd or greater during pregnancy. 1 observational study[8] reported nephritis history is associated with increased risk of prematurity RR= 1.6 (1.0-2.0).

Two observational studies[1,4] report the outcome of SGA in patients with SLE and lupus nephritis (severity of renal disease varied). SGA was noted in 16.4%-24% of live births.

Flare of RD was reported in 9 observational studies[1,2,4-9,11]. 1 observational study[1] found renal flares during and after pregnancy can be predicted by renal status assessed before pregnancy. Patients in partial remission prior to pregnancy (defined as proteinuria from 0.2 to 1g/24h, GFR > 60ml/min/1.73m^2) had RR of flare of renal disease of 3.0; 90% CI 1.23-7.34. Patients with nonremission prior to pregnancy had RR 9.0; 90% CI 3.59-22.57. Nonremission was not defined. 1 observational study[2] of 103 cases of SLE and pregnancy reported that of 75 patients with inactive SLE at conception, 27 flared during pregnancy and 7 postpartum. This study included 28 patients with proteinuria >0.5g/d and 11 patients with HTN, but the outcome of RD flare is not reported in those patients. A study by Tedeschi 2015[11] of 113 pregnancies in women with SLE, 30% of whom had a history of nephritis prior to conception (severity not specified), reported nephritis occurred in 14 (9.5%) unique women/pregnancies, of which 6 women had active nephritis during the 6mo before conception (2 had stable nephritis, 4 worse). 6 women had remote nephritis that recurred, and 2 had de novo. This study reported OR 32.5 (95%CI 6.8, 154.5) for development of active nephritis during pregnancy in women who had active nephritis 6 months prior to pregnancy vs those with inactive disease 6 months prior. 1 observational study[5] of 34 women with SLE (35% with hypertension, 43.2% with nephritis- severity not specified) reported flare in 21/32 women (65%). 1 observational study of 71 pregnancies in women with SLE and lupus nephritis reported a 19.7% rate of renal flares and 4.2% rate of extra-renal flares. Several other observational studies reported variable rates of RD flare: 40.2%[9], 62.5%[6], 22.2%[7]. Chakravarty 2005 reported no association between history of nephritis and flare of RD in SLE women (Risk of flare RR 1.1 (0.8-1.5) and risk of severe flare RR 0.9 (0.3-2.5)).[8]

Two observational studies reported risk of major birth defects, at 2%[1] and 4.1%[7] in women with SLE with variable rates and severity of renal disease. The outcome was not reported according to whether renal disease was present nor what the severity of renal disease was.

Maternal morbidity is examined in 1 observational study[4] of women with SLE and lupus nephritis (unreported severity), which reported rate of gestational diabetes of 8.4% and severe infections of 5.6%.

Maternal death was reported in 1 observational study.[2] Two mothers died, both had severe nephrotic syndrome, used AZA, and died from infection.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
Pregnancy Loss: spontaneous abortion, still birth	3635 Imbasciati 2009[1]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN (6 patients with class II, 8 with class III, 48 with class IV, 19 with class V)	Various	Overall, most patients were in complete (49%) or partial (27%) remission at conception. There were 9 spontaneous abortions, 1 stillbirth, and 5 neonatal deaths (overall 13.2% of pregnancies ended in loss).
	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy Proteinuria >0.5g/d n=28 pregnancies HTN n=11	Various	Of 117 cases of pregnancy, 103 were analyzed. Pregnancy outcome: 76 births total, 18 fetal losses (13 early, 2 late, 3 stillbirth), 5 therapeutic abortions, 4 elective abortions. Not including therapeutic or elective abortions, 17.4% of pregnancies ended in loss Fetal loss was correlated with **history of proteinuria** **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., hypertensive patients).
	3706 Rahman 2005[3]	Observational	Pregnancy	55 pregnancies in 24 patients with pre-existing lupus nephritis. Group A= quiescent nephritis, 36 pregnancies in 16 patients. Group B= active disease, 19 pregnancies in 8 patients.	Prednisone, heparin, azathioprine In group B (active disease), chronic HTN complicated 6 pregnancies with superimposed pregnancy induced HTN (PIH) in 2 of them. Severe PIH occurred in 4 pregnancies.	Stillbirth occurred in 3 pregnancies, 1 at 34 weeks (with severe PIH and abruptio placentae), 2nd at 29 weeks, 3rd at 33 weeks. Overall 5.4% of pregnancies ended in fetal loss. 1 early neonatal death occurred due to moderate respiratory distress syndrome in a premature baby delivered by C/S at 32 weeks.
	2346 Moroni 2016[4]	Prospective cohort study of women with	October 2016 –	Women prospectively followed after receiving a	No prednisone/ immunosuppressive therapy: 18.3%	**Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
		lupus nephritis	December 2013	counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. **SLE** diagnosed by ACR criteria and **lupus nephritis** diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	• Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) 16.9% of pregnancies ended in loss
	6696 Mokbel 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertension, 43.2% nephritis	Pregnancy	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%)
	7570 Gaballa 2012[6]	Prospective observational	March 28 to October 2010, Zagazig University	40 pregnant SLE women; 6 hypertensive, 9 active renal disease	Pregnancy	Fetal loss: 9 (22.5%) (1 renal, 1 hypertension)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
			Hospitals, Sharkia, Egypt			
	11742 Tozman 1980[7]	Prospective observational	July 1970 to December 1978	18 women with SLE (24 pregnancies); 61% renal disease	Pregnancy	Spontaneous abortion: 1 Stillbirth: 1 Overall 11.1% pregnancies were lost
	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. Lupus nephritis: 22 patients (35%) (2 of which had undergone renal transplant, and 1	Women with nephritis history: Risk of fetal loss RR 0.4 (0.1-3.0)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					who received dialysis) Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
Gestational hypertensive disease including preeclampsia	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy Proteinuria >0.5g/d n=28 pregnancies HTN n=11	Various	Of 117 cases of pregnancy, 103 were analyzed. 6 pregnancies (5.8%) were c/b hypertension (3 (2.9%) with associated proteinuria). **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., hypertensive patients).
	2346 Moroni 2016[4]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team.	No prednisone/ immunosuppressive therapy: 18.3% Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1%	• Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
				SLE diagnosed by ACR criteria and **lupus nephritis** diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	
	7642, Hwang, 2017[9]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries); renal disease (46.7%)	Pregnancy	Preeeclampsia: 10 (10.8%)
	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertension, 43.2% nephritis	Pregnancy	Pre-eclampsia: 8/37 (19.4%)
	11742, Tozman, 1980[7]	Prospective observational	July 1970 to December 1978	18 women with SLE (24 pregnancies); 61% renal disease	Pregnancy	Preeclampsia: 2 pregnancies (8.3%)
	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1)	Women who had nephritis history: Preeclampsia RR 1.3 (0.5-3.4) Nephritis was not associated with risk of adverse maternal outcomes

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. Lupus nephritis: 22 patients (35%) (2 of which had undergone renal transplant, and 1 who received dialysis) Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
Induced labor	7642, Hwang, 2017[9]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries); renal disease (46.7%)	Pregnancy	Induced labor: 19 (20.6%)
Premature rupture of membranes	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertension, 43.2% nephritis	Pregnancy	PROM: 9/37 (24%)
Preterm birth	3635 Imbasciati 2009[1]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN (6 patients with class II, 8 with class III, 48 with class IV, 19 with class V)	Various	Overall, most patients were in complete (49%) or partial (27%) remission. 31 deliveries (27.4%) were preterm.
	3706 Rahman 2005[3]	Observational	Pregnancy	55 pregnancies in 24 patients with pre-existing lupus nephritis. Group A= quiescent nephritis, 36 pregnancies in 16 patients. Group B= active disease, 19 pregnancies in 8 patients.	Prednisone, heparin, azathioprine In group B (active disease), chronic HTN complicated 6 pregnancies with superimposed pregnancy induced HTN (PIH) in 2 of them. Severe PIH occurred in 4 pregnancies.	Of the 10 pregnancies complicated by HTN, 3 spontaneous premature deliveries occurred at 29, 32, and 33 weeks. 4 required preterm delivery by c-section. (70% of pregnancies complicated by HTN resulted in preterm birth)
	3715 Clark 2003[10]	Observational, retrospective	1999-2001	73 pregnancies in women with SLE	Various treatments	28 births were preterm and 45 births were term. A maternal history of renal disease was present in 9 out of 28 (32.1%) of pregnancies with preterm deliveries compared to 13/45 (28.8%) of term deliveries (p=0.978).

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
						The study gives no information about how many women had active renal disease. Renal disease was determined based on proteinuria greater than 0.5 g/24h prior to pregnancy and biopsy results when available.
	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy Proteinuria >0.5g/d n=28 pregnancies HTN n=11	Various	Of 117 cases of pregnancy, 103 were analyzed. Pregnancy outcome: 28 full-term births, 48 premature births Prematurity was related to hypertension, and prednisone doses of 20 mg qd or greater during pregnancy **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., hypertensive patients).
	2346 Moroni 2016[4]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. **SLE** diagnosed by ACR criteria and **lupus nephritis** diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians)	No prednisone/ immunosuppressive therapy: 18.3% Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	**Fetal Outcomes** • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
				Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months		
	7642, Hwang, 2017[9]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries); renal disease (46.7%)	Pregnancy	Preterm birth: 33 (35.8%)
	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertension, 43.2% nephritis	Pregnancy	Preterm birth: 12/37 (32.4%)
	11742, Tozman, 1980[7]	Prospective observational	July 1970 to Decembe r 1978	18 women with SLE (24 pregnancies); 61% renal disease	Pregnancy	Preterm birth: 2 pregnancies (8.3%)
	5342 Chakravart y 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan	Women with nephritis history Prematurity RR 1.6 (1.0-2.0) Nephritis history is associated with increased risk of prematurity

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. Lupus nephritis: 22 patients (35%) (2 of which had undergone renal transplant, and 1 who received dialysis) Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
SGA	3635 Imbasciati 2009[1]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN (6 patients with class II, 8 with class III, 48 with class IV, 19 with class V)	Various	Overall, most patients were in complete (49%) or partial (27%) remission at conception. SGA noted in 23 of 97 (24%) of live births. 1 set of twins was excluded from calculation and 5 patients with neonatal death were excluded.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
	2346 Moroni 2016[4]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. **SLE** diagnosed by ACR criteria and **lupus nephritis** diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 18.3% Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	**Fetal Outcomes** • Small for gestational age: 12 (16.4%)
Flare of RD	3635 Imbasciati 2009[1]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN (6 patients with class II, 8 with class III, 48 with class IV, 19 with class V)	Various	Overall, most patients were in complete (49%) or partial (27%) remission at conception. During pregnancy or after delivery, there were 34 renal flares, 20 of which were reversible. Renal flares were defined as increase in urinary protein excretion of at least 2g/day if basal proteinuria was <3.5g/24h or doubled if proteinuria was >3.5g/24h associated with microscopic hematuria. - 3 patients had a progressive decline of GFR, 1 of those went on dialysis

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
						Renal flares during and after pregnancy can be predicted by renal status assessed before pregnancy: - Partial remission prior to pregnancy RR 3.0; 90% CI 1.23-7.34. Partial remission defined as proteinuria from 0.2 to 1g/24h, GFR > 60ml/min/1.73m^2 - Nonremission prior to pregnancy RR 9.0; 90% CI 3.59-22.57. Nonremission was not defined
	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy Proteinuria >0.5g/d n=28 pregnancies HTN n=11	Various	Of 117 cases of pregnancy, 103 were analyzed. Of 75 patients with inactive SLE at conception, 27 flared during pregnancy and 7 postpartum. **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., hypertensive patients).
	2427, Tedeschi, 2015[11]	Retrospective cohort study	Pregnancy	113 pregnancies in women with SLE for > 12 weeks. 30% had a history of nephritis prior to conception	HCQ (80%), prednisone, azathioprine	Nephritis occurred in 14 (9.5%) unique women/pregnancies, of which 6 women had active nephritis during the 6mo before conception (2 had stable nephritis, 4 worse). 6 women had remote nephritis that recurred, and 2 had de novo. OR 32.5 (95%CI 6.8, 154.5) for development of active nephritis during pregnancy in women who had active nephritis 6 months prior to pregnancy vs those with inactive disease 6 months prior
	6696, Mokbel, 2013[5]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies); 35% hypertension, 43.2% nephritis	Pregnancy	Flare: 21/32 (65%)
	2346 Moroni 2016[4]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning	No prednisone/ immunosuppressive therapy: 18.3% Prednisone only: 32.4%	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
				of pregnancy. All women were followed by a multidisciplinary team. **SLE** diagnosed by ACR criteria and **lupus nephritis** diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	
	7642, Hwang, 2017[9]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries); renal disease (46.7%)	Pregnancy	Flare: 37 (40.2%)
	7570, Gaballa, 2012[6]	Prospective observational	March 28 to October 2010, Zagazig University Hospitals, Sharkia, Egypt	40 pregnant SLE women; 6 hypertensive, 9 active renal disease	Pregnancy	Flare: 25 (62.5%) (including all 6 (100%) of the patients with hypertension)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
	11742, Tozman, 1980[7]	Prospective observational	July 1970 to December 1978	18 women with SLE (24 pregnancies); 61% renal disease	Pregnancy	Flare: 4 pregnancies (22.2%)
	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. Lupus nephritis: 22 patients (35%) (2 of which had undergone renal transplant, and 1 who received dialysis)	Women who had nephritis history: Risk of flare RR 1.1 (0.8-1.5) Risk of severe flare RR 0.9 (0.3-2.5)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
MBD	3635 Imbasciati 2009[1]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN (6 patients with class II, 8 with class III, 48 with class IV, 19 with class V)	Various	Overall, most patients were in complete (49%) or partial (27%) remission at conception. 2 patients (2%) had fetal malformation
	11742, Tozman, 1980[7]	Prospective observational	July 1970 to December 1978	18 women with SLE (24 pregnancies); 61% renal disease	Pregnancy	MBD: 1 (4.1%)
Maternal morbidity	2346 Moroni 2016[4]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. **SLE** diagnosed by ACR criteria and	No prednisone/ immunosuppressive therapy: 18.3% Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4%	**Maternal Outcomes** • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
				lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	Hydroxychloroquine: 54.4% Heparin: 19.1%	
Maternal death	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy Proteinuria >0.5g/d n=28 pregnancies HTN n=11	Various	Of 117 cases of pregnancy, 103 were analyzed. 2 mothers died (both had severe nephrotic syndrome, used AZA, and died from infection) **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., hypertensive patients).

112. In women with RD and pulmonary disease (pulmonary hypertension, shrinking lung, ILD), what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

113. In women with RD and cardiac disease (severe cardiac valve disease (Libman-Sacks), cardiomyopathy, CAD), what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

114. In women with RD and diffuse brain disease (psychosis, dementia), what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

Two observational studies[2,8] indirectly addresses the pregnancy loss outcome for this PICO. 6 patients had SLE with CNS disease (severity is not specified). Of those women, none had fetal loss.[8] Indirect evidence is also provided about 7 patients with SLE who had seizures/psychosis. This study also found that fetal loss was not correlated with seizures/psychosis[2]. Low Quality of Evidence across studies with very small numbers of patients.

Preterm birth in women with SLE with CNS involvement was also indirectly assessed by 2 observational studies[2,8]. In Chakravarty 2005, no mention is made about severity of CNS disease, however in women with history of CNS manifestations, the RR for prematurity is 1.1 (0.5-2.4). Indirect evidence was also provided in Le Thi Huong 1994 in which 7 women with SLE had history of seizures/psychosis. Prematurity was not related to seizures or psychosis.[2]

Gestational hypertensive disease was indirectly examined in 1 observational study[8] which reported that in women with SLE and history of CNS involvement (severity not specified), the RR of preeclampsia was 0.9 (0.2-5.7), n=6.

Flare of RD was assessed indirectly in 1 observational study[8] which reported that in women with SLE and history of CNS involvement (severity not specified), the RR of flare was 1.0 (0.5-1.8) and the risk of severe flare was 1.9 (0.6-5.8), n=6.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
Pregnancy loss	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy	Women who had CNS history: Risk of fetal loss: no cases

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. CNS disease: n=6 (10%) Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy	Seizures/psychosis n=7	Of 117 cases of pregnancy, 103 were analyzed. 76 births total, 18 fetal losses (13 early, 2 late, 3 stillbirth), 5 therapeutic abortions, 4 elective abortions. Fetal loss was **not correlated with seizures/psychosis** **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., CNS lupus patients).
Preterm birth	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of	Women who had CNS history: Prematurity RR 1.1 (0.5-2.4)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. CNS disease: n=6 (10%) Active disease at conception defined as use of prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
	5608 Le Thi Huong 1994[2]	Observational, prospective	1987-1992, France	117 cases of SLE and pregnancy	Seizures/psychosis n=7	Of 117 cases of pregnancy, 103 were analyzed. Pregnancy outcome: 28 full-term births, 48 premature births

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
						Prematurity was **NOT related to seizures or psychosis** **Note**: Multiple comparisons in this paper without statistical correction. Also, low numbers in some of the outcomes and predictor variables (e.g., CNS lupus patients).
Gestational hypertensive disease	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. CNS disease: n=6 (10%) Active disease at conception defined as use of	Women who had CNS history: Preeclampsia RR 0.9 (0.2-5.7)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					prednisone >10mg qd, SLEDAI ≥ 2, or use of immunosuppressive agent	
Flare of RD	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	At 1st prenatal visit, maternal lupus was active in 49% of pregnancies (mean SLEDAI score 4.2+/- 2.1) Mean SLEDAI of all pregnancies was 1.75+/- 2.4 among all pregnancies, and 5.3 +/- 4.0 among women whose SLE started during pregnancy 1 patient who received Cytoxan at onset of pregnancy elected to terminate the pregnancy because of severe maternal disease that required use of medication. CNS disease: n=6 (10%) Active disease at conception defined as use of prednisone >10mg	Women who had CNS history: Risk of flare RR 1.0 (0.5-1.8) Risk of severe flare RR 1.9 (0.6-5.8)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
					qd, SLEDAI ≥ 2, or use of immunosuppressive agent	

115. In women with RD and osteonecrosis (hip), what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

116. In women with RD and antiphospholipid syndrome with stroke or MI, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

Pregnancy loss was examined in 1 observational study[12] of 23 pregnancies occurring in women with APL and history of stroke or TIA. 21 of 23 pregnancies resulted in live birth (91.3%).

Gestational hypertensive disease was examined in 2 observational studies[12,13]. In Fischer-Betz 2012,[12] 23 pregnancies occurring in women with APL and history of stroke or TIA, 8 of 23 pregnancies were complicated by preeclampsia (34.8%). Kroese 2017 studied women with SLE with APS, but no mention was made of stroke or MI. 3/140 pregnancies were complicated by preeclampsia (23.1%). Additionally, 3/140 pregnancies were complicated by HELLP (23.1%).[13]

Preterm birth was examined in 1 observational study[12] of 23 pregnancies (21 resulting in live births) occurring in women with APL and history of stroke or TIA. 9 of 21 pregnancies resulted in preterm birth (42.9%).

Maternal morbidity was examined in 1 observational study[12] of 23 pregnancies (20 women) occurring in women with APL and history of stroke or TIA. 3 of 20 women had another TIA or stroke (15%).

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
Pregnancy loss	2543 Fischer-Betz 2012[12]	Prospective cohort	Pregnancy and deliver	APL and history of stroke or TIA	pregnant	23 pregnancies -21/23=91.3% live birth
Gestational hypertensive disease	2543 Fischer-Betz 2012[12]	Prospective cohort	Pregnancy and deliver	APL and history of stroke or TIA	pregnant	23 pregnancies -8/23=34.8% preeclampsia
	3376 Kroese 2017[13]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with **SLE** (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. Only patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertension was scored by a gynecologist. <u>Mild hypertensive disease</u>: hypertensive disorders of pregnancy including pregnancy induced hypertension <u>Severe hypertensive disease</u>: hypertensive disorders of	Medication use at start of pregnancies: • Hydroxychloroquine: 51.1% • Azathioprine: 27.6% Prednisone: 52.9%	Mild hypertensive disease: • Overall: 21 (14.6%) • SLE, no aPL: 18 (15.4%) • SLE, +aPL: 1 (7.1%) • SLE + APS: 2 (15.4%) Severe hypertensive disease: • Overall: 26 (18.1%) • SLE, no aPL: 19 (16.2%) • SLE, +aPL: 3 (21.4%) • SLE + APS: 4 (30.8%) Preeclamsia: • Overall: 24/140 (17.1%) • SLE, no aPL: 18/113 (15.9%) • SLE, +aPL: 3 (21.4%) • SLE + APS: 3 (23.1%) Eclampsia: • Overall: 1/139 (0.7%) • SLE, no aPL: 1/112 (0.9%) • SLE, +aPL: 0 (0%) • SLE + APS: 0 (0%) HELLP: • Overall: 7 (4.9%) • SLE, no aPL: 3 (2.6%) • SLE, +aPL: 1 (7.1%) • SLE + APS: 3 (23.1%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
				pregnancy including preeclampsia, eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome) n=96 women with 144 pregnancies • 77 women (117 pregnancies) with SLE, no aPL antibodies • 9 women (14 pregnancies) with SLE, positive aPL antibodies • 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years Non-Caucasian: 16.5% Chronic hypertension: 14.1% History of nephritis: 39.6%		
Preterm birth	2543 Fischer-Betz 2012[12]	Prospective cohort	Pregnancy and deliver	APL and history of stroke or TIA	pregnant	23 pregnancies -9/21=42.9% preterm
Maternal morbidity	2543 Fischer-Betz 2012[12]	Prospective cohort	Pregnancy and deliver	APL and history of stroke or TIA	pregnant	23 pregnancies in 20 women -3/20=15% women had another TIA or stroke

117. In women with RD and severe deformities of any joint, including cervical spine (especially C1-C2) and hips, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

118. In women with RD and advanced skin disease that interferes with labor/delivery, vascular access, nursing or childcare, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

119. In women with RD and diffuse muscle weakness including respiratory and swallowing, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

120. In women with RD and vascular damage – including stenosis and aneurysm- from vasculitis (especially Takayasu's), what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

121. In women with RD and severe neuropathies, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

No evidence

122. In women with RD and hematologic disease activity, what is the impact of pregnancy versus not undertaking or continuing pregnancy on maternal and pregnancy outcome?

One observational study[11] examined flare of RD in 147 pregnancies with SLE, of which 17 women had a history of hematologic disease activity, 12 of whom had active hematologic disease within 6mo prior to conception. Hematologic disorder defined as WBC <4,000/mm^3, hemolytic anemia, platelet count <100x10^9/l. Hematologic disorder occurred in 23 pregnancies (15.6%) carried by 18 unique women. Leukopenia occurred in 15 pregnancies, 10 of which also had leukopenia 6mo prior to conception. Of these, leukopenia was stable in 9 and worsened in 1. Thrombocytopenia occurred in 9 pregnancies, 4 of which also had it 6mo before conception. Of those 4, it was stable in 1, worsened in 3. 1 women had TTP. Hemolytic anemia developed in 2 pregnancies, both of which the woman had a remote h/o hemolysis. OR 26.0 (95%CI 7.7, 87.3) for development of active hematologic activity during pregnancy in women who had active hematologic activity 6 months prior to pregnancy vs those with inactive disease 6 months prior

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect evidence						
Flare of RD	2427, Tedeschi, 2015[11]	Retrospective cohort study	Pregnancy	147 pregnancies in women with SLE for > 12 weeks. 17 women had a h/o hematologic disease activity, 12 of whom had active hematologic disease within 6mo prior to conception. Hematologic disorder defined as WBC <4,000/mm^3, hemolytic anemia, platelet count <100x10^9/l	HCQ (80%), prednisone, azathioprine	Hematologic disorder occurred in 23 pregnancies (15.6%) carried by 18 unique women. Several pregnancies were characterized by >1 type of hematologic disorder, but were counted only once when calculating crude ORs. - Leukopenia occurred in 15 pregnancies, 10 of which also had leukopenia 6mo prior to conception. Of these, leukopenia was stable in 9 and worsened in 1 - Thrombocytopenia occurred in 9 pregnancies, 4 of which also had it 6mo before conception. Of those 4, it was stable in 1, worsened in 3. 1 women had TTP - Hemolytic anemia developed in 2 pregnancies, both of which the woman had a remote h/o hemolysis OR 26.0 (95%CI 7.7, 87.3) for development of active hematologic activity during pregnancy in women who had active hematologic activity 6 months prior to pregnancy vs those with inactive disease 6 months prior

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5J

5J. In women with RD [listed] what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes [listed]?

Population: Women with RD

- SLE
- Inflammatory arthritis
- Systemic sclerosis
- Vasculitis
- UCTD
-

Intervention: Management by a rheumatologist (defined as 'regular monitoring for rheumatic disease activity and rheumatic medication management during pregnancy')

-

Comparator: No management by a rheumatologist

-

Outcome:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity
- Maternal mortality

123. In women with SLE what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes? **EVIDENCE FOR GS63**

Summary: This PICO was addressed by 9 observational studies with indirect evidence[1-9]. It was not addressed by any studies with direct evidence. In 7 of the 9 included observational studies[1-7] all patients were followed by a Rheumatologist. In the remaining 2 studies[8,9] patients

were followed by maternal fetal medicine and a multidisciplinary team, but the studies do not directly state whether or not this group included a Rheumatologist. Given the lack of direct evidence, there are no data to report to directly address the PICO question.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
MBD	Ruffatti 1998[6]	Observational	1991-1995	55 infants born to 53 APL+posiive mothers treated during pregnancy with heparin	Heparin TID at dose varying between 15000-37500U. Treatment started at mean gestational age of ~7.75 weeks until delivery.	No malformations. 100% live births. No thrombotic complications. Children were delivered between 25th and 40th weeks (mean 37 weeks), mean Agpar score at 5 minutes ranged from 7-10. 12 children admitted to NICU, all of whom had complications related to prematurity. Note: all patients were monitored monthly (physical exam, fetal ultrasound, and routine labs) by study team until 30 weeks gestation, and every 2 weeks thereafter. . immediately after delivery, neonatal checkup was performed within 24 hours of birth, and clinical state of babies was followed by interviews with pediatricians/mothers for 1.33-5.66 years (mean 2.51+/- 0.92 yrs). There is no non-monitored arm.
Preterm delivery	Bramham 2010[5]	Retrospective observational	2000-2007	83 pregnancies in 67 women with APS.	Group 1: Recurrent miscarriages, n=21. Group started ASA 75 mg daily preconception, and LMWH od added once pregnancy confirmed. Group 2: Late fetal loss or early delivery due to placental dysfunction. ASA 75 mg started preconception and LMWH od once pregnancy confirmed. Group 3: Thrombotic APS n=41. If on warfarin pre-conception, ASA 75 mg and LMWH bd	Group 3 had higher rates of preterm delivery than Group 1 (26.8 vs 4.7%, p=0.05), and more small for gestational age babies than Group 2 (39.5% vs 4.8%, p=0.003). Group 2 had longer gestations compared with their pretreatment pregnancies (28.4 versus 24 weeks, [<0.0001), and 100% live birth rate after treatment with ASA and LMWH. Multidisciplinary care throughout pregnancy: Rheumatologist and other specialists. Women seen every 8-12 weeks, uterine artery Doppler performed at 20-22 weeks gestations and repeated at 24 weeks if abnormal. Note: everyone received the same care as described.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					once pregnancy confirmed. If not on warfarin, ASA 75 mg qd pre-conception and then LMWH od once pregnancy is confirmed. Increase LMWK to bd at 16-20 weeks.	
Pregnancy outcome	Spinillo, 2016[7]	Observational	2009-2014	Longitudinal cohort among women presenting for antenatal care over a 6-y period	arious Women received monthly rheumatologic assessments during pregnancy if they had a major or undifferentiated connective tissue disease, or those who didn't otherwise meet criteria for a definite diagnosis but had suspected disease (symptoms + antibodies)	<u>Prevalence of unrecognized rheumatic disease:</u> 0.4% for RA (19/5232) 0.25% for SLE (13/5232) 0.31% for Sjogren's (6/5232) 0.3% for primary APS (14/5232) 0.11% miscellaneous (6/5232) 2.5% UCTD (131/5232) Incidence of fetal growth restriction/preeclampsia: 6.1% (36/594) among controls, 25.3% (50/198) in subjects with unrecognized diseases. Unrecognized diseases were associated with excess incidence of 3.9 cases per 100 subjects (95% CI: 2.6-9.6), or 34% of all cases of preeclampsia or FGR Incidence of small for gestational age infant: (41/198) among subjects, 46/595 among controls. Excess risk of SGA associated with major rheum diseases/UCTD: 1.4% (95% CI: 0.6-2.1), or 25% of all SGA cases.
Pregnancy outcome	Mintz 1986[9]	Observational, prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients	Various	All pregnancies were managed by the same High Risk Clinic and received a complete examination at the time that pregnancy was confirmed, and monthly thereafter until 6th month of pregnancy, every 2 weeks during the final trimester, and monthly during postpartum period. If necessary, patients were seen more frequently or hospitalized.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Control group: 123 pregnancies in 124 healthy women seen in the same High Risk Clinic (but were not high-risk patients; were house physicians or wives of physicians)		At time that pregnancy was confirmed, patient received prednisone 10 mg daily if she wasn't receiving steroids or if the dose was lower. Dose was arbitrary even in absence of clinical or laboratory signs of active SLE. If SLE was active, prednisone dose was generally higher. 10 pregnancies began when SLE was active. 92 pregnancies started when SLE was inactive, but 55 (59.7%) of pregnancies were complicated by maternal flare either during pregnancy, postpartum, or postabortion. Over ½ of these flares began in 1st trimester and 20% during puerperium 49% premature newborns in the entire group, and 59% among mothers with active SLE 23% of newborns were small for gestational age in the entire group, which increased to 65% (n=13) in mothers with active SLE versus 35% in the inactive SLE group (n=7). Spontaneous abortions occurred in 16% of pregnancies with no difference between mothers with active or inactive disease. 5 stillbirths and one neonatal death also occurred. Total fetal loss was 22% (compared with 6.7% in the control group p< 0.001) The 1 neonatal death occurred in a IUGR baby. Mother had inactive SLE and was taking prednisone 10 mg daily but had received medications for UTI during pregnancy. No babies appeared to have neonatal lupus or adrenal insufficiency 32 Cesarean sections all had live outcomes **Note**: Low numbers in some of the outcomes and predictor variables may have prevented comparisons.
Pregnancy outcome	TambyRaja 1993[8]	Observational, prospective, 1976-1986	Pregnancy	52 pregnancies in 30 patients with SLE	All follow up noted to be by one physician, unclear specialty; publishing author in Ob/Gyn	Not relevant as unclear if management involved a rheumatologist or not

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy outcome	Strandberg 2006[3]	Cohort study	Mean 60 months duration (range 2-84 months)	12 SSA/SSB positive mothers and their 13 offspring. Maternal diagnoses: n=6 with SLE, n=5 with Sjogren's syndrome, n=1 with UCTD. 6 SSA/SSB negative mothers and their 6 offspring Maternal diagnoses: n=2 with aPL, n=1 with Sjogren's, n=2 with MCTD, n=1 with SLE	All patients were managed by rheumatologist at Karolinska rheumatology department during pregnancy	***Study not applicable to this PICO as all patients in study were followed by rheumatologist during pregnancy***
SLE flare	Kroese 2017[2]	Retrospective review of medical records from two tertiary centers in the Netherlands	2000-2015	Patients with SLE (ACR criteria) who had a pregnancy between 2000 and 2016 were identified through obstetric and rheumatology databases. **Only**	Medication use at start of pregnancies: • Hydroxychloroquine: 51.1% • Azathioprine: 27.6% Prednisone: 52.9%	**Disease Activity** (SLEDAI – median & IQR): • <6 months pre-pregnancy: 2 (0-4) • 1st trimester: 2 (0-2) • 2nd trimester: 2 (0-2) • 3rd trimester: 2 (0-2) • <6 months postpartum: 2 (0-4) **Flare** before, during pregnancy, or postpartum: 44 (30.6%) **Severe flare** before, during pregnancy, or postpartum: 5 (3.5%) **Mild/moderate flare**: 40 (27.8%) • <6 months pre-pregnancy: 9 (6.3%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				patients with obstetric and rheumatology visits during pregnancy were included. All pregnancies >16 weeks gestation included. APS diagnosed according to Sapporo criteria. Occurrence of hypertension was scored by a gynecologist. <u>Mild hypertensive disease</u>: hypertensive disorders of pregnancy including pregnancy induced hypertension <u>Severe hypertensive disease</u>: hypertensive disorders of pregnancy including preeclampsia,		• 1st trimester: 6 (4.2%) • 2nd trimester: 14 (9.7%) • 3rd trimester: 7 (4.9%) • <6 months postpartum: 20 (13.9%) **Medication started or dose increased** during pregnancy: • Prednisone: 25 (17%) • Azathioprine: 6 (4%) • Hydroxychloroquine: 4 (3%) **Maternal Complications** • Mild hypertensive disease: 21 (14.6%) • Severe hypertensive disease: 26 (18.1%) • Preeclampsia: 24/140 (17.1%) • Preeclampsia <34 weeks: 8/24 (33.3%) • Eclampsia: 1/139 (0.7%) • HELLP: 7 (4.9%) **Perinatal Complications** • Intrauterine fetal death: 6 (4.1%) • Preterm: 48 (32.7%) → 44% spontaneous • Small for gestational age: 21 (14.8%) • Neonatal lupus: 2 (1.4%) • Admitted to medium care or NICU: 55.3% of live born infants • Congenital anomalies: 9 (6.3%) *note: data available stratified by aPL-, aPL+ and APS, if needed

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				eclampsia, and HELLP (hemolysis, elevated liver enzyme, and low platelet count syndrome) n=96 women with 144 pregnancies 77 women (117 pregnancies) with SLE, no aPL antibodies 9 women (14 pregnancies) with SLE, positive aPL antibodies 10 women (13 pregnancies) with SLE and APS Average age: 31.9 (SD: 4.4) years Non-Caucasian: 16.5% Chronic hypertension: 14.1%		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Diabetes: 3.5%) History of thrombosis: 16.0%) History of nephritis: 39.6%		
Pregnancy outcome; SLE flare	Phansenee 2017[4]	Retrospective cohort of 140 pregnancies in women with SLE	Through pregnancy	Pregnant patients with SLE at Chiang Mai University Hospital seen between 2001 and 2015; mean maternal age: 28; 67/140 (48%) h/o nephritis. 46/140 (33%) had active disease at conception	medications during pregnancy: 68/140 (49%) on prednisone, 34/140 (24%) on HCQ, 11/140 (8%) on AZA, 1/140 on MMF or PO CYC; 8/140 (6%) on IV CYC; All patients were managed by both Rheumatology and MFM	Primary outcome = adverse pregnancy outcomes: preterm birth (delivery before 37 weeks), fetal growth restriction (birth weight less than 10th percentile for each gestational week), and low birth weight (birth weight less than 2500 g); secondary outcome = rates of fetal loss, preeclampsia. Results as follows: - Fetal growth restriction: 33/140 - Low birth weight: 73/140 - Preterm birth: 60/140 - Fetal loss: 13/140 - Pre-eclampsia: 26/140 - SLE flare: 42/138

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal loss; pregnancy outcome; SLE flare	Moroni 2016[1]	Prospective cohort study of women with lupus nephritis	October 2016 – December 2013	Women prospectively followed after receiving a counselling visit within 3 months before the beginning of pregnancy. All women were followed by a multidisciplinary team. ACR diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78	No prednisone/immunosuppressive therapy: 18.3% Prednisone only: 32.4% Prednisone and azathioprine: 35.2% Prednisone and cyclosporine: 14.1% Aspirin: 54.4% Hydroxychloroquine: 54.4% Heparin: 19.1%	**Maternal Outcomes** • Renal flares: 13 (19.7%) • Extra renal flares: 3 (4.2%) • Preeclampsia: 6 (8.4%) • HELLP: 2 (2.8%) • Gestational diabetes: 6 (8.4%) • Severe infections: 4 (5.6%) **Fetal Outcomes** • Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%) • Full term births: 45 (61.6%) • Preterm births: 22 (30.0%) • Small for gestational age: 12 (16.4%) • Mean birth weight (SD): 2753 (683) g • Neonatal cutaneous lupus: 0 (0%) Congenital heart-block: 0 (0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				(72.45) months		

124. In women with inflammatory arthritis what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes?

No evidence

125. In women with scleroderma what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes?

No evidence

126. In women with vasculitis what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes?

No evidence

127. In women with UCTD what is the impact of management by a rheumatologist throughout pregnancy versus no rheumatology management on maternal and pregnancy outcomes?

No evidence

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5K.

5K. In pregnant women with SLE what is the impact of monitoring laboratory tests [listed] during pregnancy versus no laboratory test monitoring on maternal and pregnancy outcomes [listed]?

Population: Pregnant SLE patients

Intervention: Checking laboratory tests -including CBC and urine prot/creat ratio -at least every trimester.

