SUPPLEMENTARY APPENDIX 4: Additional Literature Reviews on Non-RMD Populations

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

Risk of Thrombosis with ART:

Main risk of thrombosis with ART in healthy women is associated with ovarian hyperstimulation syndrome (OHSS):
IVF and other ART involve use of exogenous hormones to achieve cycle control, ovarian stimulation, and support of implantation. Supra-physiologic estradiol levels may lead to OHSS that can be associated with arterial and venous thrombotic complications (1).

- In a recent review, there were 96 reported cases of OHSS-associated thrombosis. The timing and location of arterial and venous events differed: arterial events usually occurred concurrently with onset of OHSS and were predominantly cerebrovascular events, while venous events occurred several weeks later after the clinical resolution of OHSS and were often reported in unusual sites such as the upper extremities and jugular veins.

- There is little in the literature to guide thromboprophylaxis. Thromboprophylaxis should be considered for patients who develop moderate-to-severe OHSS (and continued for an extended period of 1–2 months beyond the resolution of clinical OHSS), **and also be considered for patients with known inherited or acquired thrombophilia, while undergoing ART** (2).

There is an increased risk of severe OHSS with underlying thrombophilia:
There is an increased prevalence of underlying thrombophilia among women with severe OHSS. In one study, 17/20 patients with severe OHSS (85%) and 11/41 controls (26.8%) had one or more positive markers of thrombophilia (antithrombin, protein S, protein C, aPL, factor V Leiden, MTHFR). Eight women with OHSS and no controls had more than one positive marker of thrombophilia.

Thrombosis risk assessment should be undertaken in women undergoing ovarian stimulation with gonadotrophins, and appropriate thromboprophylaxis should be instigated if the risk of thrombosis is considered significant (3).

OHSS can be predicted and thrombosis risk modified to some extent:
Ovarian hyperstimulation syndrome (OHSS) affects 5% of IVF cycles and has a 100-fold increase in risk of VTE over natural conceptions. Healthy women at risk of OHSS can be identified using antral follicle count (AFC) and anti-Müllerian hormone (AMH). For those women, combining a GnRH antagonist with a conventional hCG trigger will reduce the risk of OHSS and still allow a fresh transfer to occur.

Complete abolition of OHSS may be possible by avoiding exposure to exogenous hCG. This can be achieved by segmentation of the IVF cycle using a GnRH agonist for final oocyte maturation and then freezing all oocytes or embryos with subsequent replacement of a single embryo in the context of a frozen embryo transfer. **This approach will ensure a VTE risk equivalent to natural conception and can be combined with conventional thromboprophylaxis strategies** (4).

1. Chan WS, Dixon ME. The "ART" of thromboembolism: a review of assisted reproductive technology and thromboembolic complications. Thrombosis research. 2008 Jan 1;121(6):713-26.
2. Chan WS. The 'ART'of thrombosis: a review of arterial and venous thrombosis in assisted reproductive technology. Current Opinion in Obstetrics and Gynecology. 2009 Jun 1;21(3):207-18.
3. Nelson SM, Greer IA. Artificial reproductive technology and the risk of venous thromboembolic disease. Journal of Thrombosis and Haemostasis. 2006 Aug 1;4(8):1661-3
4. Nelson SM. Venous thrombosis during assisted reproduction: novel risk reduction strategies. Thrombosis research. 2013 Jan 1;131:S1-3.

Thrombosis Risk of Hormonal Contraceptives:

1. Combined hormonal contraceptives (CHC's):

The overall risk of venous thromboembolism (VTE) in healthy women on current CHC's is increased by 3-6x from the baseline annual risk of 1 / 10,000.

- Both estrogen and progestin contribute to increased VTE risk. Variation in progestin accounts for most variability among pills. 3rd generation progestins confer greater VTE risk than do 2nd generation due to greater activated protein C resistance. Odds ratios for VTE risk with CHC's (same estrogen content) ranges from 2.23 to 6.61, depending on type of progestin (1). Arterial thrombosis and MI risks are also increased with CHC's, and are related to typical risk factors.
- Presence of prothrombotic risk factors (e.g. aPL, factor V Leiden, prothrombin gene mutation (G20210A), nephrotic syndrome, obesity or bedrest) additionally increase VTE risk.
- RD patients may be at an already increased thrombosis risk, even if aPL- negative. Significant risk factors for thrombosis in an SLE cohort (n=1930): smoking (OR 1.25, P=0.011), longer disease duration (OR 1.26/5 years, P= 0.027 x10-7), nephritis (OR 1.35, P=0.036), aPL (OR 3.22, P< 10-9) and immunomodulatory medication use (OR 1.40, P=0.011) (2).

Additional point about CHC use in SLE:

CHC pills in the SELENA and Sanchez-Guerrero et al. studies were 2nd generation, so absence of flare or thrombotic risk cannot necessarily be generalized to CHC's with a higher estrogen content, different progestin, or different administration method eg patch or ring. Patch suggested to yield 60% higher serum estrogen levels.

2. Progestin-only contraceptive (POC) thrombosis risk:

Use of POC methods is widely accepted as a lower risk method for patients unable to use estrogens, although degree of thrombosis risk – if any – is debated.