Comparator: SLE patients who are on any dose of prednisone or IS at the start of pregnancy who do not have these labs checks.

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of SLE
- Damage from SLE
- Maternal morbidity
- Maternal mortality

128. In pregnant women with SLE what is the impact of monitoring the CBC periodically (every trimester) during pregnancy versus no laboratory test monitoring on maternal and pregnancy outcomes? **EVIDENCE FOR GS64**

Summary: No studies directly addressed the PICO question.

For the outcome of *pregnancy loss*, 14 observational studies indirectly addressed the question.[1-14] In women with SLE, who were monitored at least every trimester during pregnancy, the frequency of spontaneous abortion ranged from 6.6 to 16%, stillbirth from 3.3 to 12.5%, and total fetal loss from 10 – 30%.[2,4-13] In women with either active or a history of LN, the frequency of miscarriage ranged from 4.1 to 11%, stillbirth from 0.8 to 8.5%, and total fetal loss from 8 to 20%.[1,3,5] Comparatively, in one study of 42 SLE

pregnancies without a standardized approach to medical management of SLE, 16.7% of pregnancies ended with a spontaneous abortion and 4.8% with fetal death in utero, with a total fetal loss rate of 26%.[14]

For the outcome of *major birth defects*, two observational studies indirectly addressed the PICO question. One study of 113 pregnancies in women with preexisting LN, 2% had malformations.[3] An additional retrospective review of 178 SLE pregnancies found 0% of infants had major congenital abnormalities.[4] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *gestational hypertensive disease including preeclampsia*, 5 observational studies indirectly addressed the PICO question. In women with SLE, 10.8 – 28.1% of pregnancies were complicated by preeclampsia.[5,7-9] In women with LN, 8.4 – 22.8% of pregnancies were complicated by preeclampsia.[1,5] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *preterm delivery*, 11 observational studies indirectly addressed the PICO question. In women with SLE, 21.5 – 49% of live births were delivered preterm.[4-11] In women with either active or a history of LN, 31 – 61% of live births were delivered preterm.[1,3,5] Comparatively, in one study of 42 SLE pregnancies without a standardized approach to medical management of SLE, 40% of live births were preterm.[14]

One study indirectly addressed the outcome of *induced labor*.[7] Among 92 pregnancies to 77 women with SLE, 21% of deliveries were induced. There was no evidence for the comparator of patients who did not have labs checked.

Two studies indirectly addressed the outcome of *premature rupture of membranes*.[5,9] In a retrospective review of women with and without a history of LN, 11.4% of deliveries to women with a history of LN had PROM, compared to 5% of deliveries to women without a history of LN.[5] In a prospective study of 37 pregnancies to women with SLE, 24% of deliveries were preceded by PROM.[9] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *small for gestational age* infants, three studies indirectly addressed the PICO question.[1,3,6] One study of 102 pregnancies among 75 women with SLE found 23% of infants were born SGA.[6] Two studies of women with LN found 16 – 24% of infants were born SGA.[1,3] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *long-term offspring effects*, two studies indirectly addressed the PICO question.[1,10] In a prospective study of 71 pregnancies to women with LN, 0% of infants were found to have congenital heart block.[1] In a prospective study of 40 pregnant women with SLE, 2.5% of infants had congenital heart block.[10] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *flare during pregnancy*, 11 studies indirectly addressed the PICO question.[1-5,7,8,10-13] In women with SLE, the frequency of flare during pregnancy ranges from 0.5 to 65% of patients.[2,4,5,7,8,10-13] Among women with LN, the frequency of renal flares ranges from 15 to 20%.[1,3,5] There was no evidence for the comparator of patients who did not have labs checked.

For the outcome of *maternal morbidity*, two observational studies indirectly addressed the PICO question.[1,8] Among 71 pregnancies in 61 women with LN, 6% developed a severe infection.[1] Among 214 prospective SLE pregnancies, 16% had worsening renal function during pregnancy and 6% experienced a VTE.[8] There was no evidence for the comparator of patients who did not have labs checked.

One observational study indirectly addressed the outcome of *maternal mortality*. Among 214 prospective SLE pregnancies, there was 1 maternal death (0.5%).[8] There was no evidence for the comparator of patients who did not have labs checked.

There was no evidence for the following outcomes:

- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Damage from SLE

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Indirect Evidence						
Pregnancy Loss	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	• Fetal loss: 6 (8.2%) • Miscarriages: 3 (4.1%) • Stillbirths: 3 (4.1%) • Neonatal deaths: 0 (0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Mean (SD) duration of LN: 100.78 (72.45) months		
	3064, Petri 1991[2]	Prospective cohort study	Pregnancy	37 pregnant women (40 pregnancies) with SLE in Hopkins Lupus cohort Patients seen at least monthly. At each visit, the following labs were done: BMP, CBC, ESR, complements, serologies (ANA, dsDNA, lupus anticoagulant), urinalysis	Unknown	• Spontaneous abortion: 5 (12.5%) • Perinatal death: 1 (2.5%) • Live birth: 34 (85%)
	3635 Imbasciati 2009[3]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN anti-dsDNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy	No therapy: 22 (19%) Low dose steroids: 65 (58%) Steroids + azathioprine or hydroxychloroquine: 20 (18%) Steroid and cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Low-dose aspirin: 68 (60%)	• Spontaneous abortion: 9 (8%) • Elective abortion: 3 (2.6%) • Stillbirth: 1 (0.8%) • Total fetal loss: 10 (8%) • Neonatal death (death within 28 days of delivery): 5/104 (5%) • Perinatal death (neonatal death + stillbirths): 6/105 (6%)
	2424 Saavedra 2015[4]	Retrospective cohort	Pregnancy	178 pregnancies in 172 lupus women All patients seen at least once each trimester. Laboratory findings (complete blood count and blood chemistry) and immunological studies (serum complement C3, C4, anti-dsDNA antibodies, anticardiolipin antibodies, anti-SSA/Ro and anti-SSB/La antibodies) were obtained	178 pregnancies -87/178=49% with AZA -91/178=51% without AZA	• Spontaneous abortions: 13 (7%) • Stillbirth: 8 (4%) • Total fetal loss: 22 (12%) Neonatal death: 6 (3%)
	2560 Saavedra 2012[5]	Retrospective cohort	Pregnancy	Women with SLE—with and without history of lupus nephritis All patients evaluated monthly during pregnancy with routine CBC and other clinical labs monthly	95 pregnancies in 92 SLE women -70/95=74% antimalarials	Women with history of LN (n=35) • Spontaneous abortion: 4 (11.4%) • Stillbirth: 3 (8.5%) • Total fetal loss: 7 (20%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						• Neonatal death: 1 (2.8%) Women without history of LN (n=60) • Spontaneous abortion: 4 (6.6%) • Stillbirth: 2 (3.3%) • Total fetal loss: 6 (10%) • Neonatal death: 2 (3.3%)
	6090 Mintz 1986[6]	Observational, prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients Lab tests were checked at baseline and at every visit (baseline, monthly until 6 months, and every 2 weeks during last trimester), but lab test findings were not reported	Various	Spontaneous abortions: 16% Stillbirth: 5% Neonatal death: 1% Total fetal loss: 22%
	7642, Hwang, 2017[7]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries) Baseline laboratory data included ANA, double-stranded DNA (dsDNA) antibodies, anti-SSA/Ro antibody, anti-SSB/La antibody, antiphospholipid antibodies (aPL), complete blood count, creatinine levels, urea, uric acid, liver function tests and urinalysis. Immunological studies were obtained in all pregnancies at the first visit and at 3-month intervals.	Steroids: 55.8% Azathioprine or cyclosporine: 15.2% Hydroxychloroquine: 55.4%	Fetal loss: 30.4%
	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective) Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	<u>Prospective arm (2010 to 2015)</u> Antihypertensive: 52.3% Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	<u>Prospective arm (2010 to 2015)</u> Spontaneous abortion: 18 (8.4%) Neonatal death: 1 (0.46%)
	6696, Mokbel, 2013[9]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	Oral prednisone: 97.3% (dose ranging from 5-20 mg/day)	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Patients seen at least monthly by a rheumatologist, and at each visit, laboratory tests included complete blood count, erythrocyte sedimentation rate, serum albumin, creatinine level, liver function tests, urine analysis and 24-h urine collection for the measurement of protein excretion.	Low dose aspirin: 89.2% Hydroxychloroquine: 100% Azathioprine: 67.6% MHW: 45.9%	
	7570, Gaballa, 2012[10]	Prospective observational	March 28 to October 2010 (Zagazig University Hospitals, Sharkia, Egypt)	40 SLE pregnant women Patients seen each trimester. Laboratory data collected at each visit included ds-DNA antibody, aCL antibodies, complements (C3 & C4), complete blood count, and urine analysis	Taken at pregnancy onset: Prednisone: 40% Aspirin: 11% Heparin: 12% Azathioprine: 9% Antimalarials: 13%	Spontaneous abortion: 3 (7.5%) Stillbirth: 5 (12.5%) Fetal loss: 8 (20%)
	2853 Cortes-Hernandez 2002[11]	Prospective	1984-1999	103 consecutive pregnancies in 60 women with SLE Patients seen at least monthly. Labs at each visit included full blood count, ESR, serum albumin, creatinine and electrolyte concentrations, urate, liver function tests, urinalysis, and 24-h urine collection	Taken at pregnancy onset: Prednisone: 38 (63%) Aspirin: 14 (23%) Azathioprine: 3 (5%) Chloroquine: 29 (48%)	Therapeutic abortion: 8 (8%) Spontaneous abortion: 15 (14%) Stillbirth: 12 (12%) Total fetal loss: 27 (26%)
	2903, Georgiou 2000[12]	Case-control	Perinatal period	47 SLE patients with 57 pregnancies The following labs performed on all patients during the study: CBC, WBC, ESR, serum glucose, urea, creatinine, uric acid, and urinalysis	8 pregnant patients treated with HCQ (200mg/day). Other treatments included: prednisone – 26, azathioprine – 1.	Therapeutic abortions: 5% Spontaneous abortions: 15% Stillbirths: 2% Elective abortions: 12% Total fetal loss: 13 (22%)
	2991, Ruiz-Irastorza 1996[13]	Case-control	Perinatal period	78 pregnancies in 68 SLE patients and a control group of 50 consecutive, non-pregnant, age-matched SLE patients. Patients enrolled in 1st trimester and see every 4 weeks until the 13th week, every 2 weeks	Prednisolone: 62% Immunosuppressants: 19% Hydroxychloroquine: 18%	Fetal loss: 22 (28%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				until the 32nd week, and then weekly until delivery At every visit, multi-stix test for proteinuria was carried out and, when positive (2+ or more), a microscopic examination for casts was performed, and a 24 h urine sample was collected for proteinuria and creatinine clearance		
	3369 Nicklin 1991[14]	Retrospective cohort 1979-1989	Pregnancy and delivery	SLE patients at single center in Australia n=42 pregnancies **No standardized approach to medical management of SLE. Treatment largely empirical**	None: 15 (36%) Prednisone: 17 (40%) Azathioprine: 4 (10%)	Therapeutic abortion: 6 (14%) Ectopic pregnancy: 2 (5%) Spontaneous abortion: 7 (16.7%) Fetal death in utero: 2 (4.8%) Total fetal loss: 11 (26%) Neonatal death: 2 (8%)
Major Birth Defect	3635 Imbasciati 2009[3]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN anti-dsDNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy	No therapy: 22 (19%) Low dose steroids: 65 (58%) Steroids + azathioprine or hydroxychloroquine: 20 (18%) Steroid and cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Low-dose aspirin: 68 (60%)	Fetal malformation: 2 (2%)
	2424 Saavedra 2015[4]	Retrospective cohort	Pregnancy outcomes	178 pregnancies in 172 lupus women All patients seen at least once each trimester. Laboratory findings (complete blood count and blood chemistry) and immunological studies (serum complement C3, C4, anti-dsDNA antibodies, anticardiolipin antibodies, anti-	178 pregnancies -87/178=49% with AZA -91/178=51% without AZA	Major congenital abnormalities: 0 (0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				SSA/Ro and anti-SSB/La antibodies) were obtained		
Gestational hypertensive disease including preeclampsia	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	Preeclampsia: 6 (8.4%)
	2560 Saavedra 2012[5]	Retrospective cohort	Pregnancy outcomes	Women with SLE—with and without history of lupus nephritis All patients evaluated monthly during pregnancy with routine CBC and other clinical labs monthly	95 pregnancies in 92 SLE women -70/95=74% antimalarials	Women with history of LN (n=35) • Preeclampsia: 8 (22.8%) Women without history of LN (n=60) • Preeclampsia: 8 (12.2%)
	7642, Hwang, 2017[7]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries) Baseline laboratory data included ANA, double-stranded DNA (dsDNA) antibodies, anti-SSA/Ro antibody, anti-SSB/La antibody, antiphospholipid antibodies (aPL), complete blood count, creatinine levels, urea, uric acid, liver function tests and urinalysis. Immunological studies were obtained in all	Steroids: 55.8% Azathioprine or cyclosporine: 15.2% Hydroxychloroquine: 55.4%	Preeclampsia: 10 (10.8%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				pregnancies at the first visit and at 3-month intervals.		
	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective) Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	<u>Prospective arm (2010 to 2015)</u> Antihypertensive: 52.3% Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	<u>Prospective arm (2010 to 2015)</u> Preeclampsia: 60 (28.1%)
	6696, Mokbel, 2013[9]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies) Patients seen at least monthly by a rheumatologist, and at each visit, laboratory tests included complete blood count, erythrocyte sedimentation rate, serum albumin, creatinine level, liver function tests, urine analysis and 24-h urine collection for the measurement of protein excretion.	Oral prednisone: 97.3% (dose ranging from 5-20 mg/day) Low dose aspirin: 89.2% Hydroxychloroquine: 100% Azathioprine: 67.6% MHW: 45.9%	Preeclampsia: 8/37 (19.4%)
Preterm Delivery	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%)	**Fetal Outcomes** • Live births: 45 (63.4%) • Preterm births: 20 (44.4%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	
	3635 Imbasciati 2009[3]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN anti-dsDNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy	No therapy: 22 (19%) Low dose steroids: 65 (58%) Steroids + azathioprine or hydroxychloroquine: 20 (18%) Steroid and cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Low-dose aspirin: 68 (60%)	Preterm delivery: 31 (31%)
	2424 Saavedra 2015[4]	Retrospective cohort	Pregnancy outcomes	178 pregnancies in 172 lupus women All patients seen at least once each trimester. Laboratory findings (complete blood count and blood chemistry) and immunological studies (serum complement C3, C4, anti-dsDNA antibodies, anticardiolipin antibodies, anti-SSA/Ro and anti-SSB/La antibodies) were obtained	178 pregnancies -87/178=49% with AZA -91/178=51% without AZA	• Live birth: 151 (85%) • Preterm: 66 (44%)
	2560 Saavedra 2012[5]	Retrospective cohort	Pregnancy outcomes	Women with SLE—with and without history of lupus nephritis All patients evaluated monthly during pregnancy with routine CBC and other clinical labs monthly	95 pregnancies in 92 SLE women -70/95=74% antimalarials	Women with history of LN (n=35) • Preterm birth: 17 (61%) • Live born: 28 (80%) Women without history of LN (n=60) • Preterm birth: 24 (44%) • Live born: 54 (90%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	6090 Mintz 1986[6]	Observational, prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients Lab tests were checked at baseline and at every visit (baseline, monthly until 6 months, and every 2 weeks during last trimester), but lab test findings were not reported	Various	Preterm: 49%
	7642, Hwang, 2017[7]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries) Baseline laboratory data included ANA, dsDNA antibodies, anti-SSA/Ro antibody, anti-SSB/La antibody, antiphospholipid antibodies (aPL), complete blood count, creatinine levels, urea, uric acid, liver function tests and urinalysis. Immunological studies were obtained in all pregnancies at the first visit and at 3-month intervals.	Steroids: 55.8% Azathioprine or cyclosporine: 15.2% Hydroxychloroquine: 55.4%	Preterm birth: 33 (35.8%)
	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective) Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	<u>Prospective arm (2010 to 2015)</u> Antihypertensive: 52.3% Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	<u>Prospective arm (2010 to 2015)</u> Preterm birth: 46 (21.5%)
	6696, Mokbel, 2013[9]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies) Patients seen at least monthly by a rheumatologist, and at each visit, laboratory tests included complete blood count, erythrocyte sedimentation rate, serum albumin, creatinine level, liver function tests, urine analysis and 24-h urine collection for the measurement of protein excretion.	Oral prednisone: 97.3% (dose ranging from 5-20 mg/day) Low dose aspirin: 89.2% Hydroxychloroquine: 100% Azathioprine: 67.6% MHW: 45.9%	Preterm birth: 12/37 (32.4%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	7570, Gaballa, 2012[10]	Prospective observational	March 28 to October 2010 (Zagazig University Hospitals, Sharkia, Egypt)	40 SLE pregnant women Patients seen each trimester. Laboratory data collected at each visit included ds-DNA antibody, aCL antibodies, complements (C3 & C4), complete blood count, and urine analysis	Taken at pregnancy onset: Prednisone: 40% Aspirin: 11% Heparin: 12% Azathioprine: 9% Antimalarials: 13%	Preterm birth: 10 (31%)
	2853 Cortes-Hernandez 2002[11]	Prospective	1984-1999	103 consecutive pregnancies in 60 women with SLE Patients seen at least monthly. Labs at each visit included full blood count, ESR, serum albumin, creatinine and electrolyte concentrations, urate, liver function tests, urinalysis, and 24-h urine collection	Taken at pregnancy onset: Prednisone: 38 (63%) Aspirin: 14 (23%) Azathioprine: 3 (5%) Chloroquine: 29 (48%)	Preterm: 19 (28%)
	3369 Nicklin 1991[14]	Retrospective cohort 1979-1989	Pregnancy and delivery	SLE patients at single center in Australia n=42 pregnancies **No standardized approach to medical management of SLE. Treatment largely empirical**	None: 15 (36%) Prednisone: 17 (40%) Azathioprine: 4 (10%)	Preterm: 10 (40%)
Induced Labor	7642, Hwang, 2017[7]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries) Baseline laboratory data included ANA, double-stranded DNA (dsDNA) antibodies, anti-SSA/Ro antibody, anti-SSB/La antibody, antiphospholipid antibodies (aPL), complete blood count, creatinine levels, urea, uric acid, liver function tests and urinalysis. Immunological studies were obtained in all pregnancies at the first visit and at 3-month intervals.	Steroids: 55.8% Azathioprine or cyclosporine: 15.2% Hydroxychloroquine: 55.4%	Induced labor: 19 (20.6%)
Premature Rupture of Membranes	2560 Saavedra 2012[5]	Retrospective cohort	Pregnancy outcomes	Women with SLE—with and without history of lupus nephritis All patients evaluated monthly during pregnancy with routine CBC and other clinical labs monthly	95 pregnancies in 92 SLE women -70/95=74% antimalarials	Women with history of LN (n=35) • PROM: 4 (11.4%) • Live born: 28 (80%) Women without history of LN (n=60) • PROM: 3 (5%) Live born: 54 (90%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	6696, Mokbel, 2013[9]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies) Patients seen at least monthly by a rheumatologist, and at each visit, laboratory tests included complete blood count, erythrocyte sedimentation rate, serum albumin, creatinine level, liver function tests, urine analysis and 24-h urine collection for the measurement of protein excretion.	Oral prednisone: 97.3% (dose ranging from 5-20 mg/day) Low dose aspirin: 89.2% Hydroxychloroquine: 100% Azathioprine: 67.6% MHW: 45.9%	Premature rupture of membrane: 9/37 (24%)
SGA	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	• Live births: 45 (63.4%) Small for gestational age: 12 (16.4%)
	3635 Imbasciati 2009[3]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN anti-dsDNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy	No therapy: 22 (19%) Low dose steroids: 65 (58%) Steroids + azathioprine or	• SGA: 23 (24%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					hydroxychloroquine: 20 (18%) Steroid and cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Low-dose aspirin: 68 (60%)	
	6090 Mintz 1986[6]	Observational, prospective	1974-1983, Mexico	102 pregnancies among 75 SLE patients Lab tests were checked at baseline and at every visit (baseline, monthly until 6 months, and every 2 weeks during last trimester), but lab test findings were not reported	Various	SGA: 23%
Long-term offspring effects	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	**Fetal Outcomes** • Live births: 45 (63.4%) • Neonatal cutaneous lupus: 0 (0%) • Congenital heart-block: 0 (0%)
	7570, Gaballa, 2012[10]	Prospective observational	March 28 to October 2010 (Zagazig University Hospitals,	40 SLE pregnant women Patients seen each trimester. Laboratory data collected at each visit included ds-DNA	Taken at pregnancy onset: Prednisone: 40% Aspirin: 11% Heparin: 12%	Congenital heart block: 1 (2.5%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			Sharkia, Egypt)	antibody, aCL antibodies, complements (C3 & C4), complete blood count, and urine analysis	Azathioprine: 9% Antimalarials: 13%	
Flare	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	Renal flares: 13 (19.7%) Extra renal flares: 3 (4.2%)
	3064, Petri 1991[2]	Prospective cohort study	Patients followed throughout pregnancy and some followed after pregnancy but overall or mean duration not provided	37 pregnant women (40 pregnancies) with SLE in Hopkins Lupus cohort Patients seen at least monthly. At each visit, the following labs were done: BMP, CBC, ESR, complements, serologies (ANA, dsDNA, lupus anticoagulant), urinalysis	Unknown	Flare: 24 (60%)
	3635 Imbasciati 2009[3]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN anti-dsDNA antibodies, C3 and C4, serum creatinine, uric acid, 24-h proteinuria and urinary microscopy were repeated every 10–12 weeks during pregnancy	No therapy: 22 (19%) Low dose steroids: 65 (58%) Steroids + azathioprine or hydroxychloroquine: 20 (18%)	Renal flares: 17 (15%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Steroid and cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Low-dose aspirin: 68 (60%)	
	2424 Saavedra 2015[4]	Retrospective cohort	Pregnancy outcomes	178 pregnancies in 172 lupus women All patients seen at least once each trimester. Laboratory findings (complete blood count and blood chemistry) and immunological studies (serum complement C3, C4, anti-dsDNA antibodies, anticardiolipin antibodies, anti-SSA/Ro and anti-SSB/La antibodies) were obtained	178 pregnancies -87/178=49% with AZA -91/178=51% without AZA	Flare during pregnancy: 66 (37%)
	2560 Saavedra 2012[5]	Retrospective cohort	Pregnancy outcomes	Women with SLE—with and without history of lupus nephritis All patients evaluated monthly during pregnancy with routine CBC and other clinical labs monthly	95 pregnancies in 92 SLE women -70/95=74% antimalarials	Women with history of LN (n=35) • Flare: 19 (54.2%) Women without history of LN (n=60) • Flare: 15 (25%)
	7642, Hwang, 2017[7]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries) Baseline laboratory data included ANA, double-stranded DNA (dsDNA) antibodies, anti-SSA/Ro antibody, anti-SSB/La antibody, antiphospholipid antibodies (aPL), complete blood count, creatinine levels, urea, uric acid, liver function tests and urinalysis. Immunological studies were obtained in all pregnancies at the first visit and at 3-month intervals.	Steroids: 55.8% Azathioprine or cyclosporine: 15.2% Hydroxychloroquine: 55.4%	Flare: 37 (40.2%)
	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1	2005 to 2010 (retrospective)	460 pregnant SLE patients (236 retrospective, 214 prospective)	<u>Prospective arm (2010 to 2015)</u> Antihypertensive: 52.3%	<u>Prospective arm (2010 to 2015)</u> Lupus flare during pregnancy: 1 (0.5%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		prospective arm)	2010 to 2015 (prospective)	Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	
	7570, Gaballa, 2012[10]	Prospective observational	March 28 to October 2010 (Zagazig University Hospitals, Sharkia, Egypt)	40 SLE pregnant women Patients seen each trimester. Laboratory data collected at each visit included ds-DNA antibody, aCL antibodies, complements (C3 & C4), complete blood count, and urine analysis	Taken at pregnancy onset: Prednisone: 40% Aspirin: 11% Heparin: 12% Azathioprine: 9% Antimalarials: 13%	Flare: 25 (62.5%)
	2853 Cortes-Hernandez 2002[11]	Prospective	1984-1999	103 consecutive pregnancies in 60 women with SLE Patients seen at least monthly. Labs at each visit included full blood count, ESR, serum albumin, creatinine and electrolyte concentrations, urate, liver function tests, urinalysis, and 24-h urine collection	Taken at pregnancy onset: Prednisone: 38 (63%) Aspirin: 14 (23%) Azathioprine: 3 (5%) Chloroquine: 29 (48%)	Flare: 34 (33%)
	2903, Georgiou 2000[12]	Case-control	Perinatal period	47 SLE patients with 57 pregnancies The following labs performed on all patients during the study: CBC, WBC, ESR, serum glucose, urea, creatinine, uric acid, and urinalysis	8 pregnant patients treated with HCQ (200mg/day). Other treatments included: prednisone – 26, azathioprine – 1.	Flare: 8 (14%)
	2991, Ruiz-Irastorza 1996[13]	Case-control	Perinatal period	78 pregnancies in 68 SLE patients and a control group of 50 consecutive, non-pregnant, age-matched SLE patients. Patients enrolled in 1st trimester and see every 4 weeks until the 13th week, every 2 weeks until the 32nd week, and then weekly until delivery	Prednisolone: 62% Immunosuppressants: 19% Hydroxychloroquine: 18%	Flare: 65%

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				At every visit, multi-stix test for proteinuria was carried out and, when positive (2+ or more), a microscopic examination for casts was performed, and a 24 h urine sample was collected for proteinuria and creatinine clearance		
Maternal Morbidity	2346 Moroni 2016[1]	Prospective cohort study of women with **lupus nephritis**	October 2016 – December 2013	Women were seen at least once a month up to the 24th week of gestation and every two weeks from the 24th week up to delivery. Complete blood count, urinalysis, lupus anticoagulant, C3 and C4 complement components were tested at screening visit and regularly checked during pregnancy and at delivery SLE diagnosed by ACR criteria and lupus nephritis diagnosed by renal biopsy or on clinical ground n=71 pregnancies in 61 women (59 Caucasians and 2 Asians) Mean (SD) age: 32.66 (4.54) years Mean (SD) duration of SLE: 130.04 (73.06) months Mean (SD) duration of LN: 100.78 (72.45) months	No prednisone/ immunosuppressive therapy: 13 (18.3%) Prednisone only: 23 (32.4%) Prednisone and azathioprine: 25 (35.2%) Prednisone and cyclosporine: 10 (14.1%) Aspirin: 37 (54.4%) Hydroxychloroquine: 37 (54.4%) Heparin: 13 (19.1%)	Severe infections: 4 (5.6%)
	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective) Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	<u>Prospective arm (2010 to 2015)</u> Antihypertensive: 52.3% Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	<u>Prospective arm (2010 to 2015)</u> Worsening of renal functions: 34 (15.8%) VTE: 12 (5.6%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Maternal mortality	7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective) Labs checked in prospective arm. Repeated antenatal care visits every 1–3 weeks Not reported for retrospective arm (outcomes not shown)	Prospective arm (2010 to 2015) Antihypertensive: 52.3% Prednisolone: 87.8% Hydroxychloroquine: 26.2% Azathioprine: 17.7% Cyclosporine: 11.2%	Prospective arm (2010 to 2015) Maternal mortality: 1 (0.46%)

129. In pregnant women with SLE what is the impact of monitoring the urinalysis and/or urine protein:creatinine ratio periodically (every trimester) during pregnancy versus no laboratory test monitoring on maternal and pregnancy outcomes?
No evidence

130. In women with SLE who are pregnant and develop laboratory or clinical evidence of SLE flare, what is the impact of new or increased treatment with prednisone or compatible immunosuppressive versus no treatment or no increased treatment on maternal and pregnancy outcomes? (also pertains to question 5L)

No evidence

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5L

5L. In women with SLE who are pregnant and develop laboratory or clinical evidence of SLE flare, what is the impact of new or increased treatment with prednisone or compatible immunosuppressive versus no treatment or no increased treatment on maternal and pregnancy outcomes [listed]?

Population: Pregnant SLE patients who have laboratory or clinical evidence of lupus flare

Intervention: Increase steroids or allowable immunosuppressive agents

Comparator: Pregnant SLE patients who do not receive increased medication

Outcomes:

- Pregnancy loss: spontaneous abortion, stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of SLE
- Damage from SLE
- Maternal morbidity
  Maternal mortality

131. In women with SLE who are pregnant and develop laboratory or clinical evidence of SLE flare, what is the impact of new or increased treatment with prednisone or compatible immunosuppressive versus no treatment or no increased treatment on maternal and pregnancy outcomes? **EVIDENCE FOR GS65**

All evidence addressing this question is indirect.

Five studies looked at rates of lupus flares during pregnancy, only one of which looked at pregnancy loss by treatment: 9/13 flares in 82 pregnancies were treated with increased prednisone with 2/9 IUFD and 1/9 therapeutic abortion at 6 wks, compared to 0 IUFD in the no-prednisone group[1]. Of the others, two mentioned increase of steroid dose for flares but not resultant outcomes[2,3] and one mentioned increase in steroid usage during the 2nd and 3rd trimesters, as well as a resultant twofold increase in pre-eclampsia (NS)

and significant threefold increased odds for preterm birth in women using prednisolone, but assessment of flares in these cases was not mentioned specifically[4]. One study noted 26% flare rate without resultant treatment-associated outcomes[5].

Two studies addressed renal flare during pregnancy, one in lupus nephritis patients in which prednisone was looked at as a risk factor for renal flare[6], but not the outcomes of treating renal flares with prednisone or increased immunosuppression and the other in lupus and lupus nephritis patients in which 1/3 developed renal flares[7]. Most patients achieved complete or partial remission, but outcomes were not analyzed based on treatment regimen.

Three studies noted rates of pre-eclampsia, one of which noted a significant increase in risk of pre-eclampsia with prednisone use (OR 2.33) but not specifically for flare.

Three studies noted rates of gestational HTN (pre-eclampsia) but not in association with flares or treatment (no evidence)[2-4].

Six studies looked at rates of pregnancy loss. Only one study looked at pregnancy loss in association with azathioprine: 2/21 pregnancies with flare during pregnancy treated with AZA had pregnancy loss, while 3/59 pregnancies with flare during pregnancy not treated with AZA had pregnancy loss[8]. The others noted rates of pregnancy loss but outcomes were not reported in association with treatment for flares[1-3,7,9].

Four studies noted rates of pre-term birth. Only one looked at preterm delivery in association with flare treatment: 9/13 flares were treated with prednisone with 5 pre-term deliveries, but 0/4 in the no-prednisone group[1]. The others noted rates of pre-term birth but outcomes were not analyzed by treatment for flares[2,4,7].

Three studies noted rates of PROM. Only one looked at PROM in association with flare treatment: 9/13 flares were treated with prednisone with 3/9 PROM but none in the no-prednisone group[1]. The other studies noted rates of PROM, but not in association with treatment for flares.[2,3]

Two studies noted rates of SGA. Only one looked at SGA in association with flare treatment: 9/13 flares were treated with prednisone with 1/9 SGA infant and 1/4 in the no-prednisone group[1]. The other noted rates of pre-term birth but outcomes were not analyzed by treatment for flares[4].

Rates of labor induction were not analyzed by treatment for flares (no evidence)[3].

One study reported rates of neonatal LE but not in association with treatment for flares (no evidence)[3].

Quality of evidence across outcomes is very low (observational studies, small numbers, indirect comparisons).

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Renal flare	3413 Moroni, 2016[6]	Cohort study		58 lupus nephritis patients	Prednisone n=23 Prednisone + Azathioprine n=25 Prednisone + cyclosporine n=10	**Prednisone dosage per mg** **Predictor Renal flare** Relative risk ratio 1.07 95% CI 0.926 – 1.232 P 0.36 14 flares, 7 treated with increase of oral prednisone, with three IV methylprednisolone pulses in two cases, 1 with increase in azathioprine, and introduction of azathioprine or cyclosporine in 3 cases. 3 flares occurred in women who were not taking specific immunosuppression, treated with prednisone and azathioprine. 4 patients continued previous treatment with prednisone and azathioprine
Renal flare	3635 Imbasciati 2009[7]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN	Various	<u>Therapy at onset or at relapse before pregnancy (no. of pregnancies)</u> Steroid (oral and/or pulse): 22 (27%) Steroid and AZA or HCQ: 12 (15%) Steroid + cytotoxic (oral and/or pulse): 47 (58%)—Cytoxan or chlorambucil <u>Therapy at conception (no. of pregnancies)</u> No therapy: 24 (21%) Steroid (low dose): 55 (49%) Steroid + AZA or HCQ: 27 (24%) <u>Therapy during pregnancy (no. of pregnancies)</u> No therapy: 22 (19%) Steroid (low dose): 65 (58%) Steroid + AZA or HCQ: 20 (18%) Steroid + cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Note: Mean cumulative dose of cyclophosphamide was 85g (range 0.4-26g) was administered in 63 patients with a median interval from drug withdrawal and pregnancy of 4 years (range: 1 month-1 years). One patient took cyclophosphamide at conception but stopped when pregnancy was confirmed Overall, most patients were in complete (49%) or partial (27%) remission PICO question is not directly answered as paper does not evaluate outcomes based on treatment regimens.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Flare	6696, Mokbel, 2013[2]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	Increase in Prednisone (97.3%) dose ranging from 5 to 20 mg/day "Occasionally, disease manifestations necessitated transiently higher dose modification."	Flare: 21/32 (65%)
Flare	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	Flare: 62 (57%)
Flare	3377 Skorpen 2017[4]	Observational nationwide register Singleton births in women with SLE included in RevNatus 2006–2015 were cases (n=180).	pregnancy	age 31.5 years; 83% live births 56.6% - 59.9% of women had inactive SLE during pregnancy and 6 weeks after birth, <10% moderate disease activity or higher (LAI-P>0.5)	Prednisone HCQ	Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). Tbere was a twofold increase in the odds of pre-eclampsia in women using prednisolone, and a statistically significant threefold increased odds for preterm birth There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%).
Flare	3306 Mecacci 2009[5]	Retrospective cohort	Pregnancy and delivery	Pregnant SLE patients +/- APl antibodies		62 pregnancies observed; 51 continued past 1st trimester - 16 flare episodes - 9/16=56% mild-mod flare→ no change in therapy - 7/17=41% severe flare→mostly nephritis. Treatment not mentioned Outcomes not listed by flares

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Flare	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	Increased steroids or immunosuppression	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2 started Prednisolone for the first time. In two cases, administrations of hydrocortisone were combined with prednisolone. A high dose of IVIG infusion (100 g/5 days) was performed in two cases. • Outcomes in these cases included: 2 intrauterine fetal deaths at 20 weeks, and one pregnancy terminated electively at 6 weeks. Five premature deliveries occurred. • Six cases were given increased Prednisolone prophylactically after delivery and none flared postpartum. Of the 4 cases in which Prednisolone was not increased, all 4 delivered between 36-40 weeks. There was one SGA.
Gestational HTN	6696, Mokbel, 2013[2]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	Increase in Prednisone (97.3%) dose ranging from 5 to 20 mg/day "Occasionally, disease manifestations necessitated transiently higher dose modification."	Preeclampsia: 8/37 (19.4%)
Gestational HTN	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	Preeclampsia: 4
Gestational HTN	3377 Skorpen 2017[4]	Observational nationwide register Singleton births in women with SLE included in	pregnancy	age 31.5 years; 83% live births 56.6% - 59.9% of women had inactive SLE during pregnancy	Prednisone HCQ	There was a substantially higher odds of pre-eclampsia when using prednisolone (OR=2.33)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		RevNatus 2006–2015 were cases (n=180). .		and 6 weeks after birth, <10% moderate disease activity or higher (LAI-P>0.5)		
Pregnancy loss	2450, Koh, 2015[8]	Retrospective cohort study	Pregnancy + 6 mo prior and 12 mo post	179 pregnancies in 128 women with SLE	Azathioprine (15% of pts with quiescent disease, 26% of pts with active disease, background HCQ, steroids	67 patients/80 pregnancies with flare 21 treated with AZA, 59 no AZA 2 patients (1 stillbirth, 1 neonatal death) with pregnancy loss on AZA 3 patients (2 neonatal death, 1 stillbirth) with pregnancy loss not on AZA otherwise outcomes with AZA not reported → exclude
Pregnancy loss	7570, Gaballa, 2012[9]	Prospective observational	March 28 to October 2010 (Zagazig University Hospitals, Sharkia, Egypt)	40 SLE pregnant women	Increase in prednisolone dosage (25 patients with flare)	Pregnancy loss: 6 (24%)
Pregnancy Loss	6696, Mokbel, 2013[2]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	Increase in Prednisone (97.3%) dose ranging from 5 to 20 mg/day "Occasionally, disease manifestations necessitated transiently higher dose modification."	Fetal loss: 9/37 (24%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%)

Pregnancy Loss	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	Neonatal death: 4 (4.5%) based on 89 successful pregnancies Intrauterine death: 5 Spontaneous abortion: 7 (37%)
Pregnancy loss	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	Increased steroids or immunosuppression	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2 started Prednisolone for the first time. In two cases, administrations of hydrocortisone were combined with prednisolone. A high dose of IVIG infusion (100 g/5 days) was performed in two cases. • Outcomes in these cases included: 2 intrauterine fetal deaths at 20 weeks, and one pregnancy terminated electively at 6 weeks.
Pregnancy loss	3635 Imbasciati 2009[7]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN	Various	PICO question is not directly answered as paper does not evaluate outcomes based on treatment regimens. <u>Therapy at onset or at relapse before pregnancy (no. of pregnancies)</u> Steroid (oral and/or pulse): 22 (27%) Steroid and AZA or HCQ: 12 (15%) Steroid + cytotoxic (oral and/or pulse): 47 (58%)—Cytoxan or chlorambucil <u>Therapy at conception (no. of pregnancies)</u> No therapy: 24 (21%) Steroid (low dose): 55 (49%) Steroid + AZA or HCQ: 27 (24%) <u>Therapy during pregnancy (no. of pregnancies)</u> No therapy: 22 (19%) Steroid (low dose): 65 (58%) Steroid + AZA or HCQ: 20 (18%) Steroid + cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Note: Mean cumulative dose of cyclophosphamide was 85g (range 0.4-26g) was administered in 63 patients with a median interval from drug withdrawal and pregnancy of 4 years (range:

						1 month-1 years). One patient took cyclophosphamide at conception but stopped when pregnancy was confirmed There were 9 spontaneous abortions, 1 stillbirth, and 5 neonatal deaths.
Preterm birth	6696, Mokbel, 2013[2]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	Increase in Prednisone (97.3%) dose ranging from 5 to 20 mg/day "Occasionally, disease manifestations necessitated transiently higher dose modification."	Preterm birth: 12/37 (32.4%)
Preterm birth	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	Increased steroids or immunosuppression	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2 started Prednisolone for the first time. • Five premature deliveries occurred. Of the 4 cases in which Prednisolone was not increased, all 4 delivered between 36-40 weeks.
Preterm birth	3377 Skorpen 2017[4]	Observational nationwide register Singleton births in women with SLE included in	pregnancy	age 31.5 years; 83% live births 56.6% - 59.9% of women had inactive SLE during pregnancy and 6 weeks after birth, <10%	Prednisone HCQ	when using prednisolone (OR=2.33), a statistically significant threefold increase in preterm birth

		RevNatus 2006–2015 were cases (n=180). .		moderate disease activity or higher (LAI-P>0.5)		
Preterm birth	3635 Imbasciati 2009[7]	Observational	1985-2004, Italy	113 pregnancies occurring in 81 women with preexisting, biopsy-proven LN	Various	<u>Therapy at onset or at relapse before pregnancy (no. of pregnancies)</u> Steroid (oral and/or pulse): 22 (27%) Steroid and AZA or HCQ: 12 (15%) Steroid + cytotoxic (oral and/or pulse): 47 (58%)—Cytoxan or chlorambucil <u>Therapy at conception (no. of pregnancies</u>) No therapy: 24 (21%) Steroid (low dose): 55 (49%) Steroid + AZA or HCQ: 27 (24%) <u>Therapy during pregnancy (no. of pregnancies)</u> No therapy: 22 (19%) Steroid (low dose): 65 (58%) Steroid + AZA or HCQ: 20 (18%) Steroid + cyclosporine: 6 (5%) Peripartum steroid pulses: 52 (46%) Note: Mean cumulative dose of cyclophosphamide was 85g (range 0.4-26g) was administered in 63 patients with a median interval from drug withdrawal and pregnancy of 4 years (range: 1 month-1 years). One patient took cyclophosphamide at conception but stopped when pregnancy was confirmed 31 deliveries were preterm. PICO question is not directly answered as paper does not evaluate outcomes based on treatment regimens.
PROM	6696, Mokbel, 2013[2]	Prospective	2007 to 2009	34 women with SLE (37	Increase in Prednisone (97.3%)	PROM: 9/37 (24%)

		observational		pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies)	dose ranging from 5 to 20 mg/day "Occasionally, disease manifestations necessitated transiently higher dose modification."	
PROM	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	Increased steroids or immunosuppression	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2 started Prednisolone for the first time. • 3 PROM Of the 4 cases in which Prednisolone was not started/increased, 0 PROM
PROM	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	PROM: 4 (7%)
Labor induction	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	Labor induction: 61 (68%)
Birth weight	3377 Skorpen 2017[4]	Observational; Observational nationwide register Singleton births in	pregnancy	age 31.5 years; 83% live births 56.6% - 59.9% of women had inactive SLE during pregnancy	Prednisone HCQ	Birth weight z-score was statistically significantly lower in offspring of women using prednisolone (mean difference 0.33).

		women with SLE included in RevNatus 2006–2015 were cases (n=180).		and 6 weeks after birth, <10% moderate disease activity or higher (LAI-P>0.5)		
SGA	3765, Kobayishi 1999[1]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	Increased steroids or immunosuppression	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2 started Prednisolone for the first time. 0 were small for dates Of the 4 cases in which Prednisolone was not increased, 2 were small for dates
Neonatal lupus	2994, Lima, 1995[3]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies)	Increase in prednisolone (51%) dose (not reported)	Neonatal lupus: 9 (8%) based on 108 total pregnancies Rash: 6 Complete heart block: 1 Complete heart block and rash: 1 Inflammatory myocardiopathy: 1 (child later died after undergoing heart transplant)

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5M

5M. In a woman with RD who is pregnant [listed] what is the impact of planned preterm delivery (<37 weeks) due to rheumatic disease, regardless of obstetric parameters (i.e. regardless of NST results, fetal growth, active preeclampsia, etc.) versus no planned preterm delivery for RD reasons on maternal and pregnancy outcomes?

Population:

- Pregnant women with quiescent or stable mild RD activity
- Pregnant women with uncontrolled RD (active RD) and major internal organ inflammation or organ dysfunction (heart, lung, kidney, CNS).
- Women RD and a hip replacement(s)

Intervention: Induction of labor prior to term (<37 weeks gestation)

Comparators:

- Induction of labor after 37 weeks gestation
- Spontaneous delivery after 37 weeks gestation

Outcomes: Health of the mother; health of the infant. Cesarean deliveries.

- Pregnancy loss: stillbirth
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth ≥ 34 and <37 weeks
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG)
- Long-term offspring effects
- Flare of RD
- Damage from RD
- Maternal morbidity
- Maternal mortality
- Cesarean section

132. In a woman with RD who is pregnant with quiescent or stable mild activity, what is the impact of planned preterm delivery (<37 weeks) due to rheumatic disease, regardless of obstetric parameters (i.e. regardless of NST results, fetal growth, active preeclampsia, etc.) versus no planned preterm delivery for RD reasons on maternal and pregnancy outcomes?

There are no data available that addresses this particular question. No studies evaluating planned delivery timing in women with RD.

This study, below, does not directly answer the PICO as it is not clear whether there was planned preterm delivery. Also, it is not clear whether the indication for "late c-section" was due to RD or pregnancy related.[1] **GS66**

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	3878, Lockshin 1984[1]	Prospective cohort study	Followed during pregnancy and 1 year after delivery (study duration unclear)	28 pregnant patients with SLE (33 pregnancies) matched by age- race- organ system- and disease severity to non-pregnant women with SLE	Late C-section performed in 7/25 pregnancies	• 11/25 pregnancies ended spontaneously before 36w; only 6/25 had uncomplicated vaginal delivery at term. • All pregnancies carried after 30 weeks resulted in living children. • Of 17 live-born children: No child had heart block, congenital SLE, or thrombocytopenia.
Cesarean section	3878, Lockshin 1984[1]	Prospective cohort study	Followed during pregnancy and 1 year after delivery (study duration unclear)	28 pregnant patients with SLE (33 pregnancies) matched by age- race- organ system- and disease severity to non-pregnant women with SLE	Late C-section performed in 7/25 pregnancies	Late C-section was performed in 7/25 pregnancies due to rising blood pressure and proteinuria (2 patients), failure to progress labor (2 patients), and thrombocytopenia, nuchal cord, and maternal genital herpes (1 patient each).

133. In a woman with RD who is pregnant with uncontrolled/active RD and major internal organ inflammation or organ dysfunction (heart, lung, kidney, CNS), what is the impact of planned preterm delivery (<37 weeks) due to rheumatic disease, regardless of obstetric parameters (i.e. regardless of NST results, fetal growth, active preeclampsia, etc.) versus no planned preterm delivery for RD reasons on maternal and pregnancy outcomes?

No data. See Question 132.

References:

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6. Management of the anti-Ro and/or La positive mother:

6A.

6A. In a pregnant woman with Ro/La antibodies [history variables listed], does fetal echo screening [intervals listed] versus no fetal echo screening impact offspring outcomes [listed]?

QUESTIONS AND DATA HERE ARE EVIDENCE FOR VOTE-ABLE STATEMENTS GS67, GS68

Population: Pregnant women with anti-Ro or Ro/La and
No history of an infant with CHB or NLE
History of an infant with CHB
History of an infant with other NLE

Intervention: Fetal echo screening at
Timing:
Weeks 20 and 24
16/18 weeks to 26/28 weeks
Frequency
Weekly
Every 2 weeks

Comparator: No screening

Outcome:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

134. In a pregnant woman with Ro/La antibodies and no history of a child with CHB or NLE, does fetal echo screening at weeks 20 and 24 versus no fetal echo screening impact offspring outcomes?

This PICO was indirectly addressed by 11 observational studies.[1-11]

Fetal echo screening was reported in 6 observational studies.[1-6] Mokbel 2013 included 34 women (37 pregnancies) with SLE; 18 Ro pregnancies. Original fetal echocardiogram screening was undergone at 20 to 22 weeks with followup screening at 36 weeks. Fetal heart monitoring was described as more frequent (not defined) for women with Ro/La antibodies.[1] Ambrosio 2010 retrospectively analyzed 107 mothers (136 pregnancies); 68 pregnancies with positive SSa/SSb antibodies. Fetal echocardiogram was performed at 24 weeks gestation in patients with SSa/SSb-positive antibodies.[7205, Amboriso 2010] Carmona 1999 prospectively analyzed 46 women (60 pregnancies) with SLE; 15 women with Ro antibodies. Fetal echocardiography was performed at weeks 17 to 18, repeated at 24 and 30 weeks in Ro/La mothers.[3] Barsalou 2017 reported on 268 pregnancies of women with connective tissue disease and positive anti-Ro and/or anti-La antibodies. Timing of echo screening not reported.[6] Lastly, we include evidence from 1 study (Hussein Aly 2016)[4] that did not report timing of fetal echo screening and 1 study (Gladman 2002) that initially performed fetal echocardiography at 18 to 20 weeks, with followup screening performed 6 and 14 weeks later. Gladman 2002 prospectively analyzed 118 pregnancies in 105 women with Ro/La antibodies; no history of a previous fetus with congenital CHB in 96 women.[5]

Of the 505 Ro pregnancies, complete heart block occurred in 14 pregnancies while first-degree heart block occurred in 1 pregnancy; 14/505 (2.8%). One study reported 1 death from CHB (0.2% of Ro pregnancies).[3] 1 study each reported one occurrence of late cardiomyopathy[5] and cardiomyopathy with EFE[6] (0.4% of Ro pregnancies). Lastly, no studies reported need for pacemaker in childhood (See Table 1).

No fetal echo screening was indirectly addressed in 5 observational studies.[7-11] Of the 208 Ro pregnancies, complete heart block was reported in 11/98 (11%) with CHB data. Fetal death was reported in 4/208 (2%). Complications included hyperechogenicity in AV without heart block in 1 fetus,[7] and inflammatory myocardiopathy (died age 2) in 1 child.[10]

Quality of Evidence across outcomes: Very low

Table 1: Evidence from Indirect Comparisons: fetal echo screening weeks 20 and 24

2 fetal ECHOs **Author, year**	**Study type**	**Duration**	**Population description**	**Treatment given to relevant population**	**Number of pregnancies**	**Outcomes**		
						Complete heart block	**Fetal death or infant death**	**Fetal hydrops/other serious complications**
7653, Hussein Aly, 2016[10]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies); prior history of CHB/NLE not reported Anti-Ro/SSA antibodies: 18 (20%) Anti-La/SSB antibodies: 26 (29%)	Fetal echo screening (timing not reported) No HCQ: 46%, no subgroup data	18	0	Data not presented for Ro pregnancies. Fetal death: 7/91 (8%) Neonatal death: 3/91 (3%)	0
6696, Mokbel, 2013[1]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies; maternal history of CHB/NLE not reported	Fetal echo screening: 20-22 weeks for original screening, followup at 36th week discovered heart block; closer fetal heart monitoring for women with anti SSA (Ro) and/or anti SSB (La) HCQ: 100%	18	CHB: 0 1st degree: 1	None from CHB. Fetal death: 4 (3 attributed to respiratory problems, and 1 attributed to intracranial hemorrhage). Binary logistic regression analysis indicated that anti Ro or La, antiphospholipid antibodies did not correlate with fetal loss.	0

2 fetal ECHOs **Author, year**	**Study type**	**Duration**	**Population description**	**Treatment given to relevant population**	**Number of pregnancies**	**Outcomes**		
						Complete heart block	**Fetal death or infant death**	**Fetal hydrops/other serious complications**
7205, Ambrosio, 2010[2]	Retrospective case series	Perinatal period	107 mothers with 136 pregnancies, 29% positive for at least one antiphospholipid antibody (aPL) and 50% with positive SSa/SSb antibodies; maternal history of CHB/NLE not reported	Fetal echocardiogram was performed at 24 weeks gestation in patients with SSa/SSb-positive antibodies. SLE-specific medication (mainly corticosteroids, hydroxychloroquine, and azatioprin): 86%	68	0	None from CHB Fetal death (<20 weeks): 8 Neonatal death: 1	
5429, Gladman, 2002[5]	Prospective single-arm study	Prenatal period	118 pregnancies in 105 women who are anti-Ro and/or La positive No history of a previous fetus with congenital complete heart block (CCHB): 96 Also addresses 2 other subquestions: History of a pregnancy with CCHB: 11 (12 pregnancies) Previous child with cutaneous NLE: 4	Fetal echocardiography at 18–20, 24–26, and 32–34 weeks' gestation Initial echo: 18–20 weeks' gestation. Follow-up echocardiograms were performed 6 and 14 weeks later	118 Ro/La	0	None from CHB Deaths: 2	2 (1 late cardiomyopathy with normal sinus rhythm, 1 atrial septal defect and pulmonary artery stenosis with normal sinus rhythm)
3343, Carmona, 1999[3]	Prospective cohort study	11 years	46 SLE patients in Spain with 60 pregnancies; 15 were anti-Ro positive; 19 anti-LA positive; maternal history of CHB/NLE not reported	Fetal echocardiography performed at weeks 17-18, repeated at 24th and 30th weeks in Ro/La+ mothers No HCQ	15	1	1 death from CHB Fetal death/infant death: 5 (intrauterine death at 21 weeks; 3 unrelated neonatal deaths)	

2 fetal ECHOs **Author, year**	**Study type**	**Duration**	**Population description**	**Treatment given to relevant population**	**Number of pregnancies**	**Outcomes**		
						Complete heart block	**Fetal death or infant death**	**Fetal hydrops/other serious complications**
2308, Barsalou, 2017[6]	Observational trial	Pregnancy	268 pregnancies/ 216 pregnancies with "full data"; women with a CTD and positive anti-Ro and/or anti-La antibodies; maternal history of CHB or NLE not reported	Timing and performance of echo not mentioned Exposure to antimalarials Anti-Ro antibody titre 550 U/mla: exposed 33 (56.9), not exposed 117 (70.5) Anti-La antibody titre 550 U/mlb: exposed 17 (28.0), not exposed 47 (27.5) Children were considered exposed to AMs (HCQ 200 to 400 mg/day or chloroquine 250mg/day) and AZA (any dose) if their mother had documented intake of these medications throughout pregnancy; 73 (27.2%) of women took AMs throughout pregnancy.	268	**12** **7 CHB** **3 CHB+EFE** **1 2nd/3rd** **1 2nd**	**NR**	**1 cardiomyopathy with EFE (without CHB)**
TOTAL:					**505 Ro pregnancies**	**13 CHB** **1 1st degree** **2.8%**	**1 death from CHB** **0.2%**	**1 late cardiomyopathy** 1 cardiomyopathy with EFE (without CHB) **0.4%**

Table 2: Additional evidence from Indirect Comparisons: No fetal echo screening

NO FETAL ECHO SCREENING **Author, year**	**Study type**	**Duration**	**Population description**	**Treatment given to relevant population**	**Number of pregnancies**	**Complete heart block**	**Fetal death or infant death**	**Fetal hydrops/other serious complications**
2327, Martinez-Sanchez, 2017[7]	Observational trial	Pregnancy	42 anti-Ro/SSA antibodies positive pregnant women; only 1 with history of an infant with CHB, 1 with neonatal cutaneous rash related to NL	***Doesn't describe fetal ECHO protocol, but they must have done them due to results. Also very detailed US data presented. Collected in Madrid between 2011 and 2015 at the main referral center for lupus pregnancy.***	42	7 CHB: 3 2nd degree; 4	None	1: Hyperechogenicity in atrioventricular valves without heart block
7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective); maternal history of CHB or NLE not reported Anti-SSA/Ro: 58 (24.5%) retrospective arm, 52 (24.3%) prospective arm Anti-SSB/La: 50 (21.2%) retrospective arm, 44 (20.6%) prospective arm	***Say fetal ECHOs should be done in Discussion but not listed in methods*** Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%) No HCQ: (<30% in each arm); no subgroup data	58 retrospective 52 prospective With RO	Not reported	From CHB: 4 (retrospective) 0 (prospective) - Probably based on wording	Not reported
2724, Whitelaw, 2008[9]	Observational, retrospective, review of pregnancies over 10 year period	Pregnancy	47 pregnancies in 31 patients were identified; Anti-SSA/SSB abs documented in 14 (39%) cases; maternal history of CHB or NLE not reported	**FETAL ECHO NOT REPORTED** ***From a developing country, so more likely to have no echos***	14 With Ro	2	None from CHB Intrauterine death: 1 (not CHB related)	none

NO FETAL ECHO SCREENING **Author, year**	**Study type**	**Duration**	**Population description**	**Treatment given to relevant population**	**Number of pregnancies**	**Complete heart block**	**Fetal death or infant death**	**Fetal hydrops/other serious complications**
				"Majority" on antimalarials.				
2994, Lima, 1995[10]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England;	90 women with SLE (108 pregnancies); maternal history of CHB or NLE not reported Anti-Ro 34 (38), Anti-La 16 (18)	**FETAL ECHO NOT REPORTED** No HCQ (13%)	34 With RO	2	None from CHB Neonatal death: 4 (4.5%) of 89 pregnancies Intrauterine death: 5	1 inflammatory myocardiopathy (died age 2)
2684, Teh, 2009[11]	Retrospective, 2006–2007, Sarawak General Hospital, Sarawak, Malaysia	Pregnancy	17 pregnancies in 16 women with SLE; half negative SSA/SSB; half SSA/SSB status unknown; maternal history of CHB or NLE not reported	**FETAL ECHO NOT REPORTED** HCQ (dose not reported): 75% AZA (dose not reported): 25% Mycophenolate mofetil: 6.3% Oral prednisone (mean dose of 5 mg/day) preconception: 81.3%	8	0	None from CHB	
TOTALS					TOTAL 208 With CHB data: 98 With CHB death data: 208 With other data: 208	11/98: 11%	4/208: 2%	2/208: 1%

135. In a pregnant woman with Ro/La antibodies and no history of a child with CHB or NLE, does fetal echo screening weekly at 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes ?

This PICO is indirectly addressed by 4 observational studies.[12-15] Jaeggi 2011 prospectively examined 165 fetuses of 142 women with Ro/La antibodies and weekly evaluations for fetal atrioventricular block (AV) conduction between 19 (range 17 to 23) and 24 (range 23 to 35) gestational weeks.[12] Trucco 2011 retrospectively observed 20 women with Ro/La antibodies (19 Ro antibodies) with fetal cardiac disease diagnosed at a median gestational age of 23 weeks (range 18 to 33 weeks.[13] Cuneo 2010 included 29 fetuses with immune-mediated second degree or third-degree AV block who were evaluated by weekly fetal echocardiography. Maternal antibodies were characterized as SSA (n=24) or both SSA and SSB (n=6) antibodies.[14] Fetal echocardiograms were performed weekly from 16 to 26 weeks and biweekly from 26 to 34 weeks in one study (Friedman 2008) analyzing 95 women with Ro/La antibodies (98 pregnancies); 74 with no history of CHB or NLE(See Table 3).[15]

Of the 306 Ro pregnancies, heart block was reported in 18 (5.8%); 14 complete heart block, and 4 1st degree heart block. Fetal death was reported in 6 (1.9%). Fetal hydrops and other serious complications were reported in 18 (5.8%) including 6 fetal hydrops, 2 heart failure, and 10 neonatal lupus. Lastly, 13 pacemakers were reported; 4.2% of Ro pregnancies. See PICO 134 above for evidence from studies indirectly addressing no fetal echo screening in patients with no history of CHB or NLE.

Quality of Evidence across outcomes: Very low

Table 3: Evidence from Indirect Comparisons: weekly fetal echo screening from 16 to 28 weeks

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
6111, Jaeggi, 2011[12]	Prospective single arm study	Nine months	165 fetuses of 142 anti-Ro/La antibody-positive women (15 untreated fetuses with AV prolongation); maternal history of CHB/NLE not reported	A total of 737 echocardiograms were performed with a median of 4 (range 2 to 12) examinations between 19 (range 17 to 23) and 24 (range 23 to 36) weeks. Our protocol included weekly evaluation of the fetal AV conduction between 19 (range 17 to 23) and 24	165 All Ro/La	Complete atrioventricular block (CAVB) diagnosed in fetuses with persistently normal AV conduction in observation period: 1/150 First degree heart block resolved/not progress but untreated: 3/15	0	0	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
				(range 23 to 35) gestational weeks Not treated with dexamethasone.					
6112, Trucco, 2011[13]	Retrospective observational	Perinatal period with a median follow-up of 2.9 years	20 women with a median gestational age of 23 weeks (range 18 to 38 weeks). 19 anti-Ro/ 8 anti-La antibody positive; 7 clinical autoimmune disease; maternal history of CHB/NLE not reported 16 with endocardial fibroelastosis; 4 with reduced ventricular function; 16 (80%) had reduced or borderline ventricular shortening fraction (≤30%) before or after birth	Timing of echo not reported. 19 pregnancies were diagnosed with fetal cardiac disease at a median gestational age of 23 weeks (range 18 to 33 weeks). Fetal echocardiography referral was for fetal bradycardia in 17 (85%) and suspected CM/EFE in 3 (15%). **<u>During pregnancy</u>** **Dexamethasone: 17/20** **IVIG: 9/20** <u>Dexamethasone administration</u>: at diagnosis of AVB (n = 13), MAb-CM/EFE (n=3), as a replacement for prednisone for AVB prescribed at a referring institution (=1). Dexamethasone max mg/day was 3 (n=1), 4 (n=5), 5 (n=1), 8 (n=9), and 16 (n=1)	19	11 (55%)	4 (20%)	Fetal hydrops: 6 (30%)	12 (63%)

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
				IVIG administration: Prenatally to 9 (47%) mothers at a dose of 70 g (~1 g/kg). Single dose (n=3), 2 pre-natal doses (n=3), and ≥ 3 doses (n=3). Multiple doses were used in the setting of worsening or persistent bradycardia and ventricular dysfunction					
6113, Cuneo, 2010[14]	Prospective single arm study		29 fetuses with immune-mediated second degree or third degree atrioventricular (AV) block; maternal antibodies were characterised as SSA (n=24) or both SSA and SSB (n=6) antibodies. No maternal history of an infant with CHB or NLE reported	Fetal echocardiography (**performed weekly**). Maternal dexamethasone therapy (4 mg orally each day), which was initiated upon the diagnosis of fetal second or third degree AV block. In utero therapy included dexamethasone (n=29), terbutaline (n=13), digoxin (n=3) and/or IVIG (n=1).	24	Treated with dexamethasone, terbutaline and digoxin Progression of echogenicity: 1 CHB: 0	0	Heart failure: 2	0
6122, Friedman, 2008[15]	Prospective single-arm study	Perinatal period	Ninety-eight pregnancies in 95 mothers with anti-SSA/Ro antibodies	Fetal echocardiograms performed weekly	98	**First-degree block:** 3 (2 previous child	Death (non-CHB history): 2 both with CHB	Neonatal lupus: 10	Pacemaker: 1 (in

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	**Fetal death or infant death**	**Fetal hydrops/other serious complications**	**Pacemaker**
			Previous child with CHB: 16 Previous child with rash: 8 First pregnancy: 44 previously healthy children: 30 Subgroup data available for previous child with CHB.	from 16 to 26 weeks' gestation and biweekly from 26 to 34 weeks Dexamethasone 4 mg/day oral; see timing under PICO 6c Authors noted that "none of the 6 affected fetuses displayed any discernible pattern of progressive PR prolongation before the primary outcome of block."		with CHB**, 1 previous children healthy**) **Third-degree block:** 3 (1 previous child with CHB, **2 previous children healthy**) .		Neonatal lupus rash only: 4 (normal ECG at birth)	child with CHB)
TOTAL					**306 Ro pregnancies**	**14 CHB** **4 1st degree** **5.8%**	**6** **1.9%**	**6 fetal hydrops** **2 heart failure** **10 neonatal lupus** **5.8%**	**13** **4.2%**

136. In a pregnant woman with Ro/La antibodies and no history of a child with CHB or NLE, does fetal echo screening every 2 weeks from 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes?

This PICO was indirectly addressed by 4 observational studies.[6096, Kan 2017; 6167 Tunks 2013; 4529 Brucato 2001; 6148 Saleeb 1999]

Kan 2017 reported on 189 pregnancies (194 fetuses) of mothers with Ro/La antibodies; serial echo 1 to 2 weekly to 24 weeks.[6096, Kan 2017] Tunks 2013 reported on 33 women with Ro antibodies; 23 underwent fetal echo screening every 2 weeks from 17 to 34 weeks gestation, 9 women underwent weekly echo.[6167 Tunks 2013] Brucato 2001 included 100 women with Ro antibodies (118

pregnancies); fetal echo screening every 2 to 4 weeks after 18 weeks gestation.[4529, Brucato 2001] Saleeb 1999 retrospectively analyzed 47 women with Ro/La antibodies. This study reported first diagnosis of CHB between 18.3 weeks and 28 weeks gestation (See Table 4).[6148 Saleeb 1999]

Of the 390 Ro pregnancies, heart block was reported in 12 (3.0%)(10 complete heart block, 2 1st degree heart block). Fetal death was reported in 23 (5.8%). Fetal hydrops and other serious complications in 21 (5.3%), and pacemakers in 25 (6.45%). See PICO 134 above for evidence from studies indirectly addressing no fetal echo screening in patients with no history of CHB or NLE.

Quality of Evidence across outcomes: Very low

Table 4: Evidence from Indirect Comparisons: screening every 2 weeks from 16 to 28 weeks

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
6096, Kan, 2017	Retrospective case-control	Prenatal period	189 pregnancies (194 fetuses) of mothers with mild-moderate (group 1; 8–49 U/mL, n=62) and high (group 2; ≥50 U/mL, n=127) anti-Ro antibody titers Previous child with cardiac NLE: 0 in group 1, 7 (6%) in group 2 Echocardiograms (median, range) Group 1: 2 (1-–7) Group 2: 4 (1–21) Echocardiograms (total) Group 1: 131 Group 2: 681	Serial echo 1 to 2 weekly to 24 weeks Ro-titers ≥50 U/mL without a previous child with cardiac NLE Serial echo weekly to 28 weeks and then at 30, 32 and 35 weeks. Ro-titers ≥50 U/mL with history of a child with cardiac NLE More frequent exams were performed at the detection of possible signs of cardiac NLE including heart block, EFE,	189 All Ro/La	CHB: 4 (1 with previous NLE) First-degree heart block: 2 (both with previous NLE) Second degree heart block: 2	Intrauterine demise: 8 (1 with previous NLE)	Isolated endocardial fibroelastosis (EFE): 1 (with previous NLE) Congenital heart disease: 2	3

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
				effusions, ventricular dysfunction and valvar regurgitation					
6167, Tunks, 2013	Observational	2007–2011	33 women anti-Ro/SSA positive; 2 with previous history of CHB Diagnosis on fetal echo: CHB: 4 (2 with prior history of CHB) First degree AVB including one resolved 2nd degree: 4	Echo every 2 weeks from 17 to 34 weeks' gestation: 23 Weekly echo: 9 Echo every 4 weeks from 19-27 weeks' gestation: 1 Average # echos: 9.24 Range of echos: 3-25 Predinsone only n=2 (5mg qd and 20mg qd) HCQ only n= 8 200mg qd – 400mg qd) No Prednisone or HCQ n=17 Prednisone + HCQ n=6	33	CHB: **4** (all treated with dexamethasone 4 mg orally once daily, no hydroxychloroquine or prednisone) 1st degree including one resolved 2nd degree: **4** (all treated prophylactically with dexamethasone, 1 also received HCQ 200 mg BID)	0	0	3
4529, Brucato, 2001	Cohort study	1985–1995	100 Anti-Ro/SSA positive women (118 pregnancies); maternal history of CHB/NLE not reported	Women followed by high-risk obstetric team monthly til 18 weeks and then every 2–4 weeks. Monitoring included fetal echo	118	Congenital complete heart block: **2** (all Ro/La mothers)	Death: 10 (7 pregnancies <10 weeks, 3 pregnancies >10 weeks) (all Ro/La mothers)	0	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
				and Doppler velocimetry					
6148, Saleeb, 1999	Retrospective cohort	Births occurring during the period 1983–1998; Research Registry for Neonatal Lupus	47 mothers whose sera contain anti-SSA/Ro or anti-SSB/La antibodies, 50 offspring with CHB; maternal history of CHB/NLE not reported	All patients screened: at least 4 echocardiograms were performed after in utero diagnosis Fetuses in group A (treated with fluorinated steroids) were first diagnosed with CHB between 18.3 weeks and 28 weeks of gestation (mean age 21.6 weeks). CHB was diagnosed later in the fetuses of group B (not treated); between 20 weeks and 34 weeks (mean age 24.2 weeks, median 23 weeks) (*P*=0.02, group A versus B)	50	0	5	<u>Hydropic changes</u> Pericardial effusions present at birth: 10 Pleural effusions present at birth: 2 Ascites present at birth: 2 Hydrops fetalis at birth: 4	25
TOTAL					**390**	**10 CHB** **2 1st degree** **3.0%**	**23** **5.8%**	**21** **5.3%**	**25** **6.4%**

137. In a pregnant woman with Ro/La antibodies and history of a child with NLE but not CHB, does fetal echo screening at weeks 20 and 24 versus no fetal echo screening impact offspring outcomes?

This PICO was indirectly addressed by one observational study providing subgroup data for children with NLE but no complete heart block.[5] Gladman 2002 prospectively analyzed 118 pregnancies in 105 women with Ro/La antibodies; previous fetus with NLE in 4 women. Fetal echocardiography was initially performed at 18 to 20 weeks, with followup screening at 24 to 26, and 32 to 34 weeks' gestation (See Table 5).[5]

This study reported no complete heart block, no fetal/infant deaths from CHB, and 2 complications. We did not identify any studies that addressed PICO 137 to PICO 139 with no fetal echo screening.

Quality of Evidence across outcomes: Very low

Table 5: Evidence from an Indirect Comparison

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
5429, Gladman, 2002[5]	Prospective single-arm study	Prenatal period	118 pregnancies in 105 women who are anti-Ro and/or La positive No history of a previous fetus with congenital complete heart block (CCHB): 96 Also addresses 2 other subquestions: History of a pregnancy with CCHB: 11 (12 pregnancies) Previous child with cutaneous NLE: 4	Fetal echocardiography at 18–20, 24–26, and 32–34 weeks' gestation Initial echo: 18–20 weeks' gestation. Follow-up echocardiograms were performed 6 and 14 weeks later	118 **Ro/La**	0	None from CHB Deaths: 2	2 (1 late cardiomyopathy with normal sinus rhythm, 1 atrial septal defect and pulmonary artery stenosis with normal sinus rhythm)	0

138. In a pregnant woman with Ro/La antibodies and history of a child with NLE but not CHB, does fetal echo screening weekly at 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes ?

No evidence

139. In a pregnant woman with Ro/La antibodies and history of a child with NLE but not CHB, does fetal echo screening every 2 weeks from 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes?

No evidence

140. In a pregnant woman with Ro/La antibodies and history of a child with CHB, does fetal echo screening at weeks 20 and 24 versus no fetal echo screening impact offspring outcomes?

This PICO is indirectly addressed by 4 observational studies.[5] 2547, Izmirly 2012; 2639 Izmirly 2010; 4590 Shinohara 1999]

Gladman 2002 reported initially screening 105 pregnant women with Ro/La antibodies (118 pregnancies) by fetal echocardiography at 18 to 20 weeks, with followup screening performed 6 and 14 weeks later; history of a previous fetus with congenital CHB (CCHB) in 11 women (12 pregnancies).[5] Authors reported 1 CCHB (.08%)(See Table 6).

No fetal echo screening in studies including women with a history of a child with CHB, was indirectly addressed by 3 studies.[2547, Izmirly 2012; 2639 Izmirly 2010; 4590 Shinohara 1999] Izmirly 2012 retrospectively examined records of 257 pregnant anti-Ro/La women with neonatal lupus and history of an infant with cardiac NLE. Izmilrly 2010 was a case-control study measuring cardiac neonatal lupus (cardiac-NL) in 201 offspring of women with SLE and Ro/La antibodies. Cases were 50 cardiac-NL children and controls were 151 non-cardiac-NL children. Patients were identified from the following three sources: Research Registry for Neonatal Lupus (RRNL), PR Interval and Dexamethasone Evaluation (PRIDE) in cardiac-NL, and Predictors of Pregnancy Outcomes: Biomarkers in Antiphospholipid Syndrome and Systemic Lupus Erythematosus (PROMISSE). Lastly, Shinohara 1999 included 40 women with anti-Ro antibodies screened by sera (See Table 7).

Of the 545 Ro pregnancies, heart block was reported in 66 (12.1%); 27 complete heart block and 32 “advanced second/third”. Fetal death was reported in 7 (1.2%). Serious complications including EFE occurred in 60 (11%) and pacemaker in 5 (.09%).

Quality of Evidence across outcomes: Very low

Table 6: Evidence from an Indirect Comparison: History of a child with CHB, screening at weeks 20 and 24

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
5429, Gladman 2002[5]	Prospective single-arm study	Prenatal period	118 pregnancies in 105 women who are anti-Ro and/or La positive	Fetal echocardiography at 18–20, 24–26, and 32–34 weeks' gestation Initial echo: 18–20 weeks' gestation. Follow-up echocardiograms were performed 6 and 14 weeks later No history of a previous fetus with congenital complete heart block (CCHB): 96 History of a pregnancy with CCHB: 11 (12 pregnancies) Previous child with cutaneous NLE: 4	118	History of an infant with CCHB (12 pregnancies in 11 women) CCHB: 1	History of an infant with CCHB (12 pregnancies in 11 women) Deaths: 0	0	History of an infant with CCHB (12 pregnancies in 11 women) Pacemaker: 0
TOTAL					**118**	**1** **.08%**	**0**	**0**	**0**

Table 7: Evidence from Indirect Comparisons: History of an Infant with complete heart block_no fetal echo screening

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
2547, Izmirly, 2012	Observational trial	Pregnancy	257 pregnancies of anti-SSA/Ro positive mothers with history of infants with prior cardiac NLE	Echo screening not reported Hydroxychloroquine was administered at least 200 mg throughout pregnancy with initiation prior to 10 weeks.	257	49 cardiac NLE Third degree heart block: 1 "Advanced Second/Third": 32 Second degree heart block: 4	0	49 cardiac NLE EFE: 6 Advanced block and cardiomyopathy /EFE: 6	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
2639, Izmirly, 2010	Observational trial	Pregnancy	Children from Ro/La pregnancies with cardiac NLE (50) and control (151) Maternal history – pregnancies with no prior affected child (78% cardiac-NL, 72.9% non-cardiac controls)	Echo screening not reported Hydroxychloroquine exposure: 14% cardiac-NL children, 37% non-cardiac NL. Pregnancy was considered exposed to hydroxychloroquine if the mother took ≥200 mg/day throughout pregnancy. HCQ dosage per day was 342.9±97.6 and 336.5±90.7 for cardiac-NL and non-cardiac NL patients, respectively.	201	Cardiac-NL (n=50) First degree heart block: 3 (6%)	0	Isolated cardiomyopathy: 4 (8%) Non-cardiac-NL (N=151) Isolated hepatic/haematological NL: 3 (2.0%) Cutaneous NL: 25 (16.6%)	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
4590, Shinohara 1999	Case series	17 years	87 offspring of 40 anti-Ro/SSA positive mothers; 15 offspring with CHB Protocol describes administration of steroids for mothers with history of CHB and NLE	No fetal echo screening (screened by sera) Treated with prednisolone or betamethasone before 16 weeks gestation: 26 offspring (25 pregnancies) Treated with prednisolone or betamethasone after 16 weeks gestation: 8 pregnancies Untreated: 53 women (11 fetuses) Oral corticosteroid: 26 women (33 pregnancies)	87	Betamethasone /prednisolone before 16 weeks gestation CHB: 0/26 No steroid/steroid after 16 weeks gestation CHB: 15/61 Untreated CHB: 11/53	Untreated Death: 7/53	Betamethasone /prednisolone before 16 weeks gestation Skin lesions of lupus dermatitis: 4/26 Untreated Skin lesions of lupus dermatitis: 12/53	Untreated Pacemaker: 5/53
TOTAL					**545 Ro pregnancies**	**27 CHB** **32 advanced second/third** **4 2nd degree** **3 1st degree** **12.1%**	**7** **1.2%**	**60** **11.0%**	**5** **.09%**

141. In a pregnant woman with Ro/La antibodies and history of a child with CHB, does fetal echo screening weekly at 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes ?

This PICO was indirectly addressed by 2 observational studies.[15,16] Friedman 2010 prospectively analyzed 20 women with Ro/La antibodies and a history of a child with CHB or NLE rash. Fetal echocardiograms were performed weekly between 16 and 26 weeks gestation followed by every two weeks until 34 weeks gestation. Friedman 2008 reported fetal echocardiograms were performed weekly from 16 to 26 weeks and biweekly from 26 to 34 weeks. 95 women with Ro/La antibodies (98 pregnancies) were included; subgroup data available for 16 women with previous child with CHB. See Table 8 for medications administered in these two studies.

Of the 118 Ro pregnancies, heart block was reported in 8 (5.9%); 4 complete heart block and 2 1st degree heart block. Fetal death was reported in 2 (1.6%), serious complications in 11 (9.3%) and pacemaker in 3 (2.5%). See PICO 140 above for indirect evidence addressing no fetal echo screening for women with a history of a child with CHB.

Quality of Evidence across outcomes: Very low

Table 8: Evidence from Indirect Comparisons: History of an Infant with complete heart block, weekly screening

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
4211, Friedman 2010[16]	Prospective observational	January 2007 and January 2009	20 women with anti-SSA/Ro antibodies, a previous child with CHB/rash, </=20 mg prednisone, <12 weeks pregnant	Fetal echocardiograms were performed weekly between 16 and 26 weeks of gestation and every two weeks thereafter until 34 weeks All patients received five IVIG infusions of 400 mg/kg from weeks 12 to 24.	20	3	0	Neonatal rash consistent with neonatal lupus: 1	2
6122, Friedman, 2008[15]	Prospective single-arm study	Perinatal period	Ninety-eight pregnancies in 95 mothers with anti-SSA/Ro antibodies Previous child with CHB: 16 Previous child with rash: 8	Fetal echocardiograms performed weekly from 16 to 26 weeks' gestation and biweekly from 26 to 34 weeks Dexamethasone	98	First-degree block: 3 (**2 previous child with CHB,** 1 previous children healthy)	Death (non-CHB history): 2 both with CHB	Neonatal lupus: 10 Neonatal lupus rash only: 4 (normal ECG at birth)	Pacemaker: 1 (in child with CHB)

			First pregnancy: 44 previously healthy children: 30 Subgroup data available for previous child with CHB.	4 mg/day oral; see timing under PICO 6c Authors noted that "none of the 6 affected fetuses displayed any discernible pattern of progressive PR prolongation before the primary outcome of block."		Third-degree block: 3 (**1 previous child with CHB,** 2 previous children healthy) .			
TOTAL					**118 Ro pregnancies**	**4 CHB** **2 1st degree** **5.9%**	**2** **1.6%**	**11** **9.3%**	**3** **2.5%**

142. In a pregnant woman with Ro/La antibodies and history of a child with CHB, does fetal echo screening every 2 weeks from 16 weeks to 28 weeks versus no fetal echo screening impact offspring outcomes?

This PICO was indirectly addressed by 1 observational study.[17] This study evaluated 22 women with Ro/La antibodies (24 pregnancies) with a history of prior CHB. This study reported fetal echocardiogram screening every 3 weeks from week 15 to week 30. Results indicated 4 complete heart block (16.6%), 3 fetal/infant deaths (12.5%), and 1 pacemaker (4.1%)(See Table 9).

See PICO 140 above for indirect evidence addressing no fetal echo screening for women with a history of a child with CHB.

Quality of Evidence across outcomes: Very low

Table 9: Evidence from an Indirect Comparison: History of an Infant with complete heart block, fetal echo screening every 2 weeks

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
6114, Pisoni, 2010[17]	Observational trial	Pregnancy	22 women/24 pregnancies, prior CHB, <12 wks pregnant, Ro and/or La positive (Sjogrens, SLE, UCTD, MG, MCTD, arthralgia), background prednisone, HCQ, dexamethasone, IVIG	Echocardiogram every 3 weeks from week 15 to week 30 IVIG (n=15) versus no IVIG (n=9) IVIG was administered 400 mg/kg at weeks 12, 15, 18, 21, and 24.	24	Complete heart block: 4 (all Ro/La mothers)	Fetal or infant death: 3 (all Ro/La mothers)	0	Pacemaker : 1 (Ro/La mother)
TOTAL					24 Ro pregnancies	4 16.6%	3 12.5%	0	1 4.1%

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6B

6B. In a pregnant woman with Ro/La antibodies [history variables listed], what is the impact of taking HCQ throughout pregnancy versus not taking HCQ on offspring outcomes [listed]?

EVIDENCE HERE FOR GS69 AND GS70

Population: women with anti-Ro or Ro/La and
No history of an infant with CHB or NLE
History of an infant with CHB
History of an infant with other NLE

Intervention: Hydroxychloroquine for prevention of CHB

Comparator: No treatment with HCQ

Outcomes:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood
- Other neonatal lupus related findings

143. In a pregnant woman with Ro/La antibodies no history of a child with CHB or NLE, what is the impact of taking HCQ throughout pregnancy versus not taking HCQ on offspring outcomes [listed]?

Summary: This PICO was directly addressed by three observational studies[1-3] and indirectly addressed by nine observational studies.[4-12]

Two studies directly addressing this PICO indicated a significant between group difference for cardiac neonatal lupus favoring hydroxychloroquine[1,2], while no significant differences were reported for other neonatal lupus (44.2% no HCQ, 38.7% HCQ) and fetal/neonatal death (no reports). Barsalou 2017 retrospectively examined records of 267 pregnant women with Ro/La antibodies (76% systemic lupus erythematosus (SLE) patients). Children were considered exposed to AMs (HCQ 200 to 400 mg/day or chloroquine 250mg/day) and AZA (any dose) if their mother had documented intake of these medications throughout pregnancy; 73 (27.2%) of women took AMs throughout pregnancy. Martinez-Sanchez 2017 prospectively examined 40 pregnant women with Ro/La antibodies (mostly SLE and Sjogren's syndrome)(See Table 1). Lastly, one case-control study (Arfaj and Khalil 2010) reported 1 neonatal death (mother Ro/la positive) after no hydroxychloroquine in 54 women with SLE planning for pregnancy. (See Table 2).[3]

Of the 9 observational studies indirectly addressing this PICO, 4 studies were categorized as “hydroxychloroquine exposure” (use ranging from 75% to 100%)[4-7], while 5 studies were categorized as “no hydroxychloroquine exposure” (use ranging from 13% to 46% with no subgroup data available).[8-12] See Table 2.

2 observational studies reported heart block (1 first degree, 2 congenital) in 3/47 (6.3%) pregnancies with hydroxychloroquine (all mothers were Ro/La positive).[4,5] 3 studies reported CHB in 7 pregnancies (3 associated with Ro/La+ mothers) without hydroxychloroquine.[8,10,11]

4 observational studies reported 1 death with hydroxychloroquine, while 5 studies reported 7 deaths without hydroxychloroquine.[4-12]

2 observational studies reported neonatal lupus in 11 patients and fetal rash in 6 patients without hydroxychloroquine.[9,11] No studies reported need for pacemaker in childhood.

Quality of Evidence across outcomes: Very low

Table 1: HCQ compared to no HCQ for pregnant women with Ro/La antibodies and no history of CHB or NLE

Bibliography: PICO 6b impact of HCQ vs no HCQ for pregnant women with Ro/La antibodies on offspring outcomes.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no HCQ	**With HCQ**		**Risk with no HCQ**	**Risk difference with HCQ**
Cardiac neonatal lupus											
308 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	18/217 (8.3%)	2/91 (2.2%)	**OR 0.18** (0.04 to 0.84) Favors HCQ	83 per 1,000	**67 fewer per 1,000** (79 fewer to 12 fewer)
Other neonatal lupus											

Table 1: HCQ compared to no HCQ for pregnant women with Ro/La antibodies and no history of CHB or NLE

Bibliography: PICO 6b impact of HCQ vs no HCQ for pregnant women with Ro/La antibodies on offspring outcomes.

Certainty assessment							Summary of findings				
216 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	68/154 (44.2%)	24/62 (38.7%)	**OR 0.80** (0.44 to 1.46)	442 per 1,000	**54 fewer per 1,000** (183 fewer to 94 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding
b. Not applicable
c. Single study. 95% CI overlaps the line of no difference.

References: 2308 Barsalou 2017, 2327 Martinez-Sanchez 2017

Table 2: Additional evidence from Direct and Indirect Comparisons

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
Direct evidence									
2621, Arfaj and Khalil 2010[3]	Case-control	27 years	319 women with SLE planning for pregnancy; 105 were anti-Ro+ while 30 were anti-La+; maternal history of CHB/NLE not reported	Prednisone+HCQ: 69 No treatment: 54	105	0	1 untreated patient (mother anti-Ro/La+)	0	0
Indirect evidence									
6696, Mokbel, 2013[4]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies); 18 anti-SSA/Ro, anti SSB/La antibodies; maternal history of CHB/NLE not reported	HCQ: 100%	18	First degree heart block: 1 (mother anti-Ro/La+) Dexamethasone therapy of 4 mg daily was given to the mother for 10 days. Baby was normal at delivery.	None from CHB. Fetal death: 4 (3 attributed to respiratory problems, and 1 attributed to intracranial hemorrhage). Binary logistic regression analysis indicated that anti Ro or La, antiphospholipid antibodies did not correlate with fetal loss.	0	0
2724, Whitelaw 2008[5]	Observational, retrospective, review of pregnancies over 10 year period	Pregnancy	47 pregnancies in 31 patients were identified; Anti-SSA/SSB abs documented in 14 (39%) cases; maternal history of CHB/NLE not reported	"Majority" on antimalarials.	14	Neonatal heart block: 2 (1 with a lupus rash; mother Ro/La+)	1	Lupus rash:1 (mother Ro/La+)	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
7640, Rezk, 2017[8]	Observational (1 retrospective arm, 1 prospective arm)	2005 to 2010 (retrospective) 2010 to 2015 (prospective)	460 pregnant SLE patients (236 retrospective, 214 prospective); maternal history of CHB or NLE not reported Anti-SSA/Ro: 58 (24.5%) retrospective arm, 52 (24.3%) prospective arm Anti-SSB/La: 50 (21.2%) retrospective arm, 44 (20.6%) prospective arm	Hydroxychloroquine: retrospective 68 (28.9%), prospective 56 (26.2%) No HCQ: (<30% in each arm); no subgroup data	110	CHB: 4 (did not indicate association with Ro/La+ mother in retrospective arm)	4 from CHB 10 (4 of 9 secondary to CHB in retrospective arm, 1 prospective arm)	0	0
3427, Ku 2016[9]	Retrospective cohort study	10 years	109 pregnancies from 83 SLE patients; 66.2% were Ro+, 28.9% were La+; 76% first pregnancy; prior history of 24% of women with second/third pregnancies not reported	No HCQ: 36.1%	72	Fetal heart malformations: 2 (association with Ro/La mother not described)	2	Neonatal lupus: 2	0
3343, Carmona 1999[10]	Prospective cohort study	11 years	46 SLE patients in Spain with 60 pregnancies; 15 were anti-Ro positive; 19 anti-LA positive; maternal history of CHB/NLE not reported	No HCQ	15	1 (mother anti-Ro+)	1 from CHB 5 (intrauterine death at 21 weeks; 4 neonatal deaths)	0	0
2994, Lima, 1995[11]	Prospective observational	5 years, Lupus Pregnancy Clinic, London, England	90 women with SLE (108 pregnancies); maternal history of CHB or NLE not reported Laboratory features: Anti-Ro 34 (38), Anti-La 16 (18), Anti-Sm 5 (6), Anti-RNP 12 (13), Anti-phospholipids 44 (49)	No HCQ: (13%); no subgroup data	34	CHB: 1 (mother anti-Ro+) CHB and rash: 1 (mother anti-Ro+)	None from CHB. Neonatal death: 4 (4.5%) of 89 pregnancies Intrauterine death: 5	Neonatal lupus: 9 (8%) of 108 pregnancies Fetal rash: 6 Inflammatory myocardiopathy: 1 (child later died after undergoing heart transplant; mother anti-Ro+)	0

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
7205, Ambrosio 2010[6]	Retrospective case series	Perinatal period	107 mothers with 136 pregnancies, 29% positive for at least one antiphospholid antibody (aPL) and 50% with positive SSa/SSb antibodies; history of NLE not reported	SLE-specific medication (mainly corticosteroids, hydroxychloroquine, and azatioprin): 86%	68 50% with positive SSa/SSb antibodies	0	None from CHB. Fetal death (<20 weeks): 8 Neonatal death: 1	0	0
2684 Teh 2009[7]	Observational, retrospective, 2006-2007, Sarawak General Hospital, Sarawak, Malaysia	Pregnancy	17 pregnancies in 16 women with SLE; half negative SSA/SSB; half SSA/SSB status unknown; no history of an infant with CHB or NLE	HCQ (dose not reported): 75% AZA (dose not reported): 25% Mycophenolate mofetil: 6.3% Oral prednisone (mean dose of 5 mg/day) preconception: 81.3%	9	0	None from CHB. 3 (2 first trimester, 1 second trimester)	0	0
7653, Hussein Aly, 2016[12]	Prospective observational	October 2010 to January 2015, Cairo University Hospitals	84 pregnant SLE patients (91 pregnancies); maternal history of CHB/NLE not reported Anti-Ro/SSA antibodies: 18 (20%) Anti-La/SSB antibodies: 26 (29%)	No HCQ: 46%, no subgroup data	18	0	Data not presented for Ro pregnancies. Fetal death: 7 (8%) Neonatal death: 3 (3%)	0	0
TOTAL					**463 Ro pregnancies**	**7 CHB 1 1st degree 2 fetal heart malformations 1 inflammatory myocardiopathy 2.3%**	**8 1.7%**	**18 3.8%**	**0**

HCQ: Hydroxychloroquine

144. In a pregnant woman with Ro/La antibodies history of a child with NLE without CHB, what is the impact of taking HCQ throughout pregnancy versus not taking HCQ on offspring outcomes [listed]?

No evidence

145. In a pregnant woman with Ro/La antibodies history of a child with CHB, what is the impact of taking HCQ throughout pregnancy versus not taking HCQ on offspring outcomes [listed]?

Summary: This PICO was directly addressed by two observational studies,[2547 Izmirly 2012; 2639 Izmirly 2010] and indirectly addressed by one observational study.[13] Izmirly 2012 retrospectively examined records of 257 pregnant anti-Ro/La women with neonatal lupus and history of an infant with cardiac NLE. Hydroxychloroquine was administered at least 200 mg throughout pregnancy with initiation prior to 10 weeks. Izmirly 2010 was a case-control study measuring cardiac neonatal lupus (cardiac-NL) in offspring of women with SLE and Ro/La antibodies. Cases were 50 cardiac-NL children (14% hydroxychloroquine exposed) and controls were 151 non-cardiac-NL children (37% hydroxychloroquine exposed). Pregnancy was considered exposed to hydroxychloroquine if the mother took ≥200 mg/day throughout pregnancy. HCQ dosage per day was 342.9±97.6 and 336.5±90.7 for cardiac-NL and non-cardiac NL patients, respectively. Patients were identified from the following three sources: Research Registry for Neonatal Lupus (RRNL), PR Interval and Dexamethasone Evaluation (PRIDE) in cardiac-NL, and Predictors of Pregnancy Outcomes: Biomarkers in Antiphospholipid Syndrome and Systemic Lupus Erythematosus (PROMISSE). Lastly, Tunks 2013 reported use of hydroxychloroquine in 8 women, and prednisone and hydroxychloroquine in 6 women from a cohort of 33 anti-Ro/SSA positive women. Prednisone (n=2), and dexamethasone (n=8) were also administered.[13]

Results indicated a significant between group difference favoring hydroxychloroquine exposure for cardiac neonatal lupus (25.1% no hydroxychloroquine, 9.7% hydroxychloroquine).[2547 Izmirly 2012; 2639 Izmirly 2010] No significant differences were reported for non-cardiac-NL and no fetal/neonatal deaths occurred.[2547 Izmirly 2012] Neither study reported a need for pacemaker in childhood (See Table 3).

Tunks 2013 reported CHB in 4 fetuses (3 needing pacemakers), and 1st degree heart block in 4 fetuses (including 1 resolved 2nd degree block)(See Table 4).[13]

Quality of Evidence across outcomes: Very low

Table 3: HCQ versus no HCQ with history of CHB for pregnant women with Ro/La antibodies on offspring outcomes

Bibliography: PICO 6b impact of HCQ vs no HCQ for pregnant women with Ro/La antibodies on offspring outcomes.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no HCQ	**With HCQ**		**Risk with no HCQ**	**Risk difference with HCQ**
Cardiac neonatal lupus											
458 (2 observational studies)	serious [a]	not serious	not serious	not serious	none	⨁◯◯◯ VERY LOW	89/355 (25.1%)	10/103 (9.7%)	**OR 0.29** (0.14 to 0.58) Favors HCQ	251 per 1,000	**162 fewer per 1,000** (206 fewer to 88 fewer)
Other neonatal lupus											
211 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	19/171 (11.1%)	2/40 (5.0%)	**OR 0.42** (0.09 to 1.89)	111 per 1,000	**61 fewer per 1,000** (100 fewer to 80 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding; retrospective

b. Not applicable

c. Single study. 95% overlaps the line of no difference.

References: 2547 Izmirly 2012, 2639 Izmirly 2010

Table 4: Additional Evidence from an Indirect Comparison: History of Complete Heart Block on Echocardiography

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	**Fetal death or infant death**	**Fetal hydrops/other serious complications**	**Pacemaker**
6167, Tunks, 2013[13]	Observational	2007–2011	33 women anti-Ro/SSA positive; 2 with previous history of CHB Diagnosis on fetal echo: CHB: 4 (2 with prior history of CHB) First degree AVB including one resolved 2nd degree: 4	Predinsone only n=2 (5mg qd and 20mg qd) HCQ only n= 8 200mg qd – 400mg qd) No Prednisone or HCQ n=17 Prednisone + HCQ n=6	33	CHB: 4 (all treated with dexamethasone 4 mg orally once daily, no hydroxychloroquine or prednisone) 1st degree including one resolved 2nd degree: 4 (all treated prophylactically with dexamethasone, 1 also received HCQ 200 mg BID)	**0**	0	3
TOTAL					**33**	**4 CHB** **4 1st degree** **24.2%**	**0**	**0**	**3** **9.0%**

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6C.

6C. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed] what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?

EVIDENCE HERE FOR GS71, GS72, GS73, GS74

Population: women with anti-Ro or Ro/La and
Fetus with first degree heart block on echo
Fetus with second degree heart block on echo
Fetus with complete heart block on echo
Fetus with isolated endocardial fibroelastosis on echo

Intervention: Dexamethasone/betamethasone treatment (any dose or duration)

Comparator: No treatment with dexamethasone/betamethasone

Outcomes:

- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

146. In a pregnant woman with Ro/La antibodies with a fetus with first-degree heart block on fetal echo what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?

Summary: This PICO was indirectly addressed by 2 observational studies.[1,2]

Friedman 2008 prospectively analyzed 95 women with Ro/La antibodies (98 pregnancies) with first-degree and third-degree heart block on fetal echocardiogram. Due to the identification of CHB on fetal echo, this study also addresses PICO 148, below.[1] Results indicated CHB in 3 children (see below), fetal/infant death in 2 children (with CHB), first-degree block in 3 children, and pacemaker placement in 1 child with CHB. Complications also included neonatal lupus in 10 children, and neonatal lupus rash in 4 children (See Table 1).

No fluorinated steroid was reported in 15 fetuses either with AV prolongation between 2 and 6 z-scores or with type 1 second-degree block in 1 study.[2] Jaeggi 2011 included 165 fetuses of 142 anti-Ro/La antibody–positive women; 15 untreated fetuses with AV prolongation. Three fetuses were diagnosed with first-degree heart block; 2 spontaneously resolved, while 1 did not progress.

Quality of Evidence across outcomes: Very low

Table 1: Evidence from Indirect Comparisons

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/ other serious complications	Pacemaker
6122, Friedman 2008[1]	Prospective single-arm study	Perinatal period	Ninety-eight pregnancies in 95 mothers with anti-SSA/Ro antibodies; Fetal echocardiograms performed weekly from 16 to 26 weeks' gestation and biweekly from 26 to 34 weeks Previous child with CHB: 6 Previous child with rash: 4 First pregnancy: 44 Previously healthy children: 30	Dexamethasone 4 mg/day oral; see Footnote for timing to 3 mothers with fetuses who developed first-degree heart block based on prolongation of the PR interval (>150 ms)(see timing for fetuses with CHB under PICO 148) Authors noted that "none of the 6 affected fetuses displayed any discernible pattern of progressive PR prolongation before the primary outcome of block."	98 All anti-SSA/Ro+	CHB: 3 (*1 previous child with CHB, 2 previous children healthy)* 1st degree: 3 (*2 previous child with CHB, 1 previous children healthy*)	Death (non-CHB history): 2 (1 first pregnancy, 1 previous children healthy) Both deaths from CHB and severe hydrops.	Neonatal lupus: 10 Neonatal lupus rash only: 4 (normal ECG at birth)	Pacemaker: 1 (in child with CHB)
6111, Jaeggi 2011[2]	Prospective single arm study	Nine months	165 fetuses of 142 anti-Ro/La antibody–positive women (15 untreated fetuses with AV prolongation)	No dexamethasone/betamethasone	165 All anti-Ro/La+	1st degree heart block resolved/not progress but untreated: 3/15	**0**	**0**	**0**
TOTAL					**263 Ro pregnancies**	**3 CHB** **4 1st degree** **2.6%**	**2 deaths** **0.7%**	**10** **3.8%**	**1** **0.3%**

Footnote: Friedman 2008: Timing for 3 fetuses who developed 1st degree heart block**:** 1st fetus: At 20 weeks, (PR interval of 165 ms) the mother elected to take 4 mg/d dexamethasone. PR interval, 7 days later, was 135 ms. The mother continued 4 mg/d dexamethasone through rest of the pregnancy (PR intervals ranged from 110 to 133 ms). Normal ECG at birth and at 9 months; 2nd fetus: Missed 20 and 21-week echo, PR interval of 160 ms at 22 weeks, which decreased to 126 ms after 2 days of 4 mg dexamethasone. Dexamethasone continued until 26 weeks when oligohydramnios was detected. The PR intervals remained normal until birth; 3rd fetus: serial echocardiograms with normal PR intervals between 20 and 30 weeks; born prematurely at 32 weeks. The ECG at birth revealed first-degree heart block with a PR of 170 ms, which has persisted through the most recent ECG at 3 years of age (192 ms).

147. In a pregnant woman with Ro/La antibodies with a fetus with second-degree heart block on fetal echo what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?
No evidence

148. In a pregnant woman with Ro/La antibodies with a fetus with complete heart block on fetal echo, what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?

Summary: This PICO question was directly addressed by 1 observational study[6148, Saleeb 1999] and indirectly addressed by 3 observational studies.[1,3,4]

Saleeb 1999 retrospectively analyzed 47 mothers with Ro/La antibodies with 50 offspring (delivered during 1983 to 1998) with complete heart block (CHB). Fluorinated steroids including dexamethasone (4 to 9 mg/day for 3 to 19 weeks) or betamethasone (12 to 24 mg/week for > 6 weeks) were administered in 28 pregnancies, while 22 pregnancies remained untreated.[6148, Saleeb 2008] No significant between group differences were reported for death (14% fluorinated steroid, 4.5% untreated) or need for pacemaker in childhood (50% in each arm). These outcomes were rated very low due to downgrades in risk of bias (non-randomized, no blinding) and imprecision (single study with very few events (death) and point estimate indicating no difference (need for pacemaker)(See Table 2). Hydropic changes in pericardial effusions, pleural effusions, ascites, and hydrops fetalis were also reported (See Table 3). Authors noted that use of fluorinated steroid was most effective for resolving pleural effusions (2 of 2), ascites (6 of 8), and hydrops fetalis (5 of 8).

Cuneo 2010 included 29 fetuses with immune-mediated second-degree or third-degree atrioventricular (AV) block; maternal antibodies were characterized as SSA (n=24) or both SSA and SSB (n=6) antibodies. Daily dexamethasone therapy (4 mg orally) was initiated upon diagnosis of AV block. In utero treatment included dexamethasone (n=29), terbutaline (n=13), digoxin (n=3) and/or IVIG (n=1). Dexamethasone was administered to 95 women (98 pregnancies) in Friedman 2008. Tunks 2013 reported use of dexamethasone in 8 of 33 anti-Ro/SSA positive women (See Table 4). Other medications administered to patients included prednisone alone (n=2), hydroxychloroquine only (n=8), and prednisone and hydroxychloroquine (n=6).[1,3,4]

Friedman 2008 reported CHB in 3 patients, 2 fetal/infant deaths, neonatal lupus in 10 pregnancies, neonatal lupus rash in 4 pregnancies, and 1 pacemaker.[1] Cuneo 2010 reported heart failure in 2 fetuses, but no deaths. Tunks 2013 reported CHB in 4 fetuses (3 needing pacemakers), and 1st degree heart block in 4 fetuses (including 1 resolved 2nd degree block).[4] See PICO 146 above for evidence from one study evaluating no fluorinated steroid.

Quality of Evidence across outcomes: Very low

Table 2: Fluorinated steroid versus no fluorinated steroid for women with anti-Ro or Ro/La and fetus with CHB on echo

Bibliography: PICO 6C: Dexamethasone/Betamethasone for women with anti-Ro or Ro/La and fetus with CHB on echo.

• Certainty assessment							• Summary of findings				
• Nº of participants (studies) Follow-up	• Risk of bias	• Inconsistency	• Indirectness	• Imprecision	• Publication bias	• Overall certainty of evidence	• Study event rates (%)		• Relative effect (95% CI)	• Anticipated absolute effects	
							• With no • fluorinated steroid	• With fluorinated steroid		• Risk with no fluorinated steroid	• Risk difference with fluorinated steroid
Death											
50 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	1/22 (4.5%)	4/28 (14.3%)	**OR 3.50** (0.36 to 33.82)	45 per 1,000	**97 more per 1,000** (29 fewer to 571 more)
Need for pacemaker in childhood											
50 (1 observational study)	serious [a]	not serious [b]	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	11/22 (50.0%)	14/28 (50.0%)	**OR 1.00** (0.33 to 3.06)	500 per 1,000	**0 fewer per 1,000** (252 fewer to 254 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding; retrospective study

b. Not applicable
c. Single study with very few events. Very wide 95% CI overlaps the line of no difference.
d. Point estimate indicates no difference.
Reference: 6148, Saleeb 1999

Table 3: Additional Evidence from a Direct Comparisons: Fetus with Complete Heart Block on Echocardiography

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes
						Fetal hydrops/other serious complications
6148, Saleeb, 1999	Retrospective cohort	Births occurring during the period 1983–1998; Research Registry for Neonatal Lupus	47 mothers whose sera contain anti-SSA/Ro or anti-SSB/La antibodies; 50 offspring with CHB; all patients screened by Echo	Group A treated with dexamethasone 4–9 mg/day for 3–19 weeks or betamethasone 12–24 mg/week for >6 weeks (28 pregnancies) Group B untreated (22 pregnancies)	50 All anti-Ro/La	Hydropic changes *Pericardial effusions:* At presentation of bradyarrhythmia: 13 treated, 4 untreated; Developed during pregnancy: 2 treated, 2 untreated Present at birth: 7 treated, 3 untreated *Pleural effusions:* At presentation of bradyarrhythmia: 2 treated, 0 untreated; Developed during pregnancy: 1 treated, 1 untreated; Present at birth: 1 treated, 1 untreated *Ascites:* At presentation of bradyarrhythmia: 8 treated, 0 untreated; Developed during pregnancy: 0 treated, 1 untreated; Present at birth: 2 treated, 0 untreated *Hydrops fetalis:* At presentation of bradyarrhythmia: 8 treated, 0 untreated; Developed during pregnancy: 0 treated, 2 untreated; Present at birth: 3 treated, 1 untreated
TOTAL					**50 Ro pregnancies**	**Hydropic complications present at birth: 18** **36%**

Table 4: Additional Evidence from Indirect Comparisons: Fetus with Complete Heart Block on Echocardiography

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
6113, Cuneo, 2010[3]	Prospective single arm study		29 fetuses with immune-mediated second degree or third degree atrioventricular (AV) block Maternal antibodies were characterised as SSA (n=24) or both SSA and SSB (n=6) antibodies. Fetal echocardiography performed weekly	Maternal dexamethasone therapy (4 mg orally each day), which was initiated upon the diagnosis of fetal second or third degree AV block In utero therapy included dexamethasone (n=29), terbutaline (n=13), digoxin (n=3) and/or IVIG (n=1).	24	Treated with dexamethasone, terbutaline and digoxin Progression of echogenicity: 1 CHB: 0	Treated with dexamethasone, terbutaline and digoxin 0	Treated with dexamethasone, terbutaline and digoxin Heart failure: 2	0
6122, Friedman, 2008[1]	Prospective single-arm study	Perinatal period	Ninety-eight pregnancies in 95 mothers with anti-SSA/Ro antibodies; fetal echocardiograms performed weekly from 16 to 26 weeks' gestation and biweekly from 26 to 34 weeks Previous child with CHB: 16 Previous child with rash: 8 First pregnancy: 44 Previously healthy children: 30	Dexamethasone 4 mg/day oral; see Footnote below for 3 mothers with fetuses who developed third-degree block	98	Third degree block: 3 (1 previous child with CHB, 2 previous children healthy) Overall heart block: 6 (in 3/16 pregnancies (19%) in mothers with a previous child with CHB, in 3 of 74 pregnancies (4%) in mothers without a previous child with CHB or rash).	Death: 2 (1 first pregnancy, 1 previous child healthy)	Neonatal lupus: 10 Neonatal lupus rash only: 4 (normal ECG at birth)	1

6167, Tunks, 2013[4]	Observational	2007–2011	33 women anti-Ro/SSA positive; 2 with previous history of CHB Diagnosis on fetal echo: CHB: 4 (2 with prior history of CHB) First degree AVB including one resolved 2nd degree: 4	Predinsone only n=2 (5mg qd and 20mg qd) HCQ only n= 8 200mg qd – 400mg qd) No Prednisone or HCQ n=17 Prednisone + HCQ n=6	33	CHB: 4 (all treated with dexamethasone 4 mg orally once daily, no hydroxychloroquine or prednisone) 1st degree including one resolved 2nd degree: 4 (all treated prophylactically with dexamethasone, 1 also received HCQ 200 mg BID) Pacemaker: 3	0	0	3
TOTAL					**155**	**7 CHB** **4 1st degree** **7%**	**2 deaths** **1.2%**	**10** **6.4%**	**4** **2.5%**

Footnote: Friedman 2008: Timing of dexamethasone for 3 mothers with fetuses who developed third-degree block: 1st fetus:.Transient mild tricuspid regurgitation at 17 weeks, persistent atrial echodensity at 22 weeks', third-degree block at 23 weeks. Despite initiation of maternal treatment with 4 mg dexa orally per day, the pregnancy **terminated** at 24 weeks due to severe hydrops; 2nd fetus: Moderate/severe tricuspid regurgitation observed at 19 weeks, third-degree block diagnosed at 21 weeks. Despite 4 mg dexa, third-degree block persisted through follow-up at 8 months of age; the child received a pacemaker at birth; 3rd fetus: Third-degree block with severe hydrops noted after 18 weeks. Pregnancy terminated at 20.5 weeks for severe hydrops unresponsive to 4 mg/d maternal dexamethasone.

149. In a pregnant woman with Ro/La antibodies with fetus with isolated endocardial fibroelastosis on echo what is the impact of taking fluorinated steroid versus no fluorinated steroid treatment on offspring outcomes [listed]?

Summary: This PICO was indirectly addressed by 1 observational study.[5] Trucco 2011 retrospectively reviewed records for 20 women with Ro/La antibodies; 16 fetuses with endocardial fibroelastosis and 4 with reduced ventricular function (See Table 5). Women were treated with dexamethasone (17/20) and IVIG (9/20). Dexamethasone was administered for a diagnosis of AVB (n = 13), MAb-CM/EFE (n=3), and as a replacement for prednisone for AVB prescribed at a referring institution (=1). Dexamethasone max mg/day was 3 (n=1), 4 (n=5), 5 (n=1), 8 (n=9), and 16 (n=1). Results indicated CHB in 11 (55%) patients, 4 (20%) fetal/infant deaths, fetal hydrops in 6 (30%) patients, and pacemaker placement in 12 (63%) patients. Authors noted that AV conduction improved in 4 fetuses (2 dexamethasone only, 2 dexamethasone plus IVIG), while AVB progressed in 2 fetuses (both dexamethasone only). See PICO 148 above for evidence from one study evaluating no fluorinated steroid.

Quality of Evidence across outcomes: Very low

Table 5: Evidence from an Indirect Comparison: Fetus with Isolated Endocardial Fibroelastosis (EFE) on Echocardiography

Author, year	Study type	Duration	Population description	Treatment given to relevant population	Number of pregnancies	Outcomes			
						Complete heart block	Fetal death or infant death	Fetal hydrops/other serious complications	Pacemaker
6112, Trucco, 2011[5]	Retrospective observational	Perinatal period with a median follow-up of 2.9 years	20 women with a median gestational age of 23 weeks (range 18 to 38 weeks). 19 anti-Ro/ 8 anti-La antibody positive; 7 clinical autoimmune disease Fetal echocardiography referral was for fetal bradycardia in 17 (85%) and suspected CM/EFE in 3 (15%). 16 with endocardial fibroelastosis; 4 with reduced ventricular function; 16 (80%) had reduced or borderline ventricular shortening fraction (≤30%) before or after birth	<u>During pregnancy</u> Dexamethasone: 17/20 IVIG: 9/20 <u>Dexamethasone administration</u>: at diagnosis of AVB (n = 13), MAb-CM/EFE (n=3), as a replacement for prednisone for AVB prescribed at a referring institution (=1). Dexamethasone max mg/day was 3 (n=1), 4 (n=5), 5 (n=1), 8 (n=9), and 16 (n=1) <u>IVIG administration</u>: Prenatally to 9 (47%) mothers at a dose of 70 g (~1 g/kg). Single dose (n=3), 2 pre-natal doses (n=3), and ≥ 3 doses (n=3). Multiple doses were used in the setting of worsening or persistent bradycardia and ventricular dysfunction.	19	11 (55%)	4 (20%)	6 (30%)	12 (63%)

TOTAL	**19 Ro pregnancies**	**11 CHB** **57.8%**	**4 deaths** **57.8%**	**6 complications** **31.5%**	**12 pacemakers** **63.1%**

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5. Trucco SM, Jaeggi E, Cuneo B, Moon-Grady AJ, Silverman E, Silverman N, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. Journal of the American College of Cardiology. 2011;57(6):715-723.

6D.

6D. In a pregnant woman with Ro/La antibodies with abnormal fetal ECHO [listed] what is the impact of IVIG therapy versus no IVIG therapy on offspring outcomes [listed]?

EVIDENCE HERE FOR GS75, GS76, GS77, GS78

Population: women with anti-Ro or Ro/La and
- Fetus with first degree heart block on echo
- Fetus with second degree heart block on echo
- Fetus with CHB on echo
- Fetus with isolated endocardial fibroelastosis on echo

Intervention: IVIG

Comparator: No treatment with IVIG

Outcomes:
- Complete heart block
- Fetal hydrops/other serious complications
- Fetal death or infant death
- Need for a pacemaker in childhood

150. In a pregnant woman with Ro/La antibodies with a fetus with first degree heart block on fetal echo what is the impact of taking IVIG versus no IVIG treatment on offspring outcomes [listed]?

No evidence.

151. In a pregnant woman with Ro/La antibodies with a fetus with second degree heart block on fetal echo what is the impact of taking IVIG versus no IVIG treatment on offspring outcomes [listed]?

No evidence.

152. In a pregnant woman with Ro/La antibodies with a fetus with complete heart block on fetal echo, what is the impact of taking IVIG versus no IVIG treatment on offspring outcomes [listed]?

Summary: This PICO was directly addressed by one observational study[1] and indirectly addressed by one observational study.[2]

Pisoni 2010[1] directly compared IVIG (n=15) with no IVIG (n=9) in 24 pregnancies involving women with Ro/La antibodies. Most common diagnoses included Sjogren's syndrome (n=11), undifferentiated connective tissue disease (n=3), asymptomatic (n=3), and mixed connective tissue disease (n=2). IVIG was administered 400 mg/kg at weeks 12, 15, 18, 21, and 24. Complete heart block (CHB) was identified on fetal echo screening undergone at least every 3 weeks from weeks 15 to 30. No significant differences were reported for all outcomes including 3rd degree CHB, fetal death, and pacemaker placement. Evidence was rated very low due to downgrades in risk of bias (lack of randomization and blinding) and imprecision (small single study with very few events reported).

Additional evidence was provided by Friedman 2010 who prospectively followed 20 women with anti-SSA/Ro antibodies and a previous child with CHB/rash. All patients similarly received five IVIG infusions of 400 mg/kg from weeks 12 to 24. Results included 3 CHB, 1 case of neonatal rash consistent with neonatal lupus, and need for pacemaker placement in 2 infants.[2]

Quality of Evidence across outcomes: Very low

Table 1: IVIG compared to no IVIG for Ro/La positive pregnant women with fetus with CHB on echo

Bibliography: PICO 6d: IVIG for Ro/La positive pregnant women.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no IVIG	**With IVIG**		**Risk with no IVIG**	**Risk difference with IVIG**
3rd degree CHB											
24 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	1/9 (11.1%)	3/15 (20.0%)	**OR 2.00** (0.18 to 22.80)	111 per 1,000	**89 more per 1,000** (89 fewer to 629 more)
Fetal death (termination)											

Table 1: IVIG compared to no IVIG for Ro/La positive pregnant women with fetus with CHB on echo

Bibliography: PICO 6d: IVIG for Ro/La positive pregnant women.

Certainty assessment							Summary of findings				
24 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	1/9 (11.1%)	2/15 (13.3%)	**OR 1.23** (0.10 to 15.87)	111 per 1,000	**22 more per 1,000** (99 fewer to 554 more)
Pacemaker placement											
24 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	0/9 (0.0%)	1/15 (6.7%)	**OR 1.97** (0.07 to 53.48)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding

b. Not applicable

c. Small single study with very few events reported. Very wide 95% CI overlaps the line of no difference.

References: 6114 Pisoni 2010

Table 2: Additional Evidence from an Indirect Comparison

Outcome	Author, year	Study type	Duration	Population description	Treatment given to relevant population	Results
Complete heart block	4211, Friedman 2010[2]	Prospective observational	January 2007 and January 2009	20 women with anti-SSA/Ro antibodies, a previous child with CHB/rash, </= 20 mg prednisone, < 12 weeks pregnant. CHB on screening	All patients received IVIG infusions of 400mg/kg over 3 to 4 hours at 12 weeks, 15 weeks, 18 weeks, 21 weeks and 24 weeks of gestation.	CHB: 3
Fetal hydrops or other complications	4211, Friedman 2010[2]	Prospective observational	January 2007 and January 2009	20 women with anti-SSA/Ro antibodies, a previous child with CHB/rash, </= 20 mg prednisone, < 12 weeks pregnant. CHB on screening	All patients received IVIG infusions of 400mg/kg over 3 to 4 hours at 12 weeks, 15 weeks, 18 weeks, 21 weeks and 24 weeks of gestation.	Neonatal rash consistent with neonatal lupus: 1
Pacemaker	4211, Friedman 2010[2]	Prospective observational	January 2007 and January 2009	20 women with anti-SSA/Ro antibodies, a previous child with CHB/rash, </= 20 mg prednisone, < 12 weeks pregnant. CHB on screening	All patients received IVIG infusions of 400mg/kg over 3 to 4 hours at 12 weeks, 15 weeks, 18 weeks, 21 weeks and 24 weeks of gestation.	Need for pacemaker: 2

153. In a pregnant woman with Ro/La antibodies with fetus with isolated endocardial fibroelastosis on echo what is the impact of taking IVIG versus no IVIG treatment on offspring outcomes [listed]?

Summary: This PICO was directly addressed by one observational study retrospectively following 20 consecutive pregnant women with Ro/La antibodies and known cardiomyopathy on fetal echocardiography.[3] Endocardial fibroelastosis (EFE) was identified in 16 fetuses, and suspected in 4 fetuses. IVIG 1g/kg plus steroids were administered to 9 women, and steroids alone were administered to 11 women. IVIG was administered prenatally to 9 (47%) mothers at a dose of 70 g (~1 g/kg); 3 mothers receiving 3 doses. Multiple doses were used in the setting of worsening or persistent bradycardia and ventricular dysfunction. Results indicated a statistically significant difference for fetal hydrops favoring no IVIG. No significant differences were reported for the three remaining outcomes although IVIG was favored for 2 outcomes (CHB and pacemaker placement), while no IVIG was favored for 1 outcome (fetal or infant death). Fetal hydrops occurred in 6 infants (5 IVIG) and pacemakers were placed in 12 infants (8 no IVIG).

Quality of Evidence across outcomes: Very low

Table 3: IVIG compared to no IVIG in known cardiomyopathy for Ro/La positive pregnant women

Bibliography: PICO 6d: IVIG for Ro/La positive pregnant women.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no IVIG	**With IVIG**		**Risk with no IVIG**	**Risk difference with IVIG**
Complete heart block											
20 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	8/11 (72.7%)	3/9 (33.3%)	**OR 0.19** (0.03 to 1.28)	727 per 1,000	**391 fewer per 1,000** (653 fewer to 46 more)
Fetal hydrops											
28 (1 observational study)	serious [a]	not serious [b]	not serious	not serious	none	⨁◯◯◯ VERY LOW	1/19 (5.3%)	5/9 (55.6%)	**OR 22.50** (2.03 to 249.24) Favors no IVIG	53 per 1,000	**503 more per 1,000** (49 more to 880 more)
Fetal or infant death											

Table 3: IVIG compared to no IVIG in known cardiomyopathy for Ro/La positive pregnant women

Bibliography: PICO 6d: IVIG for Ro/La positive pregnant women.

Certainty assessment							Summary of findings				
20 (1 observational study)	serious [a]	not serious [b]	not serious	serious [d]	none	⨁◯◯◯ VERY LOW	1/11 (9.1%)	3/9 (33.3%)	**OR 5.00** (0.42 to 59.66)	91 per 1,000	**242 more per 1,000** (51 fewer to 766 more)
Pacemaker placement											
20 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	8/11 (72.7%)	4/9 (44.4%)	**OR 0.30** (0.05 to 1.94)	727 per 1,000	**283 fewer per 1,000** (610 fewer to 111 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding

b. Not applicable

c. Small single study. 95% CI overlaps the line of no difference.

d. Small single study with very few events reported. Wide 95% CI overlaps the line of no difference.

References: 6112 Trucco 2011

References:

1. Pisoni CN, Brucato A, Ruffatti A, Espinosa G, Cervera R, Belmonte-Serrano M, et al. Failure of intravenous immunoglobulin to prevent congenital heart block: Findings of a multicenter, prospective, observational study. Arthritis and rheumatism. 2010;62(4):1147-1152.
2. Friedman DM, Llanos C, Izmirly PM, Brock B, Byron J, Copel J, et al. Evaluation of fetuses in a study of intravenous immunoglobulin as preventive therapy for congenital heart block: Results of a multicenter, prospective, open-label clinical trial. Arthritis and rheumatism. 2010;62(4):1138-1146.

3. Trucco SM, Jaeggi E, Cuneo B, Moon-Grady AJ, Silverman E, Silverman N, et al. Use of intravenous gamma globulin and corticosteroids in the treatment of maternal autoantibody-mediated cardiomyopathy. Journal of the American College of Cardiology. 2011;57(6):715-723.

7. Menopause:

7A.

7A. In postmenopausal women with SLE, what is the impact of HRT versus no HRT on risk of SLE flare?

Population: Post-menopausal women with SLE

Intervention:

- Use of oral postmenopausal hormone therapy (estrogen or estrogen/progestin)
- Use of estrogen-progestin patch

Comparison: Similar patients not using postmenopausal hormone therapy

Outcome: SLE flare

154. In postmenopausal women with SLE, what is the impact of oral postmenopausal hormone therapy (estrogen or estrogen/progestin) versus no HRT therapy on risk of SLE flare? **GS79**

Four studies provided direct evidence for this PICO. The two RCTs[1,2] showed no difference between placebo and HRT for severe flare. Two observational studies showed more flares in the placebo group compared to the HRT group.[3,4] One observational trial provided indirect information regarding rates of flare in the pre- and postmenopausal period, but no information regarding HRT was available.[5]

Quality of evidence across outcomes (RCTs): Moderate

HRT compared to Placebo for Post-menopausal Women with SLE
Bibliography: Shah A. PICO 11a. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With Placebo	With HRT		Risk with Placebo	Risk difference with HRT
SLE flare											

HRT compared to Placebo for Post-menopausal Women with SLE

Bibliography: Shah A. PICO 11a. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
457 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	57/226 (25.2%)	47/231 (20.3%)	**OR 0.53** (0.27 to 1.02)	252 per 1,000	**101 fewer per 1,000** (169 fewer to 4 more)
Multiple SLE flare											
106 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	24/52 (46.2%)	26/54 (48.1%)	**OR 1.08** (0.51 to 2.32)	462 per 1,000	**19 more per 1,000** (157 fewer to 204 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Direct Evidence						
SLE Flare	6425, Mok, 1998[3]	Observational	Median follow up for HRT = 35 months Median follow up for non-HRT = 50 months	34 postmenopausal SLE women	HRT vs. non-HRT A major relapse was one that involved a major organ/system of the body which required commencement or augmentation of prednisolone to a dose of more than 0.5 mg/kg/day, with or without subsequent use of cytotoxic agents (azathioprine or cyclophosphamide). A minor relapse was a mild flare of the disease not to the extent of above but requiring augmentation or commencement of prednisolone at a dose of less than 0.5 mg/kg/day, with or without subsequent	**HRT n=11** Number of minor flares/patient = 0.45+/-0.25 Number of major flares/patient = 0.09+/-0.09 **Non-HRT n=23** Number of minor flares/patient = 0.61+/-0.22 Number of major flares/patient = 0.30+/-0.15

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					azathioprine, hydroxychloroquine, or non-steroidal anti-inflammatory drugs (NSAID) for control.	
	11583 Kreidstein, 1997[4]	observational	12 months	16 postmenopausal SLE women taking HRT for at least 12 months 32 postmenopausal SLE women not taking HRT	HRT vs. non-HRT	**HRT n=16** Clinical flare w/ or w/out serologic abnormalities = 5/16 (31%) **Non-HRT n=32** Clinical flare w/ or w/out serologic abnormalities = 17/32 (53%)
Indirect Evidence						
SLE Flare	6424 Sanchez-Guerrero, 2001[5]	Observational	They were studied for a mean of 6.4 +/- 1.7 years (range, 4 to 8 years). The mean premenopausal period was 3.3 +/- 0.9 years (range, 2 to 4 years), and the mean postmenopausal period was 3.2 +/- 0.9 years (range, 2 to 4 years)	30 postmenopausal SLE women	No treatment given	There were 55 disease flares during 98 patient-years in the premenopausal period, compared with 40 flares during 93 patient-years in the postmenopausal period (RR=1.3; 95% CI: 0.9 to 2.0). There were 17 severe flares in the premenopausal period, and 11 during the postmenopausal period (RR=1.5; 95% CI: 0.7 to 3.5).

155. In postmenopausal women with SLE, what is the impact of estrogen patch (plus progesterone) as postmenopausal hormone therapy versus no HRT therapy on risk of SLE flare?

No Evidence

References:

1. Sanchez-Guerrero J, Gonzalez-Perez M, Durand-Carbajal M, Lara-Reyes P, Jimenez-Santana L, Romero-Diaz J, et al. Menopause hormonal therapy in women with systemic lupus erythematosus. Arthritis and rheumatism. 2007;56(9):3070-3079.
2. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Annals of internal medicine. 2005;142(12 Pt 1):953-962.
3. Mok CC, Lau CS, Ho CT, Lee KW, Mok MY, Wong RW. Safety of hormonal replacement therapy in postmenopausal patients with systemic lupus erythematosus. Scandinavian journal of rheumatology. 1998;27(5):342-346.
4. Kreidstein S, Urowitz MB, Gladman DD, Gough J. Hormone replacement therapy in systemic lupus erythematosus. The Journal of rheumatology. 1998;24(11):2149-2152.
5. Sanchez-Guerrero J, Villegas A, Mendoza-Fuentes A, Romero-Diaz J, Moreno-Coutino G, Cravioto MC. Disease activity during the premenopausal and postmenopausal periods in women with systemic lupus erythematosus. The American journal of medicine. 2001;111(6):464-468.

7B.

7B. In postmenopausal women with RD and aPL [variables listed] who experience menopausal symptoms, what is the impact of HRT versus no HRT on thrombosis risk? GS80, GS81, GS82, GS83

Population: Postmenopausal women with RD and positive aPL

- With positive aPL and no history of thrombosis
- With thrombotic APS on long-term anticoagulation

Intervention:

- Oral postmenopausal hormone therapy (estrogen or estrogen/progestin)
- Estrogen-progestin patch

Comparison: Similar patients not using postmenopausal hormone therapy

Outcome: Thrombosis

156. In postmenopausal women with RD who have positive aPL and no history of thrombosis and who experience menopausal symptoms, what is the impact of oral postmenopausal hormone therapy (estrogen or estrogen/progestin) versus no HRT therapy on likelihood of thrombosis?

The two RCTs (Cravioto 2011 & Buyon 2005) showed no difference between HRT compared to placebo. Both studies focused on patients with SLE, not aPL. The Buyon study excluded patients with lupus anticoagulant and high titer aCL, both studies excluded previous thrombosis (Cravioto if within three months)

Quality of Evidence across outcomes: Moderate

HRT compared to Placebo for Post-menopausal Women with SLE and aPL
Bibliography: Shah A. PICO 11b. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With HRT	**With Placebo**		**Risk difference with HRT**	**Risk difference with Placebo**
Thrombosis											
457 (2 RCTs)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	6/226 (2.7%)	2/231 (0.9%)	**OR 0.32** (0.06 to 1.59)	27 per 1,000	**18 fewer per 1,000** (25 fewer to 15 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

157. In postmenopausal women with RD who have positive aPL and no history of thrombosis and who experience menopausal symptoms, what is the impact of estrogen patch (plus progesterone) as postmenopausal hormone therapy versus no HRT therapy on likelihood of thrombosis?

No Evidence

158. In postmenopausal women with RD who have thrombotic APS on long-term anticoagulation, and who experience menopausal symptoms, what is the impact of oral postmenopausal hormone therapy (estrogen or estrogen/progestin) versus no HRT therapy on likelihood of thrombosis?

No Evidence

159. In postmenopausal women with RD who have thrombotic APS on long-term anticoagulation and who experience menopausal symptoms, what is the impact of estrogen patch (plus progesterone) as postmenopausal hormone therapy versus no HRT therapy on likelihood of thrombosis?

No Evidence

References:

1. Cravioto MD, Durand-Carbajal M, Jimenez-Santana L, Lara-Reyes P, Seuc AH, Sanchez-Guerrero J. Efficacy of estrogen plus progestin on menopausal symptoms in women with systemic lupus erythematosus: a randomized, double-blind, controlled trial. Arthritis care & research. 2011;63(12):1654-1663.
2. Buyon JP, Petri MA, Kim MY, Kalunian KC, Grossman J, Hahn BH, et al. The effect of combined estrogen and progesterone hormone replacement therapy on disease activity in systemic lupus erythematosus: a randomized trial. Annals of internal medicine. 2005;142(12 Pt 1):953-962.

8. Long-Term Issues:

8A: No Evidence

8A. In women with OB APS (revised Sapporo criteria), what is the impact of long-term, low-dose aspirin after pregnancy versus no long-term, low-dose aspirin on the risk of thrombosis?

Population:
- Women with positive aPL who meet criteria of OB-APS but do not have a history of thrombosis

Intervention:
- Low-dose aspirin long-term

Comparator:
- No treatment with long-term, low-dose aspirin

Outcome:
- Risk of thrombosis

PART II: MEDICATION USE BEFORE, DURING, AND AFTER PREGNANCY

1. Paternal Medication Exposure:

1A.

1A. In males with RD on medication who are planning to father a child, what is the impact of stopping medication [listed] prior to conception versus continuing medication on fertility issues and pregnancy outcome?

Population: males with RD who are planning to father a child and who are on medication, including…

- Nonimmunosuppressive:
  - Classic NSAIDs
  - Cox2 inhibitors
  - Antimalarials
  - Sulfasalazine
  - Colchicine
- Classic, or synthetic, immunosupressives:
  - Methotrexate
  - Leflunomide
  - Azathioprine / 6-MP
  - Mycophenolate mofetil / mycophenolic acid
  - Cyclosporine
  - Tacrolimus
  - Cyclophosphamide
  - Thalidomide
- Biologic immunosuppressives: TNF-inhibitors:
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Biologic immunosuppressives: Non-TNF biologics:
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab

    - Secukinumab
    - Ustekinumab
- Novel small molecules:
    - Tofacitinib
    - Baracitinib
    - Apremilast
- Other:
    - IVIG
    - Anticoagulants:
        - Warfarin
        - DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)
        - heparin/LMWH
        - other antiplatelet agents

Intervention: stop medication prior to conception

Comparator: continue chronic medication

Outcomes:

- MBD
- Spontaneous abortion
- Sperm quality (sperm count, morphology, motility)
- Time to conception
- Need for assisted reproductive technology (ART)
- Pregnancy
- RD flare
- RD damage

160. In males with RD on medication who are planning to father a child, what is the impact of stopping classic NSAIDs prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **EVIDENCE FOR GS85**

A single study evaluated pregnancy outcomes with paternal exposure to NSAIDS within three months prior to conception using administrative data from the Norwegian Prescription Database.[1] No major congenital malformations were identified in the 705 children with paternal NSAID exposure. No other pregnancy outcomes were discussed. Indirect evidence only.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment conducted to relevant population	Results
Congenital malformations	6168 Viktil 2012[1]	Observational	2004-2007	Pregnancies in Norway over 3 years Maternal and fetal exposures to anti-rheumatic drugs.	Patients treated with any of the following: NSAIDs, CS, SSZ, AZA, HCQ, ETAN, MTX, LEF, ADA.	154,976 expectant pregnancies. 1461 mothers and 1198 fathers were given anti-rheumatic drugs at least once during the study period. Exposures: 8 methotrexate, 2 leflunomide, 58 HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab. No major malformations associated with mtx, leflunomide, etanercept, or adalimumab. OR for malformations in children with fathers who had been exposed: 1.19 (0.93-1.51) OR for major malformation in children with fathers: 1.26 (0.93-1.71) No children born to mothers exposed to MTX, LEF, ETAN, ADA had major malformations.

161. In males with RD on medication who are planning to father a child, what is the impact of stopping Cox2 inhibitors prior to conception versus continuing the medication on fertility issues and pregnancy outcome?
No evidence

162. In males with RD on medication who are planning to father a child, what is the impact of stopping antimalarials prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

163. In males with RD on medication who are planning to father a child, what is the impact of stopping sulfasalazine prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **EVIDENCE FOR GS94 AND GS94A**

A single study reported pregnancy outcomes following paternal exposure to sulfasalazine among other DMARDs using Norwegian Nationwide administrative data.[2] Among 110 identified pregnancies with paternal DMARD exposure within 12 weeks prior to conception, 17 were exposed to sulfasalazine. No congenital malformations were reported among paternal sulfasalazine-exposed pregnancies. Other pregnancy outcomes were not separated by individual DMARD. Indirect evidence only in a small sample size.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment conducted to relevant population	Results
Congenital malformations	922, Wallenius 2015[2]	Case-control study	12 weeks	1,796 men with inflammatory joint disease associated with 2,777 births in the MBRN.	In 110 of these births, the fathers were exposed to DMARDs within 12 weeks before conception, and in 230 births the fathers had never been exposed to DMARDs before conception. The DMARDs (monotherapy or combination treatment) to which the fathers were mostly exposed within 12 weeks of conception were methotrexate (n = 49), sulfasalazine (n = 17), and tumor necrosis factor inhibitors (n = 57).	• The relative risk of serious malformation for DMARD-exposed births was RR 1.22 [CI 0.45, 3.31]; for never DMARD-exposed births was RR =0.70 [CI 0.26. 1.86]. Malformations in 4 of the 110 preconception DMARD exposed births. • The mean differences in birth weights in the DMARD-exposed group (25.1 gm [CI 68.9, 119.2]) and the never DMARD-exposed group (-3.6 gm [CI 14.5, 7.3]).

164. In males with RD on medication who are planning to father a child, what is the impact of stopping colchicine prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

165. In males with RD on medication who are planning to father a child, what is the impact of stopping methotrexate prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **EVIDENCE FOR GS101**

One study was identified that compared pregnancy outcomes with paternal exposure to methotrexate to those without paternal exposure to methotrexate or other teratogens[3]. 525 pregnancies were identified using a Teratology Information Service in

Germany, 113 of which had paternal exposure to methotrexate within three months of conception (median dose 15 mg/week) and 412 were fathered by men not taking methotrexate or other known teratogens. No statistical differences in pregnancy outcomes were identified. Live birth rate was 77% for methotrexate exposed pregnancies compared to 84.7% of unexposed pregnancies. Spontaneous abortion rate was not different between groups (Hazard ratio 1.19, 95% CI 0.81-3.51). Major birth defects were seen in 1.1% of both groups (Odds ratio 1.02, 95%CI 0.4-2.5).

Two additional studies identified pregnancies with paternal exposure to methotrexate among other DMARDs, both using administrative data from Norway[1,2]. One identified 50 pregnancies with paternal methotrexate use within three months of conception[1]. Of these 50 pregnancies, three infants were born with major congenital malformations (6%). The second study identified 49 pregnancies with paternal methotrexate exposure (21 with concomitant tumor necrosis factor inhibitor exposure[2]. Two congenital malformations were identified among the methotrexate-exposed group. In both of these studies, No comparator group of pregnancies without paternal methotrexate were included, nor was any information regarding maternal health conditions or medication use provided. It is very likely that many of the same pregnancies were analyzed in both studies, given the use of the same database during overlapping periods of time. **Indirect evidence only.**

In summary, three studies examined rates of major congenital anomalies among infants with paternal exposure to methotrexate at doses used for rheumatic diseases. Two studies, using overlapping data, found low rates of congenital anomalies among exposed infants (4-6%) without comparator groups. The third study directly compared paternal methotrexate exposure to non-exposed pregnancies and found no statistical differences in any pregnancy outcomes examined. With a limited number of evaluated pregnancies, (<200), there does not appear to be evidence of an increase in adverse pregnancy outcomes with paternal methotrexate exposure.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment conducted to relevant population	Results
Direct Evidence						
Birth defects	1029, Weber-Schoendorfer 2014[3]	prospective observational cohort study	> than 12 months	113 pregnancies with paternal low-dose MTX treatment compared with 412 nonexposed pregnancies.	The median MTX dose was 15 mg/week for fathers. The median duration of MTX administration after LMP in the post-conception exposed cases was 10 weeks.	• Major birth defects in MTX group is 1 vs control group 4 • Chromosomal Aberrations in MTX group is 1 vs control group 2 • Minor birth defects in MTX group is 4, not reported for control group

						• Rate of major birth defects between groups OR 1.02, (CI=0.05, 7.0) • The cumulative incidence of live births 65.2% (CI 54.4, 75.8) vs 69.1% (CI 1.5, 76.4). • Stillborn infants 0 vs 3
Spontaneous abortion	1029, Weber-Schoendorfer 2014[3]	prospective observational cohort study	> than 12 months	113 pregnancies with paternal low-dose MTX treatment compared with 412 nonexposed pregnancies.	The median MTX dose was 15 mg/week for fathers. The median duration of MTX administration after LMP in the post-conception exposed cases was 10 weeks.	• Spontaneous abortions HR 1.19, (CI=0.65, 2.17) • The cumulative incidence of SAB 21.4%, (CI 13.4, 33.2) vs (22.4, CI 16.0, 30.8). • The HR for SAB 1.19 (CI 0.65, 2.17). • SAB (percentage after exclusion of ETOPs) 15 (14.7%) vs 40 (10.2%) • The cumulative incidence of ETOP 13.4% (CI 7.5, 23.3) vs 8.5% (CI 5.2, 13.7); (HR 1.69, CI 0.81, 3.51).
Indirect Evidence						
Congenital malformations	922, Wallenius 2015[2]	Case-control study	12 weeks	1,796 men with inflammatory joint disease associated with 2,777 births in the MBRN.	In 110 of these births, the fathers were exposed to DMARDs within 12 weeks before conception, and in 230 births the fathers had never been exposed to DMARDs before conception. The DMARDs (monotherapy or combination treatment) to which the fathers were mostly exposed within 12 weeks of conception were methotrexate (n = 49), sulfasalazine (n = 17), and tumor necrosis factor inhibitors (n = 57).	• The relative risk of serious malformation for DMARD-exposed births was RR 1.22 [CI 0.45, 3.31]; for never DMARD-exposed births was RR =0.70 [CI 0.26. 1.86]. Malformations in 4 of the 110 preconception DMARD exposed births. • The mean differences in birth weights in the DMARD-exposed group (25.1 gm [CI 68.9, 119.2]) and the never DMARD-exposed group (-3.6 gm [CI 14.5, 7.3]).
	6168 Viktil 2012[1]	Observational	2004-2007	Pregnancies in Norway over 3 years	Patients treated with any of the following: NSAIDs, CS, SSZ, AZA, HCQ, ETAN, MTX, LEF, ADA.	154,976 expectant pregnancies. 1461 mothers and 1198 fathers were given anti-rheumatic drugs at least once during the study period. Exposures: 8

				Maternal and fetal exposures to anti-rheumatic drugs.		methotrexate, 2 leflunomide, 58 HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab. No major malformations associated with mtx, leflunomide, etanercept, or adalimumab. OR for malformations in children with fathers who had been exposed: 1.19 (0.93-1.51) OR for major malformation in children with fathers: 1.26 (0.93-1.71) • No children born to mothers exposed to MTX, LEF, ETAN, ADA had major malformations.

ETOP: elective termination of pregnancy; SAB: Spontaneous abortion

166. In males with RD on medication who are planning to father a child, what is the impact of stopping leflunomide prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

167. In males with RD on medication who are planning to father a child, what is the impact of stopping azathioprine / 6-MP prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

168. In males with RD on medication who are planning to father a child, what is the impact of stopping mycophenolate mofetil or mycophenolic acid prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

169. In males with RD on medication who are planning to father a child, what is the impact of stopping cyclosporine prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

170. In males with RD on medication who are planning to father a child, what is the impact of stopping tacrolimus prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

171. In males with RD on medication who are planning to father a child, what is the impact of stopping cyclophosphamide prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

172. In males with RD on medication who are planning to father a child, what is the impact of stopping thalidomide prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

173. In males with RD on medication who are planning to father a child, what is the impact of stopping tumor necrosis factor inhibitors (as a class) prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **EVIDENCE FOR GS143, GS146, GS149, GS152, GS155**

Several studies have examined pregnancy outcomes following paternal exposure to TNFi, the majority of which look at the group of available medications as a class rather than individual therapies. The largest study is a cohort study using administrative data from Denmark[4]. This study identified 372 singleton pregnancies with paternal exposure to TNFi agents and compared outcomes to those of 399,498 children born to fathers without paternal TNFi exposure. Rates of congenital anomalies, preterm delivery, and small for gestational age were not significantly different between groups. Additional analyses evaluating only fathers with inflammatory bowel disease or with dermatological/rheumatological diagnoses found similar results (See Table, below).

Quality of Evidence across outcomes: Very low.

Paternal use of medication for RD impact on pregnancy outcome compared to placebo in males with RD on pregnancy outcome

Bibliography: PICO 1a: Impact of stopping v continuing medication in males with RD on pregnancy outcome.

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With placebo	**With medication**		**Risk with placebo**	**Risk difference with use of medication**
Paternal anti-TNF impact on rate of congenital abnormalities											
399870 (1 observational study)	serious [a]	not serious [b]	not serious	serious [c]	none	⨁◯◯◯ VERY LOW	23244/399498 (5.8%)	21/372 (5.6%)	**OR 0.97** (0.62 to 1.50)	58 per 1,000	**2 fewer per 1,000** (21 fewer to 27 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Non-randomized, no blinding

b. Not applicable

c. 95% CI overlaps the line of no difference.

Reference: 2344, Larsen 2016

Two additional studies (both using Norwegian administrative data) included TNFi among paternal DMARD exposure[1,2]. One study identified 57 pregnancies fathered by TNFi exposed men, of these 21 (36.8%) had concomitant methotrexate exposure[2]. Three congenital malformations were seen in infants of TNFi exposed fathers (5.2%), one of which was also paternally exposed to methotrexate. The other study identified 46 pregnancies with paternal TNFi exposure (40 etanercept and 6 adalimumab)[1]. One child (2.2%), exposed to etanercept, was diagnosed with a major congenital malformation. In both of these studies, comparisons to unexposed fathers were made by DMARD exposure as a group, not individual classes of medications. Additionally, it is highly likely

that these studies included overlapping observations. Maternal considerations were not addressed in the studies. In conclusion, although the evidence is mostly indirect and sample sizes relatively small, there does not appear to be an increased risk of congenital malformations with paternal TNFi exposure within three months of conception.

Two studies evaluated the impact of Tumor necrosis factor inhibitors (as a class) in seminal fluid analysis in men with spondyloarthropathies[5,6]. One study compared semen analysis in 20 men after 3-6 months of TNFi therapy to that of 42 healthy men[6]. No differences in oligospermia, semen volume, or sperm concentration were identified between groups. A separate study compared sperm quality in10 men with spondyloarthropathies after 12-month treatment with TNFi with healthy, control men[5]. After 12-months of TNFi therapy, sperm quality was not different than that of healthy control men with the exception of a lower proportion of sperm aneuploidies among TNFi-treated men. While the numbers of participants remains very low, there is no evidence of abnormal spermatogenesis with TNFi treatment. Indirect evidence only.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment conducted to relevant population	Results
Direct Evidence						
Congenital malformations	922, Wallenius 2015[2]	Case-control study	12 weeks	1,796 men with inflammatory joint disease associated with 2,777 births in the MBRN.	In 110 of these births, the fathers were exposed to DMARDs within 12 weeks before conception, and in 230 births the fathers had never been exposed to DMARDs before conception. The DMARDs (monotherapy or combination treatment) to which the fathers were mostly exposed within 12 weeks of conception were methotrexate (n = 49), sulfasalazine (n = 17), and tumor necrosis factor inhibitors (n = 57).	• The relative risk of serious malformation for DMARD-exposed births was RR 1.22 [CI 0.45, 3.31]; for never DMARD-exposed births was RR =0.70 [CI 0.26. 1.86]. Malformations in 4 of the 110 preconception DMARD exposed births. • The mean differences in birth weights in the DMARD-exposed group (25.1 gm [CI 68.9, 119.2]) and the never DMARD-exposed group (-3.6 gm [CI 14.5, 7.3]).
	6168 Viktil 2012[1]	Observational	2004-2007	Pregnancies in Norway over 3 years	Patients treated with any of the following: NSAIDs, CS, SSZ, AZA, HCQ, ETAN, MTX, LEF, ADA.	154,976 expectant pregnancies. 1461 mothers and 1198 fathers were given anti-rheumatic drugs at least once during the study period. Exposures: 8 methotrexate, 2 leflunomide, 58

				Maternal and fetal exposures to anti-rheumatic drugs.		HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab. No major malformations associated with mtx, leflunomide, etanercept, or adalimumab. OR for malformations in children with fathers who had been exposed: 1.19 (0.93-1.51) OR for major malformation in children with fathers: 1.26 (0.93-1.71) No children born to mothers exposed to MTX, LEF, ETAN, ADA had major malformations.
Indirect Evidence						
Sperm quality	2481, Micu 2014[6]	Case-control	12 months	23 active AS patients and 42 healthy controls	Patients' sperm samples were analysed before and at 3-6 months after TNF-a therapy (adalimumab, infliximab, etanercept) administration.	• At baseline and follow-up normozoospermia in 91% and oligozoospermia in 9% of patients, in the control group 71.42% had normospermia, 5 (11.90%) had normoasthenozoospermia, 4 (9.52%) had oligozoospermia and 3 (7.14%) had oligoasthenozoospermia. • Last intercourse, median (IQR), days: 5% and 5% vs 4% in control • Semen volume, median (IQR), ml: 3 and 3 vs 2.75 • Sperm concentration, median (IQR), millions/ml: 40 and 50 vs 47 • Sperm cell motion (progressive), %: 61.21 and 61.16 vs 55.46 • Sperm cell motion (non-progressive), %: 25 and 30 vs 0 Immobile sperm cell, mean: 19.32 and 18.95 vs 41.76
	6182, Ramonda 2014[5]	Prospective case-control study	12 months	10 SpA outpatient males and 20 healthy controls	Evaluation of sperm parameters and sexual hormones in young males affected with	• At t0 33% of the patients had sperm concentrations <15 mil/m), only 1 patient was oligozoospermic at t12.

					spondyloarthritis (SpA) before and after 1 year of anti–tumor necrosis factor (TNF) a treatment.	• Total sperm count <39 million at baseline 45% of the patients, and at t12, 22%. • At t0, 55% of the patients were asthenozoospermic (progressive motility <32%), and at t12, 33%. The mean total number of sperm with progressive motility increased from 34.6 ± 16.9 million to 51.1 ± 24 million (at t0 and t12, respectively). • A significant decrease in the percentage of sperm aneuploidies at t12 was observed. Plasma LH, FSH, and T levels at t12 (6 [3.3–7.7] UI/L, 4 [2.8–5.7] UI/L, and 18.9 [11.1–20.4] nmol/L, respectively) were similar to those in the control subjects.

174. In males with RD on medication who are planning to father a child, what is the impact of stopping infliximab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No individual drug data, see paternal TNFi exposure data above.

175. In males with RD on medication who are planning to father a child, what is the impact of stopping etanercept prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No individual drug data, see paternal TNFi exposure data above.

176. In males with RD on medication who are planning to father a child, what is the impact of stopping adalimumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No individual drug data, see paternal TNFi exposure data above.

177. In males with RD on medication who are planning to father a child, what is the impact of stopping golimumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

178. In males with RD on medication who are planning to father a child, what is the impact of stopping certolizumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **GS155**

In addition to the data regarding paternal exposure to TNFi as a class, one additional observational study using the certolizumab global safety database followed outcomes of reports of paternal exposure to certolizumab identified in clinical trials or through voluntary reporting.[7] Thirty-three pregnancies were identified with paternal exposure. Of these, 27 (82%) resulted in live births, one stillbirth, and one elective termination of pregnancy. No information about maternal health or medications was provided. Indirect evidence only.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal loss/stillbirth	2403 Clowse 2015[7]	Observational	Pregnancy case reports in UCB Pharma safety database up to 9/1/14	46 CZP-exposed pregnancies.	All patients received CZP. Paternal exposures n=33. Unknown outcomes n=13.	33 pregnancies following paternal exposure, 27 resulted in live birth, 4 miscarriages, 1 induced abortion, 1 stillbirth

179. In males with RD on medication who are planning to father a child, what is the impact of stopping anakinra prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

180. In males with RD on medication who are planning to father a child, what is the impact of stopping rituximab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

181. In males with RD on medication who are planning to father a child, what is the impact of stopping belimumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

182. In males with RD on medication who are planning to father a child, what is the impact of stopping abatacept prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

183. In males with RD on medication who are planning to father a child, what is the impact of stopping tocilizumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **GS175**

A single observational study from the tocilizumab global safety database identified thirteen pregnancies with paternal exposure to drug and complete data[8]. Of these, seven ended in live birth (one pair of twins), four ended in spontaneous abortion, and one ended in therapeutic pregnancy termination. Indirect evidence only. No data suggesting increased incidence of major birth defects. Occurrence of spontaneous abortion cannot be exclusively attributable to paternal drug exposure.

Quality of Evidence across outcomes: Very low.

Outcome	Ref ID, Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Live births	2365 Hoeltzenbein 2016[8]	observational	Identified during pregnancy	Cases of pregnancy after exposure to tocilizumab identified from search of Roche Global Safety Database through 12/14 13 pregnancies with paternal exposure to tocilizumab; 22 pregnancies retrieved from the database-- 17 reported prospectively and 5 retrospectively. 6 pregnancies lost to f/u, 3 pregnancies ongoing, leaving 13 pregnancies for analysis.	Tocilizumab	7 live births (1 pair of twins), 4 SABs, 1 TAB Incomplete data: 9/22 pregnancies (41%)

184. In males with RD on medication who are planning to father a child, what is the impact of stopping secukinumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

185. In males with RD on medication who are planning to father a child, what is the impact of stopping ustekinumab prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

186. In males with RD on medication who are planning to father a child, what is the impact of stopping tofacitinib prior to conception versus continuing the medication on fertility issues and pregnancy outcome? **GS188**

A single observational study of pregnancy outcomes identified from the tofacitinib global safety database following paternal exposure to tofacitinib around the time of conception or during the first trimester identified 28 pregnancies with complete data[7]. One pregnancy had concomitant paternal exposure to methotrexate. Of these, five ended in spontaneous abortion. No information was provided regarding maternal health or medication exposures. Indirect evidence only. No data suggesting increased incidence of major birth defects. Occurrence of spontaneous abortion cannot be exclusively attributable to paternal drug exposure.

Quality of Evidence across outcomes: Very low.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Spontaneous abortion	754 Clowse 2016[7]	Observational	Identified during pregnancy	cases of pregnancy identified from search of RCT data for tofacitinib for RA/psoriasis through 4/14 44 cases of paternal exposure to tofacitinib were identified in RA (n=3, age 35-42 years) and psoriasis (n=41, age 22-54 years). In 39 cases where sufficient details were provided, exposure occurred around the time and conception and within the first trimester.	tofacitinib in all 44 cases; concurrent MTX in 1 case	Outcome = SAB; 5/28 SAB; outcomes not available for 16 pregnancies incomplete data: 16 (36%) were lost to follow up

187. In males with RD on medication who are planning to father a child, what is the impact of stopping baracitinib prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

188. In males with RD on medication who are planning to father a child, what is the impact of stopping apremilast prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

189. In males with RD on medication who are planning to father a child, what is the impact of stopping IVIG prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

190. In males with RD on medication who are planning to father a child, what is the impact of stopping warfarin prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

191. In males with RD on medication who are planning to father a child, what is the impact of stopping DOACs prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

192. In males with RD on medication who are planning to father a child, what is the impact of stopping low molecular weight heparin prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

193. In males with RD on medication who are planning to father a child, what is the impact of stopping unfractionated heparin prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

194. In males with RD on medication who are planning to father a child, what is the impact of stopping aspirin prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

195. In males with RD on medication who are planning to father a child, what is the impact of stopping non-aspirin anti -platelet agents prior to conception versus continuing the medication on fertility issues and pregnancy outcome?

No evidence

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2. Medication safety during pregnancy:

2A.

In women with RD who are pregnant or planning pregnancy, what is the impact of continuing medications [listed] versus stopping medications before or during pregnancy on maternal and pregnancy outcomes [listed]?

Plan

- Not using the medication before pregnancy
- Not using the drug during pregnancy (stopping drug prior to pregnancy)
- Not using drug during the relevant trimesters

Outcomes: Maternal and pregnancy outcomes to include:

- Pregnancy loss, including spontaneous abortion and stillbirth
- MBD
- Gestational hypertensive disease including preeclampsia
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks
- Induced labor
- Premature rupture of membranes
- Small for gestational age infants (SGA)
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG), and efficacy of vaccines in neonates
- Long-term offspring effects (neurodevelopmental and autoimmune disease)
- Flare of RD
- Damage from RD
- Maternal morbidity including infection

196. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing classic NSAIDs through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS87,GS88**

Summary: This PICO was directly addressed by two observational studies[1,2] and indirectly addressed by one observational study[3].

Live births: The study by Zrour 2010[3] describes that 13 pregnant women with RA had successful pregnancies while using indomethacin at some point during pregnancy. It does not describe how many patients used indomethacin in the pre-, peri-, or postpartum period, so the study does not describe differences in outcomes based on the timing of indomethacin exposure. Live births were also assessed by Polachek 2017;[2] of 42 pregnancies, 95% resulted in live birth. The observational study by Ostensen 1996[1] evaluated associations between NSAID use and pregnancy outcomes among women with inflammatory arthritis. Naproxen was most commonly used. Group 1 included 45 pregnancies in which the mother was not treated with NSAIDs, and Group 2 included 49 pregnancies were exposed to NSAID. 92 of 94 pregnancies overall resulted in live birth.

Maternal disease activity: Maternal psoriatic arthritis disease activity was also assessed by Polachek 2017.[2] While 41.7% of women used NSAIDs only or no pharmacologic treatment (vs biologics), the study did not directly evaluate associations between NSAIDs and maternal disease activity.

MBD: In Ostensen1996, 2/45 (4.4%) congenital anomalies occurred in the control group but not the NSAID-exposed group. 1 stillbirth occurred per group.[1]

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy outcome (live birth)	Zrour 2010[3]	Observational prospective	2004-2007	Pregnant women with RA (n=13)	Indomethacin	All 13 pregnancies were successful. Study was not designed to assess how many patients used indomethacin pre, peri-, or post-partum, so the effects of indomethacin on pregnancy cannot be assessed. Disease relapse occurred in 92% of cases, at a mean delay of 80 +/- 63 days Indomethacin dose (mg/d): -Beginning of pregnancy: 53 ± 46 -End of pregnancy: 8 ± 28 -Postpartum immediate: 8 ± 28 -Postpartum 3+ months: 26± 52 Indirect Evidence
Live birth and mean gestational age	Ostensen 1996[1]	Observational	1979-1985	Women with inflammatory arthritis/rheumatic disease (n=88); 94	NSAIDs Naproxen most commonly used Group 1: 43 patients with 45	Mean duration of NSAID exposure: 15.3 weeks. 92 pregnancies resulted in live birth. Mean gestational age was the same (38.6 weeks) between groups 2 congenital anomalies in control group (0 in NSAID) 1 stillbirth per group Naproxen was most commonly used NSAID.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				pregnancies examined in this cohort	pregnancies, not treated Group 2: 45 patients treated with NSAID during pregnancy, 49 pregnancies	Follow-up call in 1994, 83 of 88 patients were reached, and all offspring were living. Assumption is that women in Group 1 used NSAIDs prior to conception Direct.
Normal live birth	Polachek 2017[2]	Observational	1990-2015 in Toronto cohort	Pregnant women with PsA	NSAIDs, Prednisone, AZA, SSZ, HCQ, anti-TNF, ustekinumab	40/42 pregnancies (95%) normal live birth. Arthritis improved/ stable low activity (favorable outcome) in 24 (58.5%). Postpartum period, 21/42 (52.5%) favorable outcome vs. 16/42 (40%) had either worsening or stable high disease activity (unfavorable outcome). Favorable skin outcome in 30 (88.2%), and in the postpartum period there was worsening skin in 15 (42.9%). Logistic regression analysis: favorable skin disease course during the pregnancy period in the pregnant group compared to control (OR = 6.8, p = 0.004), but not in joint disease. Among pregnancies with favorable course, the majority (58.3%) used either DMARDS, biologic drugs, or both during pregnancy, while 41.7% used NSAIDS alone or no treatment. Table 2 Joints and skin activity during pregnancy and 1-yr postpartum period In the unfavorable group 53.9% used either DMARDS, biologic drugs, or both Direct

197. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing Cox 2 inhibitors through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

198. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **antimalarial** medication through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS91**

This PICO question was directly assessed by 9 studies and indirectedly by 8 studies.

Pregnancy loss was assessed by 1 direct and 2 indirect studies. Costedoat-Chalumeau 2003[4] in a direct study compared pregnancy outcomes among 160 women treated with either Hydrocychloroquine (HCQ)/prednisone vs prednisone without HCQ; 1 fetal death occurred in the former group (0.8%) and 2 deaths occurred in the latter group (2.9%), with no statistical comparison. Among indirect studies, Whitelaw 2008[5] reported 1 intrauterine death among 47 HCQ-exposed SLE pregnancies, and in Mokbel 2013,[6] fetal losses occurred in 9 of 37 SLE pregnancies in which HCQ was continued through pregnancy. Finally, Huong 2001[7] reported several embryonic losses, but it is unclear if the patients were on HCQ alone, or also exposed to prednisone, ASA, azathioprine, or heparin; therefore, it is not counted in the evidence. Overall quality of the evidence is low because it mainly involves indirect studies.

In a direct study, preeclampsia was not associated with HCQ use among 13 exposed SLE pregnancies (RR 1.2, 95%CI (0.4-3.7))[8]. Among indirect studies, preeclampsia was assessed in a study by Moroni 2016, in which HCQ use among 37 women was inversely but not significantly associated with risk of preeclampsia or HELLP (p=0.17).[9] In addition, Hwang 2017[10] reported that preeclampsia occurred in 10 of 92 SLE pregnancies in which HCQ was continued throughout pregnancy. Preeclampsia complicated 8 of 37 SLE pregnancies in Mokbel 2013,[6] and 12 of 47 SLE pregnancies in Whitelaw 2008.[5] The quality of the evidence overall is low.

Maternal disease flare was assessed by 1direct and 4 indirect observational studies. Among direct studies, Chakravarty 2005[8] found that risk of severe flare was not different among 63 SLE pregnancies exposed vs unexposed to HCQ, but only 13 pregnancies were exposed to HCQ (RR 1.1 (0.8-1.7)). Among indirect studies, Tedeschi 2015[11] found that of 113 SLE pregnancies with 80% exposed to HCQ, OR 32.5 (95%CI 6.8-154.5) for nephritis flare, 12 pregnancies with skin flare (OR 14.0 (95%CI(3.7-52.3)), 8 pregnancies with arthritis (OR 7.7 (95%CI(1.6-37.2)), serositis in 7 pregnancies (OR 18.2 (95%CI 2.4-134.9)). The results were not delineated by HCQ users vs nonusers. Among SLE patients who used HCQ throughout pregnancy, disease flare was reported among 37 of 92 pregnancies in Hwang 2017[10] and among 21 of 32 pregnancies in Mokbel 2013.[6] In Moroni 2016,[9] HCQ use during pregnancy among lupus nephritis mothers was not associated with renal flare (note: only 37 of 71 pregnancies were exposed to HCQ): RR 0.98 (95%CI: 0.296-3.3). A direct study found lower flare rates in HCQ exposed pregnancies compared to unexposed 32.7 vs. 47.4% (OR 0.54, 95%CI 0.28-1.02).[12]

Summary: HCQ may reduce maternal flares during SLE pregnancies

Preterm birth was assessed by 2 direct studies: 1) Costedoat-Chalumeau 2003[4] reported that premature birth occurred in 33 of 90 pregnancies (28%) treated with HCQ/prednisone vs 12 of 53 pregnancies treated with prednisone alone (17%); statistical comparison was not made, 2) Chakravarty 2005[8] reported that HCQ was not associated with prematurity among 63 pregnancies, in which 13 were exposed to HCQ (RR 1.1 (0.6-2.0). Indirect studies included Whitelaw 2008,[5] in which premature births occurred in 5 of 47 SLE pregnancies in which all were exposed to HCQ, and 33 of 77 (35.8%) SLE pregnancies in which all were exposed to

HCQ, were complicated by prematurity. A more direct study found a lower (but not statistically significant) rate of preterm birth among HCQ exposed pregnancies: 36.5 vs. 46.9% (OR 0.65, 95%CI 0.35-1.22).[12]

Evidence summary: Some suggestion that HCQ may reduce preterm delivery in SLE pregnancies

Induced labor was assessed by an indirect observational study by Hwang 2017;[10] 19/ 77 (24.7%) HCQ exposed SLE pregnancies were complicated by induced labor. No comparator group.

Summary: Inconclusive

Quality of Evidence across outcomes: extremely low

Premature rupture of membranes was assessed by an observational, indirect study by Mokbel 2013,[6] and occurred in 9/37 (24.3%) SLE pregnancies in which HCQ was continued. No comparator group.

Summary: Inconclusive

Quality of Evidence across outcomes: Very low

Antimalarial compared to no antimalarial

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no antimalarial__subQ3_continue thru preg	With Antimalarial		Risk with no antimalarial__subQ3_continue thru preg	Risk difference with Antimalarial
Flare											

Antimalarial compared to no antimalarial

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
265 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	101/213 (47.4%)	17/52 (32.7%)	**OR 0.54** (0.28 to 1.02)	474 per 1,000	**147 fewer per 1,000** (273 fewer to 5 more)
Preterm birth											
265 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	100/213 (46.9%)	19/52 (36.5%)	**OR 0.65** (0.35 to 1.22)	469 per 1,000	**104 fewer per 1,000** (233 fewer to 50 more)
SGA											
265 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	43/213 (20.2%)	11/52 (21.2%)	**OR 1.06** (0.50 to 2.23)	202 per 1,000	**10 more per 1,000** (90 fewer to 159 more)
Spontaneous abortion											
265 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	14/213 (6.6%)	7/52 (13.5%)	**OR 2.21** (0.84 to 5.79)	66 per 1,000	**69 more per 1,000** (10 fewer to 224 more)
Stillbirth											

Antimalarial compared to no antimalarial

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
265 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	19/213 (8.9%)	3/52 (5.8%)	**OR 0.63** (0.18 to 2.20)	89 per 1,000	**31 fewer per 1,000** (72 fewer to 88 more)
Impact on pure tone high frequency thresholds on audiometry											
19 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	10	9	-	The mean impact on pure tone high frequency thresholds on audiometry was **0**	MD **1.1 higher** (2.86 lower to 5.06 higher)
Cardiac neonatal lupus											
766 (4 observational studies)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	107/572 (18.7%)	12/194 (6.2%)	**OR 0.26** (0.14 to 0.50)	187 per 1,000	**131 fewer per 1,000** (156 fewer to 84 fewer)
Other non-cardiac neonatal lupus											
427 (2 observational studies)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	87/325 (26.8%)	26/102 (25.5%)	**OR 0.73** (0.42 to 1.28)	268 per 1,000	**57 fewer per 1,000** (135 fewer to 51 more)

CI: Confidence interval; **OR:** Odds ratio; **MD:** Mean difference

Explanations

a. Crosses no effect line

References:2746 Clowse 2006, Borba 2004, Barsalou 2017, Martinez-Sanchez 2017, Izmirly 2012, Izmirly 2010

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Preeclampsia/ HELLP Nephritis flare	2346 Moroni 2016[9]	Cohort	Unreported	71 lupus nephritis patients	HCQ n=37 Prednisone n=23 Prednisone + Azathioprine n=25 Prednisone + cyclosporine n=10 Aspirin n=37 Heparin n=13	**HCQ** **Predictor Renal flare** Relative risk ratio 0.98 95% CI 0.296 – 3.299 P 0.98 **Predictor of preeclampsia/HELLP** Relative risk ratio 0.29 95% CI 0.052 – 1.686 P 0.17 Indirect
Preeclampsia Prematurity Risk of flare	Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used HCQ versus none: Risk of flare RR 1.1 (0.8-1.7) Risk of severe flare RR 0.7 (0.2-2.8) Preeclampsia RR 1.2 (0.4-3.7) So HCQ use was not associated with adverse maternal outcomes. Women who used HCQ versus none (fetal outcomes): No events reported for fetal loss or 5-minute Agpar<7 Prematurity RR 1.1 (0.6-2.0) Small numbers in HCQ group. Surprising that HCQ was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe. Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%). Direct
Pregnancy outcomes and maternal disease activity only	Tedeschi, 2015[11]	Retrospective cohort	Pregnancy + 6 mo prior	113 pregnancies in women with SLE > 12 weeks	HCQ (80%), prednisone, azathioprine	29% of pts with APL Ab, 60% of pts on HCQ but outcomes not separated□exclude No fetal outcomes

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Hematologic activity, nephritis, skin disease, arthritis, and serositis.		Heme: 18 women/23 pregnancies, of which 10/15 had leukopenia, 9 pregnancies with thrombocytopenia, 2 hemolytic anemia. OR 26.0 95%CI (7.7, 87.3) for heme activity vs 6 mo prior to pregnancy Nephritis: 14 women/pregnancies, of which 2 had stable nephritis, 4 worse, 6 with remote nephritis that recurred, and 2 with de novo. OR 32.5 95%CI (6.8, 154.5) for nephritis vs 6 mo prior to pregnancy Skin: 11 women/12 pregnancies, OR 14.0 95% CI (3.7, 52.3) Arthritis: 8 women/8 pregnancies, OR 7.7 95% CI (1.6, 37.2) Serositis: 7 women/7 pregnancies, pleural, OR 18.2 95% CI (2.4, 134.9) for serositis vs 6 mo prior to pregnancy Indirect
Pregnancy outcomes only	Tedeschi, 2016[13]	Retrospective cohort	Pregnancy + 6 mo prior	114 pregnant women with SLE cytopenias, nephritis, skin disease, arthritis, and serositis	HCQ 60%, prednisone 56%, azathioprine 15.6%	10% of pts on azathioprine, 60^ of pts on HCQ but outcomes not separated→exclude? 13 pregnancies with adverse pregnancy outcome—of them, 3 were on AZA and leukopenia and had preterm delivery Indirect
Pregnancy and maternal outcomes	7642, Hwang 2017[10]	Prospective observational	2007 to 2013	77 pregnant SLE patients (92 deliveries)	Continuing HCQ	Preeeclampsia: 10 (10.8%) Preterm birth: 33 (35.8%) Induced labor: 19 (20.6%) Flare: 37 (40.2%) Indirect
Pregnancy and maternal outcomes Fetal Outcomes: -Miscarriage -Neonatal deaths -Preeclampsia	6696, Mokbel 2013[6]	Prospective observational	2007 to 2009	34 women with SLE (37 pregnancies) ; 18 anti-SSA/Ro, anti SSB/La antibodies)	Continuing HCQ (100%)	Fetal loss: 9/37 (24%) Flare: 21/32 (65%) Miscarriage rate: 5/37 (13.5%) Neonatal deaths: 4/30 (13%) Pre-eclampsia: 8/37 (19.4%) Preterm birth: 12/37 (32.4%) Premature rupture of membrane: 9/37 (24%) Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy outcomes	2669 Carvalheiras 2010[14]	Retrospective cohort	Pregnancy outcomes	51 pregnancies in 43 SLE women -5/52=10% not carried to term	No discussion of stopping medications	Pregnancy outcomes not broken down by therapies used or discontinued during pregnancy. Not relevant to question Indirect
Pregnancy outcomes but these are not related to meds	2882, Huong 2001[7]	Retrospective study	Perinatal period	32 pregnancies in 22 women with past or present histologically proven SLE nephritis	11 patients on HCQ. Other treatments included prednisone (n=31), aspirin (n=22), heparin (n=12), and azathioprine (1)	The outcome of 6 non-planned pregnancies: (these are not associated with HCQ or meds) 1 feto-maternal death, 1 embryonic loss, 1 fetal death, 4 premature births 1 cesarean section The outcome of the 25 planned pregnancies: 6 full term births, 14 premature births (one twin), 4 embryonic losses, 1 fetal death 6 Caesarean sections Maternal outcomes: 5 women with proteinuria In 1 woman a proliferative glomerulonephritis occurred while receiving hydroxychloroquine Indirect
Pregnancy and fetal outcomes	2824, Costedoat-Chalumeau 2003[4]	Case-control study	Perinatal period	160 pregnant women with connective tissue diseases	Group A: 90 women were treated with 200 mg of HCQ and prednisone vs group B: 53 women (70 consecutive pregnancies) with similar disorders with prednisone, no HCQ.	<u>Group A vs Group B:</u> Spontaneous abortion: 15 (11.3%) vs 7 (10%) Fetal death: 1 (0.8%) vs 2 (2.9%) Therapeutic abortion: 0 (0%) vs 2 (2.9%) Live birth: 117 (88%) vs 59 (84.3%) Premature birth: 33 (28%) vs 12 (17%) Full-term birth: 84 (72%) vs 47 (67%) Gestational age, mean (range) in weeks: 37.1 (26–41) 38.1 (29–41) 0.02 Weight, mean (range) in grams: 2,754 (500–4,300) 2,897 (1,200–4,250)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					Labs for anti-SSA/Ro and anti-SSB/La antibodies	Direct
Risk of flare Fetal outcomes -Preeclampsia -Prematurity	5342 Chakravarty 2005[8]	Observational	1991-2001	63 pregnancies among 48 women with SLE	13 pregnancies were exposed to HCQ (21%).	Women who used HCQ versus none: Risk of flare RR 1.1 (0.8-1.7) Risk of severe flare RR 0.7 (0.2-2.8) Preeclampsia RR 1.2 (0.4-3.7) So HCQ use was not associated with adverse maternal outcomes. Women who used HCQ versus none (fetal outcomes): No events reported for fetal loss or 5-minute Agpar<7 Prematurity RR 1.1 (0.6-2.0) Small numbers in HCQ group. Surprising that HCQ was used in so few pregnancies. Notably, there were many flares. 42 pregnancies were c/b flare (68%), of which 71% were mild or moderate, and 29% were severe. Preeclampsia complicated 12 pregnancies (22%), HELP complicated 2 pregnancies (4%), and diabetes complicated 3 pregnancies (5%). Direct
Fetal Outcomes Maternal outcomes	2724 Whitelaw 2008[5]	Observational, retrospective, review of pregnancies over 10 year period	pregnancy	47 pregnancies in 31 patients SLE	The majority had inactive disease at conception as a result of our policy of planned pregnancy and the use of antimalarials, which are beneficial	1 intrauterine death 36 (77%) live births, 8 first trimester abortions, 2 elective abortions, 1 still birth No maternal deaths Pre-eclampsia in 12 (33%) 5 premature births (42%) Indirect

199. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing sulfasalazine through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS95, GS95A**

Summary: This PICO was indirectly assessed by an observational study by Polachek 2017.[2] As sulfasalazine was not assessed directly (it was combined with other non-biologic DMARDs), it is unclear whether sulfasalazine has an impact on pregnancy, fetal, or maternal outcomes.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Normal live birth Maternal disease activity	Polachek 2017[2]	Observational;	1990-2015 in Toronto cohort	Women with PsA who were pregnant	NSAIDs, Prednisone, AZA, SSZ, HCQ, anti-TNF, ustekinumab	Of the 42 pregnancies, 40 (95%) resulted in normal live birth. Arthritis improved or was stable low activity in 24 (58.5%) of pregnancies. During the postpartum period, 21 (52.5%) had either improvement or stable low PsA activity, whereas 16 (40%) had either worsening or stable high disease activity. The skin activity during pregnancy either improved or stayed in a stable low state in 30 (88.2%), and in the postpartum period there was worsening in 15 (42.9%). A logistic regression analysis revealed a favorable skin disease course during the pregnancy period in the pregnant group compared to the control group (OR = 6.8, p = 0.004), but not in joint disease. Among the pregnancies with favorable course, the majority (58.3%) used either DMARDS, biologic drugs, or both during pregnancy, while 41.7% used NSAIDS alone or no treatment. Table 2 Joints and skin activity during pregnancy and 1-yr postpartum period In the unfavorable course group, more than half (53.9%) used either DMARDS, biologic drugs, or both Indirect

200. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing colchicine through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

201. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **methotrexate** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS102, GS103, GS104, GS105**

There is not sufficient evidence to answer this question. Brouwer 2015,[15] an indirect, observational study, assessed pregnancies among RA patients, but none used methotrexate throughout pregnancy, and only a portion may have used methotrexate prior to pregnancy. Polachek 2017[2] assessed DMARD use in pregnancies of psoriatic arthritis mothers, but it is unclear how many methotrexate exposures there were as DMARDs were assessed collectively.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Flare Miscarriage	2429, Brouwer, 2015[15]	Prospective observational	2002 to 2008 Pregnancy-Induced Amelioration of RA (PARA) study, The Netherlands	162 pregnancies from women with RA	Methotrexate was not used during pregnancy, but may have been used pre-conception	Flare post-miscarriage: 6/19 (32%) Spontaneous abortion: 28 (17.3%) Women who had spontaneous abortion were more likely to have received methotrexate in the past Indirect

202. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing leflunomide through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? ***Note: no studies evaluate leflunomide use throughout pregnancy.*** **GS109, GS110, GS111, GS112**

This question was assessed by 2 direct[16,17] and 1 indirect study[18].

MBD was assessed by Cassina 2012.[16] 16 pregnancies exposed to leflunomide in 1st trimester were associated with fetal MBD, whereas 29 that were exposed pre-conception (but not during pregnancy) were not associated with MBD. MBD was also assessed by Chambers 2010,[17] in which PsA/RA patients exposed to leflunomide at some point during pregnancy (at least 1 dose) were compared to patients who did not take leflunomide: no significant differences in rate of MBD in exposed women. In an indirect study by Weber-Schoendorfer 2017,[18] 47 pregnancies had 1st trimester leflunomide exposure, and 18 were exposed before conception; among these 65 pregnancies, 1 had MBD (and had undergone cholestyramine washout), whereas 3/65 had minor anomalies; results were not delineated by pregnancies exposed to leflunomide vs pregnancies that were not exposed. All patients discontinued leflunomide before or at discovery of pregnancy.

Summary: No evidence for increased risk of MBD in pregnancies exposed to leflunomide pre conception or 1st trimester provided cholestyramine washout.

Fetal loss was assessed in a direct observational study by Cassina 2012:[16] all 16 pregnancies exposed to leflunomide in 1st trimester were live births. In an indirect observational study by Weber-Schoendorfer 2017,[18] 37/65 (56.9) pregnancies resulted in live births: 19/65 (29.3%) ended in elective termination, 10/65 (15.4%) ended in spontaneous abortion (remaining fetal losses are not specified). Note that all women stopped leflunomide as soon as pregnancy was confirmed.

Quality of Evidence across outcomes: Very Low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
MBD	Cassina 2012[16]	Observational	Patients exposed to LEF between 1999 and 2009, who contacted OTIS.	45 women exposed to LEF. 16 were exposed during 1st trimester and 29 were exposed preconception	All pregnancies exposed to leflunomide	All 16 pregnancies exposed to LEF resulted in live births. 27 (93%) of the pregnancies with exposure prior to conception resulted in live births. 2 structural defects among women exposed to LEF during pregnancy Minor anomalies observed in 14. No MBD among women exposed prior to conception. Minor structural anomalies observed in 21 without a unifying anomaly. Direct
MBD	2650 Chambers 2010[17]	Prospective observational cohort	Patients enrolled btw 1999 and 2009	Pregnant women with diagnosis of RA or JRA exposed to at least 1 dose of LEF during 1st trimester vs disease-matched group that didn't take LEF vs comparison group of healthy women	Leflunomide versus none	No sig differences in rate of major structural defects in exposed group relative to either comparison group; rates were similar overall to the 3-4% expected in general population. No specific pattern of anomalies. Direct
	6663 Weber-Schoendorfer 2017[18]	German pharmacovigilance database—leflunomide exposed pregnancies. Prospective data collection	Pregnancy outcomes And MBD	Women with RA (54) Psoriatic arthritis (6) Other diseases (4)	Leflunomide-exposed pregnancies 47 with 1st trimester exposure 18 with pre-conception exposure	65 pregnancies with complete data -19/65=29% elective termination -10/65=15% spontaneous abortion -37/65=57% live birth -1/65=1.5% MBD (cholestyramine washout) -3/65%=4.6% minor anomalies All patients discontinued Leflunomide before or at discovery of pregnancy—not relevant to the question Indirect

203. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **azathioprine (or 6-MP)** through pregnancy versus not using the drug during pregnancy on maternal and pregnancy outcomes? **GS116**

Fetal loss: This was assessed by 1 direct and 2 indirect studies. A direct observational study by Saavedra 2015[19] assessed 178 pregnancies among 172 women with SLE; 87/178 used AZA and 91/178 did not use AZA. 83% of pregnancies ended in live births when AZA was used, as compared to 87% in which AZA was not used. 6/87 (6.9%) exposed pregnancies ended with stillbirth compared to 2/91 (2.2%) unexposed. Not statistically significant. An indirect case-control study by Martinez-Rueda 1996[20] found that among 46 SLE pregnancies and 39 lupus nephritis pregnancies, AZA use at any point during pregnancy was significantly associated with fetal loss (OR 3.2, 95%CI 1.01-10.3, p=0.04). AZA use in 1st trimester was also associated with fetal loss (OR 3.7, 95% CI: 1.1-11.7, p=0.02), as well as the 2nd trimester (OR 3.1, 95% CI: 1.01-9.9, p=0.04). AZA use in 3rd trimester was not associated with fetal loss. There was an overall association of AZA with fetal loss across trimesters (p=0.03). An indirect observational study by Croft 2015[21] found that 100% of ANCA vasculitis pregnancies ended in live birth; 12 of the 15 pregnancies were exposed to AZA at the time of conception. The overall evidence relies on observational studies with a small number of pregnancies, and is poor.

Preeclampsia: A direct observational study by Saavedra 2015[19] assessed 178 pregnancies among 172 women with SLE; 87/178 used AZA and 91/178 did not use AZA. 16.4% of pregnancies were complicated by preeclampsia when AZA was used, as compared to 16.6% when AZA was not used. An indirect observational study by Croft 2015[21] found that 1 of 15 ANCA vasculitis pregnancies was complicated by preeclampsia. The overall evidence relies on observational studies with a small number of pregnancies (the majority arising from 1 study), and is poor.

Maternal Disease flare: An indirect observational study by Croft 2015[21] found that 1 of 15 ANCA vasculitis pregnancies was complicated by maternal disease flare. It is unclear if this pregnancy was exposed to azathioprine, so the evidence is poor.

Preterm delivery: An indirect observational study by Croft 2015[21] found that 1 of 15 ANCA vasculitis pregnancies was complicated by preterm delivery, but this occurred in a twin pregnancy; there were no preterm deliveries in singleton pregnancies. The evidence for association AZA with preterm delivery is poor.

Quality of Evidence across outcomes: Very low

AZA compared to no AZA_subQ8_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no AZA_subQ8_continue thru	**With AZA**		**Risk with no AZA_subQ8_continue thru**	**Risk difference with AZA**
Preterm delivery											
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	32/91 (35.2%)	34/87 (39.1%)	**OR 1.18** (0.64 to 2.17)	352 per 1,000	**39 more per 1,000** (94 fewer to 189 more)
Abortions											
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	6/91 (6.6%)	7/87 (8.0%)	**OR 1.24** (0.40 to 3.85)	66 per 1,000	**15 more per 1,000** (38 fewer to 148 more)
Stillbirth											
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	2/91 (2.2%)	6/87 (6.9%)	**OR 3.30** (0.65 to 16.80)	22 per 1,000	**47 more per 1,000** (8 fewer to 252 more)
All fetal loss											

AZA compared to no AZA_subQ8_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	9/91 (9.9%)	13/87 (14.9%)	**OR 1.60** (0.65 to 3.96)	99 per 1,000	**50 more per 1,000** (32 fewer to 204 more)
Neonatal death											
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	4/91 (4.4%)	2/87 (2.3%)	**OR 0.51** (0.09 to 2.87)	44 per 1,000	**21 fewer per 1,000** (40 fewer to 73 more)
Low birth weight at term											
178 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	4/91 (4.4%)	4/87 (4.6%)	**OR 1.05** (0.25 to 4.33)	44 per 1,000	**2 more per 1,000** (33 fewer to 122 more)
Use of speech therapy age >2											
60 (1 observational study)	not serious	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	5/47 (10.6%)	6/13 (46.2%)	**OR 7.20** (1.72 to 30.13)	106 per 1,000	**355 more per 1,000** (64 more to 676 more)
ADHD age >2											

AZA compared to no AZA_subQ8_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
60 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/47 (2.1%)	2/13 (15.4%)	**OR 8.36** (0.69 to 100.77)	21 per 1,000	**133 more per 1,000** (6 fewer to 665 more)
Use of special educational services age <2											
60 (1 observational study)	not serious	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	5/47 (10.6%)	5/13 (38.5%)	**OR 5.25** (1.23 to 22.43)	106 per 1,000	**278 more per 1,000** (21 more to 621 more)
Hearing impairment age <2											
60 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	0/47 (0.0%)	1/13 (7.7%)	**OR 11.40** (0.44 to 297.17)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Fine motor deficit age <2											
60 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/47 (2.1%)	1/13 (7.7%)	**OR 3.83** (0.22 to 65.85)	21 per 1,000	**56 more per 1,000** (17 fewer to 567 more)
Gross motor deficit age <2											

AZA compared to no AZA_subQ8_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
60 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	0/47 (0.0%)	1/13 (7.7%)	**OR 11.40** (0.44 to 297.17)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Speech delay age <2											
60 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	2/47 (4.3%)	1/13 (7.7%)	**OR 1.88** (0.16 to 22.47)	43 per 1,000	**35 more per 1,000** (35 fewer to 457 more)
Use of special educational services age >2											
60 (1 observational study)	not serious	not serious	not serious	serious [b]	none	⨁◯◯◯ VERY LOW	7/47 (14.9%)	7/13 (53.8%)	**OR 6.67** (1.72 to 25.82)	149 per 1,000	**390 more per 1,000** (82 more to 670 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line
b. Wide C.I.
References: Saavedra 2015, Marder 2013

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	Martinez-Rueda 1996[20]	Case-control	Pregnancies from 1968 to 1991 (cases were fetal wastage, controls were live births)	46 pregnant SLE patients; 39 with renal disease (73 pregnancies)	Continuing Azathioprine and Cyclophosphamide	AZA use (during any period) was significantly associated with fetal loss (OR 3.2, 95% Confidence Interval (CI) 1.01 to 10.3; p=0.04). AZA use (in first trimester) was significantly associated with fetal loss (OR 3.7, 95% CI: 1.1 to 11.7; p=0.02). AZA use (in second trimester) was significantly associated with fetal loss (OR 3.1, 95% CI: 1.01 to 9.9; p=0.04). AZA use (during third trimester) was not significantly associated with fetal loss. Multivariate analysis indicated a significant association of AZA (any trimester) with fetal loss (p=0.03). Cyclophosphamide use was significantly associated with fetal loss (OR 2.9, 95% CI: 1.9 to 4.3; p=0.04).
Pregnancy outcomes	2451 Croft 2015[21]	Retrospective review of medical notes and obstetric records	Unknown	Women diagnosed with AAV according to Chapel Hill Consensus Criteria either during or prior to pregnancy n=13 patients had 15 pregnancies (11 women had GPA and 2 women had MPA) Median age at diagnosis: 25 years (range: 15-33)	n=12 pregnancies were taking AZA at conception	Live births: 100% Preterm delivery: n=1 (8.3%) – twin pregnancy (no preterm deliveries in singleton pregnancies) Cesarean delivery: n=3 (25%) Preeclampsia: n=1 (8.3%) Disease flare: n=1 (8.3%) No neonatal complications on their initial neonatal health check within the first 24 h of delivery No neonatal vasculitis No patients had a flare (“relapse”) in the first 12 months postpartum

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				Median BVAS at diagnosis: 12 (range: 4-19)		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Lupus activity	3690, Clowse 2005[22]	Single-arm study	Perinatal period	267 pregnant women with lupus, 27 of which had APS.	Women were maintained on the necessary medications to control their lupus. Principal medications included prednisone, hydroxychloroquine, nonsteroidal antiinflammatory drugs (NSAIDs), and azathioprine. The use of cyclophosphamide and methotrexate was avoided during pregnancy. LDA, Heparin, or both: 23 (92%) of the pregnancies affected by APS. LDA: Prednisone: 62% of women with low-activity lupus 95% of women with high-activity lupus Hydroxychloroquine (HCQ): 33% of pregnancies NSAIDs, other than LDA: 12% of the pregnancies, with no difference in use	The study measures outcomes related to lupus activity, not medications use.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					between high- and low-activity lupus patients. Azathioprine: 25% of the women with high-activity lupus Cyclophosphamide: 1 patient with sever lupus, and another patient had inadvertent exposure to it in the week following conception.	

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Live births	2424 Saavedra 2015[19]	Retrospective cohort	Pregnancy outcomes	178 pregnancies in 172 lupus women	178 pregnancies - 87/178= 49% with AZA - 91/178= 51% without AZA	-no group identified or included that stopped AZA who were previously taking it. Not clearly relevant to question -72/87=83% live birth with AZA -79/91=87 live birth without AZA 12/87=16.4% preeclampsia with AZA 14/91=16.6% preeclampsia without AZA Direct evidence

204. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **mycophenolate mofetil** (or mycophenolic acid) through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence (Data on teratogenicity in other literature)

205. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **cyclosporine** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence (Data may be available in solid organ transplantation literature)

206. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **tacrolimus** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence (Data may be available in solid organ transplantation literature)

207. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **cyclophosphamide** (po or IV) through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS134, GS135, GS136**

Two indirect observational studies answer this question. In Martinez-Rueda 1996,[20] a case-control study, cyclophosphamide was continued in 15 of 73 pregnancies, and was associated with increased risk of fetal loss (OR 2.9, 95%CI: 1.9-4.3); the duration of the exposure during pregnancy was not delineated. In Tuin 2012,[23] women with ANCA-associated vasculitides were exposed to

cyclophosphamide before pregnancy, but none during pregnancy. Fetal outcomes were normal with exception of cleft palate in one newborn of a twin pregnancy, and hypothyroidism in another. Most babies were born at term. The role of disease activity and concomitant medications not addressed.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	Martinez-Rueda 1996[20]	Case-control	1968 to 1991 (cases were fetal wastage, controls were live births)	46 pregnant SLE patients; 39 with renal disease (73 pregnancies)	Continuing Azathioprine and Cyclophosphamide	Cyclophosphamide use was significantly associated with fetal loss (OR 2.9, 95% CI: 1.9 to 4.3; p=0.04). Was used in 15 pregnancies, unclear how long it was continued through pregnancy. Indirect
Pregnancy and fetal outcomes	Tuin 2012[23]	Single-center retrospective observational study	Not reported	Pregnancies in women with GPA (13) and MPA (1) included—22 pregnancies in 14 women The ear, nose, and throat region (71%) and kidneys (50%) were predominantly involved. All women were in remission at conception	cyclophosphamide had been administered to 9 women (15 pregnancies). CYC free period before conception ranged from 10-67 months CYC had previously been administered to 9 women (15 pregnancies)	- 14 pregnancies off medication throughout - 1 pregnancy with relapse, requiring prednisone at week 28 - 1 pregnancy cotrimazole first month until pregnancy confirmed - 4 on therapy throughout: prednisone in all, AZA in 2 - 2 AZA and cyclosporine (s/p renal transplant) The median gestational age was 39+4 weeks, including 2 preterm deliveries. The median birth weight was 3,400 gm (1,860 –3,890 gm). Hypothyroidism occurred in 1 newborn and a cleft palate in 1 newborn of a twin pregnancy. Otherwise, the fetal outcome was excellent. Preeclampsia was diagnosed in 2 pregnancies. A caesarean section was performed in 2 patients. The median followup after the last conception was 98 months (range 11–307 months). Eight women experienced a relapse 21 months (range 7– 62 months) after conception, 1 during pregnancy, and 7 after delivery Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Not reported	Bobrie 1987[24]	Retrospective case series	23 years	73 patients with SLE who had 213 pregnancies with lupus nephritis; Study comparing SLE in remission before conception versus SLE active at conception	High dose corticosteroids administered in 58 patients and associated with immunosuppressive drugs (mainly cyclophosphamide) in 30 of them	No results discussed related to the subgroup of patients receiving CYC on any pregnancy/maternal outcomes

208. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **thalidomide** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence (Teratogenicity addressed in other literature)

209. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **Tumor Necrosis Factor inhibitors** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS144, GS147, GS150, GS153, GS156**

One observational study addressed this question[25]. It evaluated 136 pregnancies in women with RA or axial spondyloarthropathies. Of these, 97 discontinued TNFi at conception and 39 continued treatment. 17/79 (17.5%) women who discontinued TNFi therapy experienced a flare of RD, compared to 20/39 (51.5%). These results were statistically significant (OR 4.95; 95%CI 2.19-11.22).

Summary: In a single study, continuation of TNFi therapy beyond conception reduced rates of maternal RD flare during pregnancy.

Quality of Evidence across outcomes: Low

TNFI compared to no TNFi_subQ52 and 53_stop at conception for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no TNFi_subQ52 and 53_stop at conception	With TNFI		Risk with no TNFi_subQ52 and 53_stop at conception	Risk difference with TNFI
RD flare											
136 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	17/97 (17.5%)	20/39 (51.3%)	**OR 4.95** (2.19 to 11.22)	175 per 1,000	**337 more per 1,000** (142 more to 529 more)

CI: Confidence interval; **OR:** Odds ratio

References: 2321 Van Den Brandt 2017

210. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **infliximab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

See question 209 on TNF inhibitors as a class

211. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **etanercept** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes

See question 209 about TNFi as a class

There were several studies that answered the effects of TNFa inhibitors as a whole on pregnancy, but fewer that examined individual TNFa inhibitors. Carman 2017[26] is an observational study that directly answers this PICO question for women with chronic

inflammatory arthritis or psoriasis. Risk of **MBD** among etanercept-exposed pregnancies as compared to unexposed pregnancies was not significant (OR 1.03, 95%CI: 0.51-2.10) for women with chronic inflammatory arthritis. Note that exposure was defined as 365 days prior to the estimated date of conception, so some pregnancies may not have been directly exposed to etancercept.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
MBD	7584 Carman 2017[26]	Observational retrospective	1995-2012	Claims-based data delineated pregnancy exposures and outcomes of live or nonlive births among women with chronic inflammatory arthritis (cIA) and/or psoriasis (PsO)	All pregnant women who were diagnosed with cIA or PSO were treated as follows: 1. Etanercept (ETN) during pregnancy 2. Not treated with any TNFi Also, 4 disease subcohorts were created: 1. cIA with ETN exposure 2. cIA without ETN exposure 3. PsO with ETN exposure 4. PsO without ETN exposure **Exposure defined as 365 days prior to the estimated date of conception.**	4383 pregnancies among women with cIA or PsO, with 3523 live births, of which 3238 infants had claims data cIA-EXP women had higher proportions of baseline methotrexate use than cIA-unEXP (21.5 vs 17%), and prepregancy ETN use (91.0% vs 7.3%)—so some women in the "unexposed" group had indeed been exposed to ETN at some point in the past. Prevalence estimates of having at least 1 major congenital malformation (MCM): -cIA-EXP: 6.1% -cIA-unEXP: 5.5% -General population: 5.7% -PsO-EXP: 2.0% -PsO-unEXP: 4.2% -General population: 4.7% -cIA-EXP: OR for having at least 1 MCM = 1.03 (95% CI: 0.51-2.10) -PsO-EXP: OR for having at least 1 MCM= 0.9 (95%CI: 0.05-2.98) Doesn't exactly answer the PICO as it doesn't mention how many women were treated with ETN right before the pregnancy versus those who continued it through pregnancy Direct

212. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **adalimumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No studies available to look at risk of RD flare. Please see question 209 regarding TNFi use as a class.

One observational study (Burmester 2017)[27] evaluated the effects of antenatal adalimumab exposure on MBD. 3/65 (4.6) of exposed infants were diagnosed with a MBD, compared to 4/74 (5.4%) of unexposed infants. Results were not statistically significant. **GS150**

Summary of evidence: One study found no increased risk of MBD with antenatal adalimumab exposure.

Quality of Evidence across outcomes: Very low

ADA compared to no ADA_subQ 16 and 40 for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no ADA_subQ 16 and 40	**With ADA**		**Risk with no ADA_subQ 16 and 40**	**Risk difference with ADA**
Major Birth Defects											
139 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	4/74 (5.4%)	3/65 (4.6%)	**OR 0.85** (0.18 to 3.93)	54 per 1,000	**8 fewer per 1,000** (44 fewer to 129 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

References: Burmester 2017

213. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **golimumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

See question 209 on TNF inhibitors as a class

214. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **certolizumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? One direct and one indirect observational study answer this question. **GS156**

Two studies were found that addresses this question, although neither included a comparator group of unexposed pregnancies. One study evaluated pregnancy outcomes in 339 women with maternal exposure to certolizumab. The timing of exposure was not clear. 75% pregnancies resulted in live birth, 52 resulted in spontaneous abortion, 32 terminations. Twelve of 254 (4.7%) exposed infants were diagnosed with a MBD.

The second study was much smaller, including a total of 21 certolizumab-exposed studies. Of these, one pregnancy was preterm, and one delivery was associated with a maternal infection (perineal infection) .

Evidence summary: Without a control group, it is difficult to compare outcomes based on exposure.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Live births Spontaneous abortion Stillbirth Congenital malformations Birthweight MBD	2403 Clowse 2015[28]	Observational	Prospective and retrospective cohort	Entire cohort was exposed to CZP during pregnancy, with a total of 625 pregnancies. Maternal exposures with available outcomes n=339.	Certolizumab pegol (CZP) Note: unclear how many were exposed at various trimesters of pregnancy. All pregnancies were exposed.	Gestational age at birth, birthweight, Cesarean delivery, multiple gestation, congenital malformations were assessed. Also assessed CDAI at baseline/visit prior to pregnancy/change from baseline, DAS28, concomitant medications, maternal age, trimester of CZP exposure 625 pregnancies with 372 known outcomes. - 254/ 339 (74.9%) live birth - 52/339 (15.3%) spontaneous abortion - 1 stillbirth - 1 neonatal death - 32/324 (9.4%) therapeutic terminations - 12/254 (4.7%) congenital malformations Note: 240 maternal pregnancies had unknown outcomes. 64 of these pregnancies were ongoing at the time the study was done, but 176 were lost to follow-up.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						Direct
Gestational age Maternal morbidity	2293 Mariette 2017[29]	observational	Identified during pregnancy	16 pregnant women receiving CZP; PK study of women >= 30 weeks pregnant receiving commercial CZP for a locally approved indication (last dose <= 35 days p/t delivery); 21 patients screened; 1 excluded 2/2 preterm birth, 4 due to ineligibility. 16 pregnant women receiving CZP had plasma levels checked and completed the study.	CZP All pregnancies were exposed.	Outcome = preterm birth, maternal infection. 1/21 preterm birth 1/21 maternal morbidity (infection)= perineal abscess Indirect

215. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **anakinra** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

216. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **rituximab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS164, GS165**

There is a single study (Chakravarty 2011)[8] that addressed this issue. This study analyzed all reported pregnancies in the global rituximab safety database through the end of 2009. Exposure to rituximab ranged from 12 months prior to conception to administration during the third trimester for severe maternal disease. Indications included autoimmune diseases (SLE, RA, TTP, ITP, and MS) and lymphoma. Of 153 reported pregnancies with known outcomes, 90 (59%) resulted in live births, of which 75% were full term. Spontaneous abortions occurred in 21% of pregnancies and 18% were electively terminated. 2 MBD occurred in rituximab-exposed infants. The data is confounded by differences in severity/activity of maternal disease; and many pregnancies were also exposed to numerous other medications, some of which were known teratogens (MMF, MTX, etc). There is no comparator group.

Summary of evidence: There does not appear to be an increased risk to pregnancy outcomes with Rituximab exposure

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy outcomes: live birth, preterm delivery, miscarriage, maternal death, stillbirth	Chakravarty 2011[8]	Retrospective obsrvational	Reported pregnancies through November 30, 2009	Pregnant women exposed to rituximab for all indications: RA, SLE, TTP, ITP, MS and lymphoma	All women had been exposed to Rituximab between 12 months prior to through the 3rd trimester or pregnancy	153 pregnancies with known outcomes - 33/13 (21.5%) spontaneous abortions - 28/153 (18.3%) therapeutic terminations - 1 stillbirth - 90/153 (58.8%) live births - 68/90 (75.5%) full term - 16/90 (17.7%) preterm - 3 MBC (1 Turners syndrome diagnosed before rituximab administration) Note that many of these pregnancies were complicated by active underlying maternal disease and concomitant administration of numerous medications, including teratogens Indirect evidence

217. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **belimumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

218. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **abatacept** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

219. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **tocilizumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS177**

Three studies were found that addressed tocilizumab exposure during pregnancy, all were observational. The largest (Hoeltzenbein 2016)[30] retrospectively analyzed 108 pregnancies with some tocilizumab exposure. The timing of exposure was not clear, and no unexposed group was used as a comparator. Of 108 pregnancies, 31 (28.7%) ended in spontaneous abortions; 22 (20%) were terminated. 55 (50.9%) ended in live births, of which one was preterm. 3 MBD were reported, within the range expected in the general population.

A second study evaluated pregnancy outcomes among 16 pregnancies in women with RA treated with tocilizumab. Four (25%) ended in spontaneous abortion. One infant was born prematurely.

A third study, a retrospective analysis of the Chugai safety database (Japan) identified 61 tocilizumab exposed pregnancies.[31] In the majority of cases, 40/61 (65.6%), drug was discontinued prior to conception or during the first trimester. Timing of exposure was unknown in 19/61 (31%), and only two pregnancies continued with tocilizumab throughout pregnancy. Methotrexate was also taken during the first trimester in some of the pregnancies. Pregnancy outcomes were listed for the entire cohort, and not separated by exposure timing. Of the 50 pregnancies with known outcomes, 9 (18%)ended in spontaneous abortions, 5(10%) therapeutic terminations; 36 (72%) live births. No MBD were reported.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy outcomes and MBD	2365 Hoeltzenbein 2016[30]	Observational	Identified during pregnancy	cases of pregnancy after exposure to tocilizumab identified from search of Roche Global Safety Database through 12/14 Retrospectively reported	Tocilizumab	Retrospectively reported pregnancies (n = 108) resulted in 55 live births (50.9%), 31 spontaneous abortions (28.7%), and 22 elective terminations (20.4%). 3 infants/fetuses with congenital anomalies were reported in this group. Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				pregnancies (n = 108)		
Pregnancy outcomes	2391, Weber-Schoendoefe 2016[32]	Prospective observational	2011/2012 through 2014, Recruited from an annual pool of 13,500 consultations at Embryotox Berlin for drug risk assessment during pregnancy.	22 patients treated for RA with tocilizumab (TCZ); 16 women exposed	TCA during pregnancy	Hydrops fetalis: 1/16 (9%) Preterm birth: 1/11 (9%) Small for gestational age: 1/10 (10%) Spontaneous abortion: 4 Indirect
Spontaneous abortion; MBD	Nakajima 2016[31]	Observational retrospective	Chugai Safety database Japan 2005-2014	61 exposed pregnancies	Tocilizumab -10 d/c before conception -30 d/c 1st trimester -2 continued throughout pregnancy -19 unknown timing of exposure	Outcomes of pregnancies not separated by exposure timing -11 with unknown outcome -9/50 (18%) spontaneous abortions -5/50 (10%) elective terminations -36/50 (72%) live birth -24/36 with unknown gestational age at birth -10/12 full term delivery -2/12 preterm delivery -0 MBD Indirect

220. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **secukinumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

221. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **ustekinumab** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

222. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **tofacitinib** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS189**

This study is answered by 1 observational study by Clowse 2016.[33] Among 47 women who received tofacitinib monotherapy through pregnancy, 34 pregnancies resulted. 4 infants were lost to follow-up.

MBD: 1 of 34 live pregnancies and 47 overall pregnancies had a major birth defect.

Spontaneous abortion: 4 of 47 pregnancies were complicated by spontaneous abortion.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
MBD Spontaneous abortion	754 Clowse 2016[33]	Observational	Identified during pregnancy	cases of pregnancy identified from search of RCT data for tofacitinib for RA/psoriasis through 4/14 47 pregnant women identified, including 33 who received tofacitinib monotherapy, 13 who received tofacitinib + MTX, and 1 patient whose therapy was still blinded	Tofacitinib; Tofacitinib + MTX	Tofacitinib monotherapy= 34: 1 MBD (congenital pulmonary valve stenosis), 4 SAB, 5 TAB, 20 healthy infants, 4 lost to follow up. Tofacitinib + MTX=13: 3 SAB, 3 TAB, 5 healthy infants, 2 lost to follow up. Note: 6/47 (13%) pending/lost to follow up; Indirect

223. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **baracitinib** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

224. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **apremilast** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

225. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **intravenous immunoglobulin** through pregnancy versus not using the drug during pregnancy on maternal and pregnancy outcomes? **GS209**

3 indirect studies answer this question.

Live births: In Vaquero 2001,[36] an observational study, women with APS and history of recurrent spontaneous abortions were treated with prednisone and LDA, and 53 received IVIG. Live birth rates did not differ between the treatment arms, and 78% of IVIG-exposed pregnancies ended in live birth. In Triolo 2003,[37] a RCT, 42 pregnant women with obstetric APS received IVIG 400 mg/kg/d every month and outcomes were compared to patients who received LMWH and LDA. There were 12 live births of 21 women who received IVIG (57%), compared to 16 of 19 live births among women who received LMWH and LDA (84%), which was marginally significant p=0.06. In Perricone 2008[34] 24 pregnancies in women with SLE and recurrent pregnancy loss were studied; 12 treated with IVIG during pregnancy and 12 were treated with prednisolone and NSAIDs. The IVIG treated group had no pregnancy losses vs. 3/12 in the prednisolone group. However, a different study[37] performed a RCT comparing IVIG vs. low dose aspirin and low molecular weight heparin in women with recurrent fetal loss and antiphospholipid antibodies (not SLE or other autoimmune diseases). In this trial, pregnancy loss occurred in 7/21 (33.3%) of IVIG women compared to 0 heparin+aspirin women. Note that the diseases in these studies were not comparable.

First-trimester miscarriage was assessed by Dendrinos 2009[38], an observational study of 78 women with obstetric APS, all of whom were exposed to IVIG through 32 weeks' gestation. 21 of these pregnancies ended in first-trimester miscarriage.

Preterm births were assessed by Vaquero 2001,[36] and occurred in 9% of IVIG-exposed pregnancies; in the RCT by Triolo 2003[37], 1 of 21 IVIG-exposed pregnancies was preterm, and preterm delivery occurred in 1 of 78 pregnancies in Dendrinos 2009[38].

Mean gestational age in Vaquero 2001[36] was 38.6±1.8 weeks for IVIG-exposed pregnancies, and was 38.3±2.1 in Dendrinos 2009[38].

Gestational hypertensive disease was assessed by Vaquero 2001[36], and occurred in 5% of pregnancies exposed to IVIG. Gestational hypertension occurred in 1/21 IVIG-exposed pregnancies in Triolo 2003.[37]

Fetal hydrops occurred in 4 of 20 pregnancies in Trucco 2011[39], an observational study of women with SSA/SSB positivity, some of whom received IVIG (9/20); however, results were not delineated between IVIG and dexamethasone users; therefore, the PICO question is not answered.

Quality of Evidence across outcomes: Very low

IVIG compared to no IVIG_subQ29_continue thru preg for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no IVIG_subQ29_continue thru preg	With IVIG		Risk with no IVIG_subQ29_continue thru preg	Risk difference with IVIG
Pregnancy loss											
24 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	3/12 (25.0%)	0/12 (0.0%)	**OR 0.11** (0.00 to 2.36)	250 per 1,000	**215 fewer per 1,000** (250 fewer to 190 more)
Preterm birth											
21 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	5/9 (55.6%)	3/12 (25.0%)	**OR 0.27** (0.04 to 1.70)	556 per 1,000	**303 fewer per 1,000** (508 fewer to 124 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

References: Perricone 2008

IVIG compared to no IVIG_RCT_subQ29_continue thru preg for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no IVIG_RCT_subQ29_continue thru preg	**With IVIG**		**Risk with no IVIG_RCT_subQ29_continue thru preg**	**Risk difference with IVIG**
Congenital heart block											
40 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	0/19 (0.0%)	0/21 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Pregnancy loss											
40 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	0/19 (0.0%)	7/21 (33.3 %)	**OR 20.17** (1.06 to 382.45)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Preterm delivery <37 wks											

IVIG compared to no IVIG_RCT_subQ29_continue thru preg for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
40 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	0/19 (0.0%)	1/21 (4.8%)	**OR 2.85** (0.11 to 74.34)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Gestational hypertension											
40 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	0/19 (0.0%)	1/21 (4.8%)	**OR 2.85** (0.11 to 74.34)	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Premature rupture of membranes											
40 (1 RCT)	not serious	not serious	not serious	serious [c]	none	⨁⨁⨁◯ MODERATE	1/19 (5.3%)	0/21 (0.0%)	**OR 0.29** (0.01 to 7.47)	53 per 1,000	**37 fewer per 1,000** (52 fewer to 241 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. No events in either group
b. Wide C.I.
c. Crosses no effect line
References: Triolo 2003

IVIG compared to no IVIG_observational_subQ29_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no IVIG_observational_subQ29_continue thru	**With IVIG**		**Risk with no IVIG_observational_subQ29_continue thru**	**Risk difference with IVIG**
Congenital heart block											
24 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/9 (11.1%)	3/15 (20.0 %)	**OR 2.00** (0.18 to 22.80)	111 per 1,000	**89 more per 1,000** (89 fewer to 629 more)
Pregnancy loss											
68 (3 observational studies)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	4/32 (12.5%)	3/36 (8.3%)	**OR 0.80** (0.11 to 5.80)	125 per 1,000	**22 fewer per 1,000** (110 fewer to 328 more)
Neonatal death											

IVIG compared to no IVIG_observational_subQ29_continue thru for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
44 (2 observational studies)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/20 (5.0%)	2/24 (8.3%)	**OR 2.86** (0.21 to 37.99)	50 per 1,000	**81 more per 1,000** (39 fewer to 617 more)
Other non-cardiac neonatal lupus											
24 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/9 (11.1%)	0/15 (0.0%)	**OR 0.18** (0.01 to 5.00)	111 per 1,000	**89 fewer per 1,000** (110 fewer to 274 more)
Preterm birth											
21 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	5/9 (55.6%)	3/12 (25.0 %)	**OR 0.27** (0.04 to 1.70)	556 per 1,000	**303 fewer per 1,000** (508 fewer to 124 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line

References: Pisoni 2010, Trucco 2011, Perricone 2008

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy and fetal outcomes	Vaquero 2001[36]	Prospective cohort	Perinatal period	82 recurrent aborters with aPL syndrome	29 were treated with prednisone and LDA, 53 received IVIG	Live Birth Rates IVIG: 78% Prednisone + LDA: 76% (no difference between groups) Pregnancy-induced hypertension IVIG: 5% Prednisone + LDA: 14% -Higher in Prednisone + LDA group ($p < 0.05$) Gestational Diabetes IVIG: 5% Prednisone + LDA: 14% -Higher in Prednisone + LDA group ($p < 0.05$) IUGR: No cases Preterm births < 37 wks IVIG: 9% Prednisone + LDA: 5% Mean week of delivery did not vary between groups IVIG: 38.6±1.8 [range, 32 – 42] Prednisone + LDA: 38.01±2.5 [range, 32.6 – 41.1] Indirect
Fetal/Neonatal outcomes	6112, Trucco 2011[39]	Retrospective observational	Perinatal period with a median follow-up of 2.9 years	20 women with a median gestational age of 23 weeks (range 18 to 38 weeks). 19 anti-Ro/ 8 anti-La antibody positive; 7 clinical autoimmune disease.	During pregnancy dexamethasone: 17/20 IVIG: 9/20	Complete heart block: 11 (55%) Fetal hydrops: 6 (30%) Fetal/infant death: 4 (20%) Pacemaker placement: 12 (63%) No comparison between groups Indirect

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				16 with endocardial fibroelastosis; 4 with reduced ventricular function; 16 (80%) had reduced or borderline ventricular shortening fraction (≤30%) before or after birth		
Pregnancy outcomes	2691, Dendrinos, 2009[38]	RCT	NR	78 women with APS and recurrent spontaneous abortion before 10 weeks of gestation. Patients with thrombophilia were excluded.	Continuing IVIG through 32 weeks of gestation (n=38)	Pregnancy outcomes: Preterm delivery: 1 First trimester abortion: 21 Intrauterine death: 2 Indirect

226. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **warfarin** versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS212**

There is one observational study by Pauzner 2001[40] that addresses this study. APS patients were switched to warfarin during mid-pregnancies in 14 pregnancies. Outcomes are as follows:

Pregnancy loss: Occurred in 2 of 14 pregnancies.

IUGR: Occurred in 2/12 pregnancies.

Preeclampsia: Occurred in 1/14 pregnancies.

Maternal thrombosis: 6/14 pregnancies.

Quality of Evidenced across outcomes: Very low

<table>
<tr><th>Outcome</th><th>Author, year</th><th>Study type</th><th>Duration</th><th>Population Description</th><th>Treatment given to relevant population</th><th>Results</th></tr>
<tr><td>Pregnancy outcomes</td><td>2866, Pauzner 2001[40]</td><td>Cohort study</td><td>Can't find this in paper (patients were followed throughout pregnancy but study duration unclear)</td><td>57 pregnancies in 42 APS patients, either primary or secondary to SLE</td><td>LMWH and LDA during pregnancy and postpartum period in 46 pregnancies
vs.
Switch to Warfarin during mid pregnancy in 14 pregnancies during weeks 15-34</td><td>
This study did not assess medication discontinuation. Outcomes related to the two treatment groups are provided below.
<table>
<tr><td colspan="4">Pauzner 2001 outcomes table</td></tr>
<tr><td>Outcomes:</td><td>Warfarin group</td><td>Non-warfarin group</td><td>p-value</td></tr>
<tr><td>Pregnancy loss</td><td>2/14 (15%)</td><td>6/46 (13%)</td><td>P=0.22</td></tr>
<tr><td>Live IUGR</td><td>2/12</td><td>4/44</td><td>P=0.45</td></tr>
<tr><td>Birth weight (grams)</td><td>2706</td><td>2833</td><td>P=0.59</td></tr>
<tr><td>Pre-eclampsia</td><td>1</td><td>2</td><td>Not provided</td></tr>
<tr><td>Maternal morbidity (thrombosis)</td><td>6</td><td>6</td><td>Not provided</td></tr>
</table>
Indirect
</td></tr>
</table>

227. In women with RD who are pregnant or planning pregnancy, what is the impact of **continuing DOACs (rivaroxaban, dabigatran, apixaban, edoxaban)** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

228. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **unfractionated heparin** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS215**

There is one observational study that answers this question: Ruffatti 1998[41]. In this study of APS+mothers treated with heparin during pregnancy, there were the following outcomes:

Live births: 100% (55/55 births)

Maternal thrombotic complications: 0% (0/55 deliveries)

Mean gestational age: 37 weeks

Prematurity: 12 of 55 infants

Quality of the Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Fetal outcomes	4609 Ruffatti 1998[41]	Observational	1991-1995	55 infants born to 53 APL+ positive mothers treated during pregnancy with heparin	Heparin TID at dose varying between 15000-37500U. Treatment started at mean gestational age of ~7.75 weeks until delivery.	No malformations. 100% live births. No thrombotic complications. Children were delivered between 25th and 40th weeks (mean 37 weeks), mean Agpar score at 5 minutes ranged from 7-10. 12 children admitted to NICU, all of whom had complications related to prematurity. indirect

229. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **low molecular weight heparin** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

There is insufficient evidence to address this question. Please see section 5A for use of LMW heparin and aspirin in antiphospholipid antibody syndrome.

230. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **low-dose aspirin** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

There is insufficient evidence to address this question. Please see section 5A for use of LMW heparin and aspirin in antiphospholipid antibody syndrome.

231. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **aspirin** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

232. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **non-aspirin antiplatelet agents** through pregnancy versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

233. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **classic NSAIDs** through the first trimester only versus stopping the medication before pregnancy on maternal and pregnancy outcomes? **GS87, GS88**

There are three observational studies that answer this PICO question. Some women used NSAIDs in the study by Viktil 2012[42] in the table, but results are not delineated by NSAID use. Additionally, there is a variety of timing of NSAID exposure in these studies, and none specifically address 1st trimester exposure.

Preeclampsia: Assessed by Palmsten 2012[43], which evaluated pregnancy outcomes related to exposure vs nonexposure to DMARDs/NSAIDs among women with AI diseases. Incidence of preeclampsia was 2.9% for past users of NSAIDs. Risk of preeclampsia by continuous NSAID users (before conception and during 1st 2 trimesters) was OR: 0.84 (95%CI : 0.63-1.10), which was not statistically significant.

Live births: Assessed by Ostensen 1996[1], a study of 94 pregnancies among women with rheumatic diseases. 49 pregnancies were exposed to NSAIDs (with mean duration of NSAID exposure 15.3 weeks), and all pregnancies ended in live births. Zrour 2010[3] also assessed indomethacin in a cohort of pregnant women with RA, and all women had a safe pregnancies.

MBD: Assessed by Ostensen 1996;[1] 2 congenital anomalies were observed in the non-NSAID group, but the NSAID group of 49 pregnancies had no congenital anomalies.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Preeclampsia	2534 Palmsten 2012[43]	Observational	1997-2006	Women with and without autoimmune diseases treated with DMARDs; outcome is preeclampsia	Exposure to DMARDs versus non-exposure 414 women had DMARD dispensed during pregnancy of 44786 women who delivered	Incidence of preeclampsia was 2.3% for past DMARD users, 2.7% for past steroid users, and 2.9% for past NSAID users. Risk of preeclampsia by continuous medication users (use before and during 1st 20 weeks): Continuous DMARD user aRR 2.29 (0.81-6.44) Steroid users aRR 0.89 (0.51-1.56) NSAID users aRR 0.84 (0.63-1.10) a=adjusted for year of delivery RR preeclampsia for rheum ds compared to women without AI diseases: SLE aRR 2.02 (1.11-3.64), 5.1% with preeclampsia RA aRR 1.26 (0.87-1.81), 3.1% IBD aRR 2.3 0.98 (0.57-1.70), 2.3% No AI disease aRR: 2.4% developed preeclampsia

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						Direct
Pregnancy and fetal outcomes	2982 Ostensen 1996[1]	Observational	1979-1985	88 women with 94 pregnancies. Pts had rheumatic diseases.	NSAID exposure. Group 1: 43 patients with 45 pregnancies, not treated Group 2: 45 patients treated with NSAID during pregnancy, 49 pregnancies	Mean duration of NSAID exposure: 15.3 weeks. 92 pregnancies resulted in live birth. Mean gestational age was the same (38.6 weeks) between groups 2 congenital anomalies in control group (0 in NSAID) 1 stillbirth per group Naproxen was most commonly used NSAID. Follow-up call in 1994, 83 of 88 patients were reached, and all were living. Assumption is that women in Group 1 used NSAIDs prior to conception. Direct
Pregnancy outcomes	2655 Zrour 2010[3]	Observational prospective cohort	2004-2007. RA evaluation was done every 3 months until 1 year post-delivery.	Pregnant women with RA (n=13). Initial assessment was before pregnancy (women needed o be patients of the practice for at least 6 months)	DMARDs Prednisone (including IM) Acetaminophen	All women had a successful pregnancy Disease relapse occurred in 92% of cases, at a mean delay of 80 +/- 63 days Indomethacin dose (mg/d): -Beginning of pregnancy: 53 ± 46 -End of pregnancy: 8 ± 28 -Postpartum immediate: 8 ± 28 -Postpartum 3+ months: 26± 52 Study is not designed to assess how many patients used indomethacin pre-pregnancy versus during or post-pregnancy. Also, study did not evaluate associations of indomethacin use with maternal or fetal outcomes. So the PICO question is not directly answered. Indirect
MBD	6168 Viktil 2012[42]	Observational	2004-2007	Pregnancies in Norway over 3 years Maternal and fetal exposures to anti-rheumatic drugs.	Patients treated with any of the following: NSAIDs, CS, SSZ, AZA, HCQ, ETAN, MTX, LEF, ADA.	154,976 expectant pregnancies. 1461 mothers were given anti-rheumatic drugs at least once during the study period. Exposures: 8 methotrexate, 2 leflunomide, 58 HCQ, 119 SSZ, 101 AZA, 37 etanercept, 3 adalimumab. No major malformations of mtx, leflunomide, etanercept, or adalimumab. OR for malformations in children with mothers who had been exposed to any drug: 1.06 (0.85-1.32)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
						OR for major malformation in children with mothers who had been exposed: 1.05 (0.79-1.40) No children born to mothers exposed to MTX, LEF, ETAN, ADA had major malformations. Indirect

234. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **tumor necrosis factor inhibitors** through the first trimester only versus not using the drug during the first trimester on maternal and pregnancy outcomes? **GS144, GS147, GS150, GS153, GS156**

Two studies were found that addressed maternal TNF exposure as a class. The first, using administrative data from Denmark and Sweden[44] looked MBD among women exposed to TNFi within 90 days before through 90 days after their last menstrual period. 683 women with chronic inflammatory diseases were exposed to TNFi compared to 21,549 women with chronic inflammatory diseases without TNF exposure. Some pregnancies were exposed to other DMARDs as well. TNF exposed pregnancies had a 6.3% MBD rate, compared to 4.7% unexposed pregnancies, but this was not statistically significant (OR 1.35, 95%CI 0.99-1.85).

The second study evaluated data from the Israeli Teratology Information Service[45]. 83 TNFi-exposed pregnancies (97.6% in the 1st trimester) was compared to 86 disease matched (non-TNF exposed) controls. Many pregnancies had concomitant exposure to other DMARDs. MBD rates were similar in the TNFi exposed and disease-matched unexposed women 4.6% exposed vs. 6.3 unexposed (OR 1.97, 95% CI 0.63-6.15). Results of other outcomes between groups (spontaneous abortion, preterm delivery, and stillbirth) were not statistically different between groups.

Summary of evidence: There does not appear to be a significant increase in MBD in pregnancies exposed to TNFi.

Quality of Evidence across outcomes: Very low

TNFi compared to no TNFi during 1st trimester only_sub39 for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no TNFi during 1st trimester only_sub39	With TNFi		Risk with no TNFi during 1st trimester only_sub39	Risk difference with TNFi
MBD											
22232 (1 observational study)	not serious	not serious	not serious	not serious	none	⨁⨁◯◯ LOW	1019/21549 (4.7%)	43/683 (6.3%)	**OR 1.35** (0.99 to 1.86)	47 per 1,000	**16 more per 1,000** (0 fewer to 37 more)

CI: Confidence interval; **OR:** Odds ratio

References: Broms 2016

TNFi compared to no TNFi during 1st trimester_sub38 for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias	Overall certainty of evidence	Study event rates (%)		Relative effect (95% CI)	Anticipated absolute effects	
							With no TNFi during 1st trimester_sub38	With TNFi		Risk with no TNFi during 1st trimester_sub38	Risk difference with TNFi

TNFi compared to no TNFi during 1st trimester_sub38 for women with RD on pregnancy and maternal outcomes

Bibliography: . PICO 2a impact of continuing medications versus stopping medications before or during pregnancy for women with RD on pregnancy and maternal outcomes. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
Spontaneous abortion											
169 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	5/86 (5.8%)	9/83 (10.8%)	**OR 1.97** (0.63 to 6.15)	58 per 1,000	**50 more per 1,000** (21 fewer to 217 more)
Stillbirth											
169 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	1/86 (1.2%)	1/83 (1.2%)	**OR 1.04** (0.06 to 16.85)	12 per 1,000	**0 fewer per 1,000** (11 fewer to 154 more)
Major anomalies											
144 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	5/79 (6.3%)	3/65 (4.6%)	**OR 0.72** (0.16 to 3.12)	63 per 1,000	**17 fewer per 1,000** (53 fewer to 111 more)
Preterm delivery											
143 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	11/77 (14.3%)	15/66 (22.7%)	**OR 1.76** (0.75 to 4.17)	143 per 1,000	**84 more per 1,000** (32 fewer to 267 more)

CI: Confidence interval; **OR:** Odds ratio

Explanations

a. Crosses no effect line
References: Diav-Citrin 2014

235 In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **infliximab** through the first trimester only versus not using the drug during the first trimester on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

236. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **etanercept** through the first trimester only versus not using the drug during the first trimester on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

237. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **adalimumab** through the first trimester only versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

238. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **golimumab** through the first trimester only versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

239. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **certolizumab** through the first trimester only versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall. Also, please see question 209. Nearly all pregnancies in Clowse 2015[28] had certolizumab exposures in the 1st trimester, but results are not delineated by women who stopped the medication in the 1st trimester or continued it through pregnancy. In Mariette 2017[29], all pregnancies were maintained on certozliumab at 30 weeks pregnancy or earlier, but results are not delineated by trimester**.**

240. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **classic NSAIDs** through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 233 for Classic NSAID exposure.

241. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **infliximab** through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

242. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **etanercept** through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

243. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **adalimumab** through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

244. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing golimumab through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

245. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing **certolizumab** through to the end of the second trimester versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence Please see question 234 for TNFi exposure overall.

246. In women with RD who are pregnant or planning pregnancy, what is the impact of taking **warfarin** during the second trimester only (and not the first or third) versus stopping the medication before pregnancy on maternal and pregnancy outcomes?

No evidence

247. In women with RD who are pregnant or planning pregnancy, what is the impact of taking **cyclophosphamide** in the second and/or third trimesters (but not the first) versus not taking the medication at all on maternal and pregnancy outcomes?

No evidence

248. In women with RD who are pregnant or planning pregnancy, what is the impact of stopping low molecular weight heparin and aspirin when pregnancy is suspected versus not using the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see section 5A for data regarding management of antiphospholipid antibody syndrome.

249. In women with RD who are pregnant or planning pregnancy, what is the impact of stopping certolizumab when pregnancy is suspected versus not using the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

250. In women with RD who are pregnant or planning pregnancy, what is the impact of stopping etanercept when pregnancy is suspected versus not using the medication before pregnancy on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

251. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing tocilizumab throughout first trimester only versus not using the drug during the first trimester on maternal and pregnancy outcomes?

No evidence. Please see question 234 for TNFi exposure overall.

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3. Corticosteroids in pregnancy:

3A.

3A. In women with RD who are pregnant or planning pregnancy, what is the impact of continuing medications [listed] versus stopping medications before or during pregnancy on maternal and pregnancy outcomes [listed]?

Population: Pregnant women with RD and

- No current RD activity but on steroid (unable to taper off steroids)
- Mild-moderate RD activity on steroid
- Severe RD activity including internal-organ inflammation from a systemic rheumatic disease (i.e. SLE, vasculitis, etc.)

Intervention: Prednisone or equivalent non-fluorinated steroid at dose of:

- <7.5mg a day (low dose)
- 7.5mg-20mg a day (moderate dose)
- >20mg a day (high dose)
- IV pulse steroids (methylprednisolone) or IM steroid

Comparator:

- No prednisone treatment
- On other DMARDs/biologics compatible with pregnancy ---*Asked in previous question*

Outcomes (studies):

- Pregnancy loss (spontaneous abortion and stillbirth) (11 studies [1-10] including 1 RCT[11])
- MBD (5 studies)[4,5,12-14]
- Preterm birth: preterm birth <34 weeks, preterm birth ≥ 34 and <37 weeks (7 studies [1-3,9,15-17] including 1 RCT[11])
- Premature rupture of membranes (3 studies [3,9] including 1 RCT[11])
- Small for gestational age infants (2 studies)[3,9]
- Gestational hypertensive disease including preeclampsia (7 studies [1,2,4,6,9,17] including 1 RCT[11])
- Gestational diabetes (1 study)[9]
- Fetal / neonatal effects: including immunosuppression, organ failure, adverse vaccine reactions in infant (eg BCG) (5 studies)[1,3,7,9,18]
- Long-term offspring effects (neurodevelopmental and autoimmune disease)
- Maternal morbidity: infection during pregnancy, adrenal insufficiency (1 study)[19]
- Maternal mortality
- RD flare (4 studies)[2,3,20,21]

This Key Question was addressed directly by 20 observational studies and 1 RCT. The overall data are presented below and no statistically significant statements can be made regarding continuing prednisone or not during pregnancy is beneficial or harmful. Due to sparse reporting of details regarding state of RD activity and specific doses of medications, we were unable to adequately address the individual PICOs, below.

GS201, GS202, GS203

Quality of evidence across outcomes: Very low

Steroid compared to no steroid for pregnant women with RD
Bibliography: PICO 3a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							With no steroid	**With Steroid**		**Risk with no steroid**	**Risk difference with Steroid**
Flare											
86 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	18/43 (41.9%)	25/43 (58.1%)	**OR 1.93** (0.82 to 4.54)	419 per 1,000	**163 more per 1,000** (47 fewer to 347 more)
Cardiac neonatal lupus											

Steroid compared to no steroid for pregnant women with RD
Bibliography: PICO 3a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
201 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	28/113 (24.8%)	22/88 (25.0%)	**OR 1.01** (0.53 to 1.93)	248 per 1,000	**2 more per 1,000** (99 fewer to 141 more)
Pregnancy loss											
34 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	0/22 (0.0%)	0/12 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Preterm delivery <37 wks											
34 (1 RCT)	not serious	not serious	not serious	not serious	none	⨁⨁⨁⨁ HIGH	3/22 (13.6%)	8/12 (66.7%)	**OR 12.67** (2.29 to 70.02)	136 per 1,000	**530 more per 1,000** (129 more to 781 more)
Gestational hypertension											

Steroid compared to no steroid for pregnant women with RD
Bibliography: PICO 3a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
34 (1 RCT)	not serious	not serious	not serious	serious [b]	none	⨁⨁⨁◯ MODERATE	0/22 (0.0%)	0/12 (0.0%)	not estimable	0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
Premature rupture of membranes											
34 (1 RCT)	not serious	not serious	not serious	serious [a]	none	⨁⨁⨁◯ MODERATE	2/22 (9.1%)	4/12 (33.3%)	**OR 5.00** (0.76 to 32.93)	91 per 1,000	**242 more per 1,000** (20 fewer to 676 more)

CI: Confidence interval; **OR:** Odds ratio
Explanations

a. Crosses no effect line

b. No events in either group

Steroid impact on maternal infection in patients with RA, PsA, AS, or IBD compared to non-biologic or TNF-i for pregnant women with RD
Bibliography: . PICO 3a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings		
№ of participants	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty**	**Study event rates (%)**		**Anticipated absolute effects**

Steroid impact on maternal infection in patients with RA, PsA, AS, or IBD compared to non-biologic or TNF-i for pregnant women with RD
Bibliography: . PICO 3a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
(studies) Follow-up						**of evidence**	**With non-biologic or TNF-i**	**With Steroid v.**	**Relative effect (95% CI)**	**Risk with non-biologic or TNF-i**	**Risk difference with Steroid**
2.1 Serious infectious event incidence rate/100 person years											
1890 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	22/1031 (2.1%)	29/859 (3.4%)	**OR 1.60** (0.91 to 2.81)	21 per 1,000	**12 more per 1,000** (2 fewer to 36 more)

CI: Confidence interval; **OR:** Odds ratio
Explanations

a. Crosses no effect line

Steroid impact on maternal infection in patients with SLE, RA, AS, IBD, or PsA compared to non-biologic for pregnant women with RD
Bibliography: . PICO 9a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].

Certainty assessment							Summary of findings				
№ of participants (studies) Follow-up	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Publication bias**	**Overall certainty of evidence**	**Study event rates (%)**		**Relative effect (95% CI)**	**Anticipated absolute effects**	
							Non-Biologic	**Steroid**		**Risk with Non-Biologic**	**Risk difference with Steroid**

Steroid impact on maternal infection in patients with SLE, RA, AS, IBD, or PsA compared to non-biologic for pregnant women with RD Bibliography: . PICO 9a: Prednisone vs no prednisone for pregnant women with RD. Cochrane Database of Systematic Reviews [Year], Issue [Issue].											
Certainty assessment							**Summary of findings**				
1.1 Serious infectious event incidence rate/100 person years											
2153 (1 observational study)	not serious	not serious	not serious	serious [a]	none	⨁◯◯◯ VERY LOW	23/991 (2.3%)	40/1162 (3.4%)	**OR 1.50** (0.89 to 2.52)	23 per 1,000	**11 more per 1,000** (3 fewer to 33 more)

CI: Confidence interval; **OR:** Odds ratio
Explanations

a. Crosses no effect line

References: 2322 Desai 2017, 2639 Izmirly 2010, 3023 Silver 1993 (RCT), 7642 Hwang 2017

Direct evidence

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Pregnancy loss	470 Huong, 2001[1]	Observational		75 pregnancies from 47 aPL women Mean age=30 +/- 4 Range 21-39	Aspirin n=17 Heparin w/ or w/out aspirin n=17 Aspirin plus prednisone n=18 Heparin w/ or w/out aspirin plus prednisone n=17 High dose immunoglobulins n=6	Embryonic loss n=2 (Aspirin plus prednisone n=1; Heparin w/ or w/out aspirin plus prednisone n=1) Fetal death and stillbirth n=19 (Aspirin n=5; Heparin w/ or w/out aspirin n=6; Aspirin plus prednisone n=5; Heparin w/ or w/out aspirin plus prednisone n=2; High dose immunoglobulins n=1)
	5342 Chakravarty 2005[2]	Observational	1991-2001	63 pregnancies among 48	Women who received prednisone during pregnancy n=30 (48%)	**Outcomes:** Women who used prednisone: (fetal outcomes) Risk of fetal loss: RR 2.3 (0.5-11.6)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				women with SLE	Mean dose of prednisone; 17 mg daily	
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	**Prednisone:** Therapeutic abortion n=7 First trimester spontaneous abortion n=3 Second trimester IUFD n=2 Live Birth n=43 **No Prednisone:** Therapeutic abortion n=0 First trimester spontaneous abortion n=3 Second trimester IUFD n=0 Live Birth n=23

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3035 TambyRaja 1993[4]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28 patients had known SLE, 2 were diagnosed during pregnancy	In 13 (25%) of patients disease was in remission during pregnancy and no meds required. In 39 (75%) pregnancies the mother received prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation occurred despite prednisolone (44%) and more than one drug had to be added.	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy - In 17 (44%) additional therapy needed 1 stillbirth due to hypoxia “optimal pregnancy outcome” in 45/52 (87%) Outcomes not stratified by Prednisone use so cannot be used as a direct comparison for PICO question
	6615 Hoeltzenbein 2012[5]	Prospective study of pregnancies reported to the European Network of Teratology Information Services prior to pregnancy outcome	Jan 1998 – June 2011	n=58 pregnancies **with mycophenolate exposure** Indications for treatment: • Organ transplantation: n=22	37 women had additional immunosuppression with glucocorticoids (median daily dose of prednisone 5–10 mg/d)	Spontaneous abortions: 10 of 37 (27.0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				• SLE: n=23 • Other autoimmune disease: n=12 Exposure to mycophenolate was in the 1st trimester (75% stopped prior to week 8)		
	4746 Out, 1992[6]	Observational		aPL n=40	Prednisone >40mg No treatment	**Prednisone n=19** Pregnancy loss: 4/11 (36.4%) **No treatment n=29** Pregnancy loss: 6/29 (20.7%)
	2621, Arfaj and Khalil 2010[7]	Case-control	27 years	319 women with SLE planning for pregnancy	In 86% of pregnancies women were treated with prednisone, 222 alone, others with other medications, and 54 did not take any therapy (control).	Treatment group vs control: Miscarriages 38 (17.1%) vs 21 (38.9%) Stillbirths 11 (4.9%) vs 2 (3.7%)
	3846 Lockshin 1989[8]	Observational, prospective	Unclear. It is mentioned that they tracked 58% of the patients in follow-up from 6 months to 4 years postpartum, and	80 pregnancies among 80 pregnant women with SLE	Various. Women who used prednisone (n=53) were also separately analyzed.	For women who had active disease, there were 5 fetal deaths/21 pregnancies For women with inactive disease, there were 14 fetal deaths/59 pregnancies For patients who were not treated with steroids and who had active disease: 3 fetal deaths/11 pregnancies For patients who were not treated with steroids and who had inactive disease: 12 fetal deaths/42 pregnancies

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
			that the remaining women were followed for up to 2 months postpartum			Fetal death was therefore not related to disease activity among total group and among women who were not treated with steroids (NS) Note: "the frequencies of abnormalities in the 80 pregnancies was low, even when excluding prednisone-treated patients"; specific abnormalities were not addressed Other medications not assessed.
	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies • Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies Other: n=12 patients with 12 pregnancies	**Prednisone/low-dose aspirin** • Spontaneous abortions: 8 (21%) • Fetal death: 8 (21%) • Live birth: 21 (54%) **Prednisone/heparin/low-dose aspirin** • Spontaneous abortions: 0 (0%) • Fetal death: 1 (8%) • Live birth: 10 (83%) **Other** • Spontaneous abortions: 2 (17%) • Fetal death: 3 (25%) • Live birth: 7 (58%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • Spontaneous abortions: 8/63 (16%) • Fetal death: 12/63 (19%) • Live birth: 38/63 (60%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosis fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	2364 Mekinian, 2016[10]	Observational	January 2010-March 2014	Women with APS n=179 with 474 pregnancies Inclusion criteria 1) ≥ 3 early miscarriage (<10 weeks gestation); 2) Intrauterine fetal death (> 10 weeks gestation); 3) preeclampsia, prematurity <34 weeks gestation related to placental insufficiency; 4) absence of inherited thrombophilia and conventional aPL	Steroids HCQ	**Pregnancy losses** Steroids = 5/20 (25%) HCQ = 2/12 (17%)
Preterm Birth	2524 Langen 2014[15]	Observational, retrospective	2001-2009	All pregnancies (n=46) to RA mothers (n=40)	Prednisone	15 women used prednisone around the time of conception, and 1 patient discontinued prednisone after conception. 70% of pregnancies were exposed to prednisone at some point. Prednisone was added or increased during pregnancy in 42% pregnancies. With Preterm birth (Y/N) as outcome and prednisone as predictor, OR 5.54 (0.64-267.93); NS. Did not evaluate potential dose effects.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	**Prednisone:** Premature Delivery n=9 **No Prednisone:** Premature Delivery n=2
	5342 Chakravarty 2005[2]	Observational	1991-2001	63 pregnancies among 48 women with SLE	Women who received prednisone during pregnancy n=30 (48%) Mean dose of prednisone; 17 mg daily	**Outcomes:** Women who used prednisone: (fetal outcomes) Prematurity RR 1.8 (1.1-3.0) Prednisone use associated with prematurity

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3715 Clark 2003[16]	Observational, retrospective	1999-2001	72 pregnancies in women with SLE	Variable. 43 women used prednisone. 24 women used prednisone ≥10 mg daily.	28 pregnancies (38.9%) resulted in preterm delivery. 24 women (53.3%) who had term deliveries used prednisone, and 19 (67.9%) who had preterm deliveries used prednisone (p=NS). More women in preterm group used prednisone ≥10 mg daily during pregnancy (p=0.028). Mean dose of prednisone in preterm group was 24.8 mg, and 16.7 mg in the term group (p=0.047).
	3377 Skorpen 2017[17]	Observational; Data from the Medical Birth Registry of Norway (MBRN) were linked with data from RevNatus, a nationwide observational register recruiting women with inflammatory rheumatic diseases. Singleton births in women with SLE included in RevNatus 2006–2015 were cases (n=180).	pregnancy	Mean age 31.5 years; 83% live births Between 56.6% and 59.9% of women with SLE had inactive disease during pregnancy and 6 weeks after birth, and less than 10% experienced moderate disease activity or higher (LAI-P>0.5)	Prednisone HCQ	Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%). Birth weight z-score was statistically significantly lower in offspring of women using prednisolone (mean difference 0.33). There was a substantially higher odds of pre-eclampsia when using prednisolone (OR=2.33), and we found a statistically significant threefold increase in preterm birth Outcomes not stratified by Prednisone use.
	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis;	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17	**Prednisone/low-dose aspirin** • Delivery ≤32 weeks: 10 (48%) **Prednisone/heparin/low-dose aspirin** • Delivery ≤32 weeks: 3 (30%) **Other**

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		women with APS treated during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin		2) recurrent pregnancy loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks	patients with 19 pregnancies • Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies Other: n=12 patients with 12 pregnancies	• Delivery ≤32 weeks: 3 (43%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • Delivery ≤32 weeks: 16/38 (42%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				or amaurosis fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		
	470 Huong, 2001[1]	Observational		75 pregnancies from 47 aPL women Mean age=30 +/- 4 Range 21-39	Aspirin n=17 Heparin w/ or w/out aspirin n=17 Aspirin plus prednisone n=18 Heparin w/ or w/out aspirin plus prednisone n=17 High dose immunoglobulins n=6	Premature birth n=16 (Aspirin n=2; Aspirin plus prednisone n=5; Heparin w/ or w/out aspirin plus prednisone n=7; High dose immunoglobulins n=2)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
MBD	4590, Shinohara 1999[12]	Case-series Direct	17 years	87 offspring of 40 anti-Ro/SSA positive mothers	Group A: Prednisolone or betamethasone started before 16 weeks' gestation in 25 pregnancies (26 offspring), Group B: after 16 weeks' gestation in 8 pregnancies. Group C: 53 mothers of 11 fetuses did not received corticosteroid treatment.	Congenital heart block: Group A – none; Group B – 15; Group C: 11 (3 died perinatally, 5 infants required permanent pacemakers, and 3 others did not require treatment) Complete congenital heart block, once developed, did not respond to corticosteroid treatment in utero (4 cases).
	6615 Hoeltzenbein 2012[5]	Prospective study of pregnancies reported to the European Network of Teratology Information Services prior to pregnancy outcome	Jan 1998 – June 2011	n=58 pregnancies **with mycophenolate exposure** Indications for treatment: • Organ transplantation: n=22 • SLE: n=23 • Other autoimmune disease: n=12 Exposure to mycophenolate was in the 1st trimester (75% stopped prior to week 8)	37 women had additional immunosuppression with glucocorticoids (median daily dose of prednisone 5–10 mg/d)	n=7 major birth defects in patients who also took glucocorticoids
	3035 TambyRaja 1993[4]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28	In 13 (25%) of patients disease was in remission	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				patients had known SLE, 2 were diagnosed during pregnancy	during pregnancy and no meds required. In 39 (75%) pregnancies the mother received prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation occurred despite prednisolone (44%) and more than one drug had to be added.	- In 17 (44%) additional therapy needed CHB observed in 1 baby • Outcomes not stratified by Prednisone use so cannot be used as a direct comparison for PICO question
	6167 Tunks, 2013[13]	Observational		33 women with RD.	Predinsone only n=2 (5mg qd and 20mg qd) HCQ only n= 8 200mg qd – 400mg qd) No Prednisone or HCQ n=17 Prednisone + HCQ n=6	**Degree of Heart Block** Predinsone only: no heart block HCQ only: 1st degree AVB n=1; no heart block n=7 No Prednisone or HCQ: CHB n=4; 1st degree AVB n=3 Prednisone + HCQ: no heart block n=6 Pacemaker: 3

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3615, Llanos 2009[14]	Case-series	15-year study period	161 pregnancies of 129 mothers with anti-SSA/Ro Antibodies	3 of 4 mothers with a child with recurrent cardiac NL who were taking steroids had received prednisone, while the other mother had received dexamethasone (dosage not stated). 17 of the mothers who had received steroids and had children with noncardiac NL were taking prednisone (mean dosage 23 mg/day) and 4 were taking dexamethasone (mean dosage 4 mg/day). For 13 mothers of children in the noncardiac NL group, information about medications was not available.	The results by type of cardiac NL for 1) First degree HB, 2) Second degree HB, 3) Third degree HB, and 4) EFE were: Death - 0, 0, 5 (18%), 1 (4%) Cardiac NL at 18–25 weeks of gestation – 0, 1 (4%), 18 (64%), 2 (7%) Pacemaker – 0, 0, 19 (68%), 0 • 4 (16%) children with recurrent cardiac NL of 25 mothers taking steroids vs 19 (20.9%) of 91 mothers not taking steroids.
Fetal / Neonatal effects	2621, Arfaj and Khalil 2010[7]	Case-control	27 years	319 women with SLE planning for pregnancy	In 86% of pregnancies women were treated with prednisone, 222 alone, others with other medications, and 54 did not take any therapy (control).	<u>Treatment group vs control:</u> Neonatal deaths 2 (0.9%) vs 1 (1.9%)
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in	**Prednisone:** Neonatal Lupus n=5 **No Prednisone:** Neonatal Lupus n=0

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion • in two of the pregnancies.	
	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies • Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies Other: n=12 patients with 12 pregnancies	**Prednisone/low-dose aspirin** • Neonatal death: 2 (5%) • Fetal distress: 14/23 (61%) **Prednisone/heparin/low-dose aspirin** • Neonatal death: 1 (8%) • Fetal distress: 4/12 (33%) **Other** • Neonatal death: 0 (0%) • Fetal distress: 3/7 (43%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • Neonatal death: 3/63 (5%) • Fetal distress: 21/42 (50%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		low-dose aspirin; 4) other combinations of these medications or immunoglobulin		required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosis fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimm		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				une disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		
	470 Huong, 2001[1]	Observational		75 pregnancies from 47 aPL women Mean age=30 +/- 4 Range 21-39	Aspirin n=17 Heparin w/ or w/out aspirin n=17 Aspirin plus prednisone n=18 Heparin w/ or w/out aspirin plus prednisone n=17 High dose immunoglobulins n=6	Neonatal death n=2 (Aspirin n=1; Aspirin plus prednisone n=1)
Gestational hypertensive disease including preeclampsia	470 Huong, 2001[1]	Observational		75 pregnancies from 47 aPL women Mean age=30 +/- 4 Range 21-39	Aspirin n=17 Heparin w/ or w/out aspirin n=17 Aspirin plus prednisone n=18 Heparin w/ or w/out aspirin plus prednisone n=17	Preeclampsia n=10 (Heparin w/ or w/out aspirin n=1; Aspirin plus prednisone n=3; Heparin w/ or w/out aspirin plus prednisone n=5; High dose immunoglobulins n=1)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					High dose immunoglobulins n=6	
	4746 Out, 1992[6]	Observational		aPL n=40	Prednisone >40mg No treatment	**Prednisone n=19** Hypertensive disease: 2/11 (18.2%) **No treatment n=29** Hypertensive disease: 3/29 (10.3%)
	5342 Chakravarty 2005[2]	Observational	1991-2001	63 pregnancies among 48 women with SLE	Women who received prednisone during pregnancy n=30 (48%) Mean dose of prednisone; 17 mg daily	**Outcomes:** Women who used prednisone: Preeclampsia RR 1.8 (0.7-5.0)
	3377 Skorpen 2017[17]	Observational; Data from the Medical Birth Registry of Norway (MBRN) were linked with data from RevNatus, a nationwide observational register recruiting women with inflammatory rheumatic diseases. Singleton births in women with SLE included in RevNatus 2006–2015 were cases (n=180).	pregnancy	Mean age 31.5 years; 83% live births Between 56.6% and 59.9% of women with SLE had inactive disease during pregnancy and 6 weeks after birth, and less than 10% experienced moderate disease activity or	Prednisone HCQ	Prednisolone was used significantly more often in the second and third trimesters among women with active (58.1% and 57.9%) compared with inactive disease (38.1% and 37.5%). There were no significant differences in the use of hydroxychloroquine or azathioprine between the groups in any of the trimesters, or of prednisolone in the first trimester (51.0% and 38.8%). Birth weight z-score was statistically significantly lower in offspring of women using prednisolone (mean difference 0.33). There was a substantially higher odds of pre-eclampsia when using prednisolone (OR=2.33), and we found a statistically significant threefold increase in preterm birth Outcomes not stratified by Prednisone use.

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				higher (LAI-P>0.5)		
	3035 TambyRaja 1993[4]	Observational	Through pregnancy	52 pregnancies in 30 patients with SLE; 28 patients had known SLE, 2 were diagnosed during pregnancy	In 13 (25%) of patients disease was in remission during pregnancy and no meds required. In 39 (75%) pregnancies the mother received prednisolone throughout. In 22 (56%) of these 39 pregnancies, prednisolone was continued throughout pregnancy and puerperium; 2/22 with exacerbation (prednisolone dose increased in 20mg/day), 1 patient on 2.5mg qod, remaining 19 on 5mg TID throughout pregnancy. In remaining 17 patients, exacerbation occurred despite prednisolone (44%) and more than one drug had to be added.	39 pregnancies patients on prednisolone throughout: - In 22 (56%) able to remain on prednisolone monotherapy - In 17 (44%) additional therapy needed Pre-eclampsia in 12 pregnancies Outcomes not stratified by Prednisone use so cannot be used as a direct comparison for PICO question
	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies	**Prednisone/low-dose aspirin** • Preeclampsia: 20/31 (65%) • Severe preeclampsia: 11/31 (35%) **Prednisone/heparin/low-dose aspirin** • Preeclampsia: 6/12 (50%) • Severe preeclampsia: 2/12 (17%) **Other**

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin		loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosi	• Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies Other: n=12 patients with 12 pregnancies	• Preeclampsia: 3/10 (30%) • Severe preeclampsia: 1/10 (10%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • Preeclampsia: 20/53 (55%) • Severe preeclampsia: 14/53 (26%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				s fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		
PROM	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone,	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies • Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies • Other: n=12 patients with 12 pregnancies	**Prednisone/low-dose aspirin** • PROM: 3/23 (13%) **Prednisone/heparin/low-dose aspirin** • PROM: 3/12 (25%) **Other** • PROM: 1/7 (14%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • PROM: 7/42 (17%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin		delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosis fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7%		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				• Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus	**Prednisone:** Premature Delivery n=6 **No Prednisone:** Premature Delivery n=2

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
					ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion • in two of the pregnancies.	
SGA	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both.	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies • Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies • Other: n=12 patients with 12 pregnancies	**Prednisone/low-dose aspirin** • Small for gestational age: 10/23 (43%) **Prednisone/heparin/low-dose aspirin** • Small for gestational age: 2/9 (22%) **Other** • Small for gestational age: 2/7 (29%) **Combination of above 3 groups (prednisone use in combination with any other medication)** • Small for gestational age: 14/42 (33%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosis fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion • in two of the pregnancies.	**Prednisone:** SGA n=10 **No Prednisone:** SGA n=4
Gestational Diabetes	3047 Branch 1992[9]	Retrospective review of medical and obstetric histories of consecutive pregnancies in women with APS treated	1983-	**APS** defined by having one of the following: 1) venous or arterial thrombosis; 2) recurrent pregnancy	• Prednisone/low-dose aspirin: n=33 patients with 39 pregnancies • Heparin/low-dose aspirin: n=17 patients with 19 pregnancies	**Prednisone/low-dose aspirin** • Gestational diabetes: 3/31 (10%) **Prednisone/heparin/low-dose aspirin** • Gestational diabetes: 5/12 (42%) **Other** • Gestational diabetes: 0/10 (0%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
		during pregnancy with 1) prednisone and low-dose aspirin; 2) heparin and low-dose aspirin; 3) prednisone, heparin and low-dose aspirin; 4) other combinations of these medications or immunoglobulin		loss (at least 3 spontaneous abortions), fetal death, or early neonatal death due to preterm delivery required because of fetal distress; or 3) autoimmune thrombocytopenia. All patients had lupus anticoagulant, medium to high positive IgG anticardiolipin, or both. n=54 women with APS included (82 pregnancies) • SLE: 32% • Thrombosis or thromboembolism: 41% • Transient ischemic attacks or amaurosi	• Prednisone/heparin/low-dose aspirin: n=11 patients with 12 pregnancies • Other: n=12 patients with 12 pregnancies	**Combination of above 3 groups (prednisone use in combination with any other medication)** • Gestational diabetes:8/53 (15%)

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
				s fugax: 24% • Thrombocytopenia: 22% • Chronic hypertension: 7% • Other autoimmune disease: 17% • Lupus anticoagulant: 96% • IgG anticardiolipin (≥20 GPL units/mL): 88%		
RD Flare	2991, Ruiz-Irastorza 1996[21]	Case-control Direct	Perinatal period	78 pregnancies in 68 SLE patients and a control group of 50 non-pregnant SLE patients.	• Prednisone, immunosupressors, HCQ.	In the pregnancy group 5 patients had disease activity at conception. 4 of them flared again during pregnancy, 1 entered study in remission. 12 renal flares during pregnancy. 8 out of 9 patients (88%) who flared during the year prior to conception flared again during pregnancy. Rate of flares during study period: Pregnancy group 51 (65%) patients, control group 21 (42%) The rates of flare per patient/month were 0.093 ± 0.006 during pregnancy and the puerperium, and 0.049 ± 0.0044 during the year after puerperium.
	5342 Chakravarty 2005[2]	Observational	1991-2001	63 pregnancies among 48 women with SLE	Women who received prednisone during pregnancy n=30 (48%) Mean dose of prednisone; 17 mg daily	**Outcomes:** Women who used prednisone: Risk of flare RR 1.6 (1.1-2.3) Risk of severe flare RR 1.0 (0.4-1.0) So prednisone was associated with risk of flare during pregnancy

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
	3765, Kobayishi 1999[3]	Retrospective	15 years	82 pregnancies of 55 patients with SLE	The treatments given to the patients with SLE before their pregnancies were as follows: Prednisolone [PSL](4-20 mg/day) in 47; PSL (10-20 mg/day) and azathioprine (50-150 mg/day) in five; PSL (10 mg/day) and aspirin (ASP; 80 mg/day) in three; only ASP in one; and no treatment in 26 pregnancies. In ten of the 26 pregnancies with no treatment, patients first began to take medications during their pregnancies. These medications consisted of ASP (80 mg/day) in two, PSL (10 mg/day) plus ASP in one, and PSL (20-50 mg/day) in five, and a high dose of intravenous immunoglobulin (IVIg) infusion in two of the pregnancies.	Of the 13 patients with SLE flare during pregnancy, • Prednisolone was increased in 7/13 cases and 2/13 started Prednisolone for the first time. In two cases, administrations of hydrocortisone were combined with prednisolone.

252. In women with RD and quiescent disease on chronic steroid, what is the impact of taking low dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

253. In women with RD and quiescent disease on chronic steroid, what is the impact of taking moderate dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

254. In women with RD and quiescent disease on chronic steroid, what is the impact of taking high dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

255. In women with RD and quiescent disease on chronic steroid, what is the impact of taking IV pulse or IM prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

256. In women with RD and mild-moderately active disease, what is the impact of taking low dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

257. In women with RD and mild-moderately active disease on chronic steroid, what is the impact of taking moderate dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

258. In women with RD and mild-moderately active disease on chronic steroid, what is the impact of taking high dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

259. In women with RD and mild-moderately active disease on chronic steroid, what is the impact of IV pulse or IM prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

260. In women with RD and severe active disease, what is the impact of taking low dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

261. In women with RD and severe active disease, what is the impact of taking moderate dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

262. In women with RD and severe active disease, what is the impact of taking high dose prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

263. In women with RD and severe active disease, what is the impact of taking IV pulse or IM prednisone or other non-fluorinated steroid versus not taking any corticosteroid on maternal and fetal outcomes [listed]?
Cannot specifically assess; general information provided in tables, above

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3B. No evidence

3B. In women with RD on chronic prednisone (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months before pregnancy, what is the impact of tapering off steroid when pregnancy is diagnosed versus continuing on the same dose on maternal and fetal outcomes [listed]?

GS201, GS202, GS203

Population:

- Women with RD on chronic prednisone or non-fluorinated steroid equivalent greater than 7.5 mg daily for greater than one year

Intervention:

- Tapering down to average daily dose of ≤ 7.5mg steroid when pregnancy diagnosed
- Tapering off steroid

Comparator:

- Continue stable steroid dose (> 7.5mg)

Outcome:

- Pregnancy loss, including spontaneous abortion and stillbirth
- MBD
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Premature rupture of membranes
- Small for gestational age infants
- Gestational hypertensive disease, including preeclampsia
- Gestational diabetes
- Long-term outcomes, including growth and development
- Maternal morbidity, including infection during pregnancy and adrenal insufficiency
- Maternal mortality
- RD flare
- RD damage

3C. No evidence

3C. In women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months prior to delivery, what is the impact of administration of stress-dose steroid at the time of delivery [listed] versus no stress-dose steroid on maternal and fetal outcomes [listed]?

GS206,GS207

Population:

- Women with RD on chronic steroid (or non-fluorinated steroid equivalent) greater than 7.5 mg daily for greater than 6 months and delivering by any mode of delivery

Intervention:

- Stress-dose steroid at the time of delivery

Comparator:

- No stress-dose steroid

Outcome:

- Pregnancy loss, including stillbirth
- MBD
- Preterm birth: preterm birth < 34 weeks, preterm birth ≥ 34 and < 37 weeks
- Premature rupture of membranes
- Small for gestational age infants
- Gestational hypertensive disease, including preeclampsia
- Gestational diabetes
- Long-term outcomes, including growth and development
- Maternal morbidity, including infection and adrenal insufficiency
- Maternal mortality
- RD flare
- RD damage

4. Lactation and medications:

4A.

4A In women with RD who are considering breastfeeding, what is the impact of taking medication [listed] during breastfeeding versus not taking medication on drug levels and neonatal outcomes [listed]?

Population: Women with RD who are lactating and considering breastfeeding

Intervention: Continuing/starting medication while breastfeeding, including…

- Nonimmunosuppressive:
  - Classic NSAIDs
  - Cox2 inhibitors
  - Antimalarials
  - Sulfasalazine
  - Colchicine
- Classic, or synthetic, immunosupressives:
  - Methotrexate
  - Leflunomide
  - Azathioprine / 6-MP
  - Mycophenolate mofetil / mycophenolic acid
  - Cyclosporine
  - Tacrolimus
  - Cyclophosphamide
  - Thalidomide / Lenalidomide?
- Biologic immunosuppressives: TNF-inhibitors:
  - Infliximab
  - Etanercept
  - Adalimumab
  - Golimumab
  - Certolizumab
- Biologic immunosuppressives: Non-TNF biologics:
  - Anakinra
  - Rituximab
  - Belimumab
  - Abatacept
  - Tocilizumab
  - Secukinumab
  - Ustekinumab
- Novel small molecules:
  - Tofacitinib

    - Baracitinib
    - Apremilast
- Other:
    - IVIG
    - Anticoagulants:
        - Warfarin
        -
        - heparin/LMWH
        - other antiplatelet agents

Comparator:

- Not taking medication while breastfeeding

Outcomes:

- Transmission to breast milk
- Transmission to infant (serum levels)
- Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

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No evidence is available for question 265 or 267-96.

264. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking classic NSAIDs verses not taking classic NSAIDs on: **GS89**

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

One single-arm study addresses piroxicam use in 4 lactating women with inflammatory arthritis, resulting in a mean breastmilk level of 78 mcg/L.[1] Piroxicam and its conjugates were not detectable in the urine of one infant. The infant daily dose was calculated to average 3.5% of the weight-based maternal dose. No evidence on clinical side effects in offspring is available.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Transmission to breast milk	Ostenson, 1988[1]	Single arm	52 days	4 women with inflammatory arthritis, background rx varies	piroxicam 20 mg daily	Breastmilk level mean 78 mcg/L at steady state, 141 mcg/L max

265. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking COX-2 inhibitors verses not taking COX-2 inhibitors on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

266. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking antimalarials verses not taking antimalarials on: **GS92**

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

No evidence is available on transmission of HCQ or other antimalarials to breastmilk or on infant serum HCQ levels. One observational study addresses exposure to HCQ 200 gm daily in 13 infants.[2] All children had normal motor quotient, normal ophthalmologic exam, and no evidence of severe or recurrent infection.

Quality of Evidence across outcomes: Very low

Outcome	Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Long term effects, including growth & development	Motta, 2004[2]	observational	1 year	13 infants exposed to hydroxychloroquine during lactation (and pregnancy)	Hydroxychloroquine 200 mg daily taken by mothers during pregnancy and breastfeeding	Normal motor quotient in all children; normal ophthalmologic exam during 1st year of life; no severe or recurrent infection

267. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking sulfasalazine verses not taking sulfasalazine on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

268. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking colchicine verses not taking colchicine on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

269. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking methotrexate verses not taking methotrexate on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:

- Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
- Long term effects, including growth & development

- **No evidence**

270. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking leflunomide verses not taking leflunomide on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
   - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
   - Long term effects, including growth & development

- **No evidence**

271. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking azathioprine/6- mercaptopurine verses not taking classic azathioprine/6-mercaptopurine on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
   - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
   - Long term effects, including growth & development

- **No evidence**

272. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking mycophenolate mofetil / mycophenolic acid
verses not taking mycophenolate mofetil / mycophenolic acid on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
   - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
   - Long term effects, including growth & development

- **No evidence**

273. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking cyclosporine verses not taking cyclosporine on:

a) Transmission to breast milk

b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

274. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking tacrolimus verses not taking tacrolimus on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

275. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking cyclophosphamide verses not taking cyclophosphamide on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

276. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking thalidomide / lenalidomide verses not taking thalidomide / lenalidomide on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

277. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking infliximab verses not taking infliximab
on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

278. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking etanercept verses not taking etanercept
on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

279. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking adalimumab verses not taking adalimumab on

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

280. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking golimumab verses not taking golimumab on:

a) Transmission to breast milk

b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

281. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking certolizumab verses not taking certolizumab on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

282. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking anakinra verses not taking anakinra on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

283. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking rituximab verses not taking rituximab on

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

284. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking belimumab verses not taking belimumab on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

285. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking abatacept verses not taking abatacept on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

286. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking tocilizumab verses not taking tocilizumab on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

287. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking secukinumab verses not takings secukinumab on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

288. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking ustekinumab verses not taking ustekinumab on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

289. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking tofacitinib verses not taking tofacitinib on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

290. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking baracitinib verses not taking baracitinib on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

291. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking apremilast verses not taking apremilast on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other

- Long term effects, including growth & development
- **No evidence**

292. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking IVIG verses not taking IVIG on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

293. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking warfarin verses not taking warfarin on

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

294. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking DOACs (rivaroxaban, dabigatran, apixaban, edoxaban) verses not taking DOACs on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
    - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
    - Long term effects, including growth & development

- **No evidence**

295. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking heparin/LMWH verses not taking heparin/LMWH on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:

- Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
- Long term effects, including growth & development

- **No evidence**

296. In women with RD who are lactating and considering continuing/starting medication while breastfeeding what is the impact of taking other anti-platelet agents verses not taking other anti-platelet agents on:

a) Transmission to breast milk
b) Transmission to infant (serum levels)
c) Clinical side effects in offspring:
   - Neonatal/ infancy: hospitalization, serious infection, myelosuppression, digestive problems, growth, CNS, adverse vaccine reaction, other
   - Long term effects, including growth & development

- **No evidence**

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