- The risk of VTE in healthy women using POC's is not increased.
- Recent meta-analysis (8 studies, 2 with patients at high risk for VTE): POC's overall not associated with increased VTE risk compared to nonusers, RR = 1.03, (0.76-1.39) (3).
- Subgroup analysis of two studies including DMPA (small numbers of patients): significant increased VTE risk with DMPA, RR = 2.67 (1.29-5.53). *Suggested to be a dose-related phenomenon: higher doses of progestins do cause hemostatic activation. DMPA peak plasma levels are 2500-7000 pg/ml (compared to 74-166 pg/ml for the LNG-IUD).*
- In contrast, POC pill VTE risk was not elevated (RR = 0.90, 0.57-1.45), nor was risk with LNG-IUD (RR = 0.61, 0.24-1.53). Little data on the etonorgestrel subdermal implant, although risk might, in theory, be slightly higher than with LNG-containing POC's due to use of a 3rd generation progestin.

More recent studies focusing only on women at elevated VTE risk (history of previous VTE) haven't identified higher risk with use of (non-DMPA) POC's (4,5).

CDC and WHO guidelines for medical eligibility for contraceptive use do not recommend any form of POC for women with SLE with positive (or unknown) aPL (category 3, "theoretical or proven risks outweigh advantages"). The ACOG guidelines for contraceptive use in women with chronic medical conditions recommend POC's as safer alternatives than CHC's for women with SLE with aPL, active nephritis and vascular disease (6).

Additional point: The effects of the LNG-IUD, etonorgestrel implant or DMPA on disease activity in any rheumatic disease have not been specifically studied although progestins in general have not been suggested to increase disease activity.

Critical to weigh VTE risk of pregnancy in RD patients against that associated with use of any hormonal contraceptive.

- Baseline VTE risk in healthy young women is 1/10,000; risk with current COC's is 5/10,000 and risk of VTE in pregnancy is 73/10,000. For those with a single (genetic) prothrombotic defect VTE risk is 197/10,000, and for those with combined prothrombotic defects, it is 776/10,000 (7).

Use of IUDs in immunosuppressed patients:

Complications associated with IUD use include risk of expulsion (5% over 5 years) and a very low risk of pelvic inflammatory disease (1.6 infections / 1000 women-years) in the 20 days following insertion (8).

- Risk of IUD-associated infection in patients on immunosuppressive medications has not been studied, but studies in immunocompromised HIV-infected women show no increased risk of infection (9). *IUD infection risk has also been raised for women undergoing chemotherapy and for women with solid organ transplants, but no significant data to date.*

Risk of lowered bone density with depot-medroxyprogesterone acetate (DMPA):

Unlike other progestin methods, DMPA suppresses ovulation and unlike the progesterone-only pill or LNG-IUD, DMPA may cause reversible bone loss.

- Reduction in bone density in healthy women is 5.7 – 7.5% after two years of use (10).

In 2004, the FDA issued a DMPA "black box warning" for to highlight the fact that prolonged use may result in significant loss of bone density, that the degree of loss is proportional to the amount of time on DMPA, and that the loss may not be completely reversible. No evidence for increased fracture risk in healthy women, however, and ACOG recommends individualized use in patients with or at at increased risk for osteoporosis (11).

References:

1. Stam-Slob MC, Lambalk CB, van de Ree MA. Contraceptive and hormonal treatment options for women with history of venous thromboembolism. BMJ. 2015;351:h4847.

2. Kaiser R, Cleveland CM, Criswell LA. Risk and protective factors for thrombosis in systemic lupus erythematosus: results from a large, multi-ethnic cohort. Ann Rheum Dis. 2009;68(2):238-41. [Also: Lee JJ, Pope JE. A meta-analysis of the risk of venous thromboembolism in inflammatory rheumatic diseases. Arthritis research & therapy. 2014 Oct;16(5):435.]
3. Mantha S, Karp R, Raghavan V, et al. Assessing the risk of venous thromboembolic events in women taking progestin-only contraception: a meta-analysis. BMJ 2012;345:e4944.
4. Conard J, Plu-Bureau G, Bahi N et al. Progestogen-only contraception in women at high risk of venous thromboembolism. Contraception 2004;70(6):437-441.
5. Le Moigne E, Tromeur C, Delluc A, et al. Risk of recurrent venous thromboembolism on progestin-only contraception: cohort study. Haematologica. 2016;101(1):e12-4.
6. ACOG Committee on Practice Bulletins – Gynecology ACOG Practice Bulletin number 73: Use of hormonal contraception in women with coexisting medical conditions. Obstet Gynecol 2006;107:1453-1472.
7. van Vlijmen EF, Veeger NJ, Middeldorp S, et al. Thrombotic risk during oral contraceptive use and pregnancy in women with factor V Leiden or prothrombin mutation: a rational approach to contraception. Blood 2011;118(8):2055-61.
8. Lyus R, Lohr P, Prager S. Use of the Mirena LNG-IUS and Paragard CuT380A intrauterine devices in nulliparous women. Contraception 2010;81(5): 367-371.
9. Stringer EM, Kaseba C, Levy J, et al. A randomized trial of the intrauterine device versus hormonal contraception in women who are infected with the human immunodeficiency virus. Am J Obstet Gynecol 2007;197(2):144-e1-144.e8.
10. Clark MK, Sowers M, Levy B, Nichols S. Bone mineral density loss and recovery during 48 months in first-time users of depot medroxyprogesterone acetate. Fertil Steril 2006;86:1466–74.
11. American College of Obstetricians and Gynecologists Committee on Gynecologic Practice. ACOG Committee Opinion, Number 602: Depo-Medroxyprogesterone acetate and bone effects. June 2014.

Thrombotic Risk of Hormone Replacement Therapy (HRT):

<u>Risk of VTE is increased with HRT use:</u>

Women's Health Initiative: VTE risk increased 2x in the estrogen-progestin group compared with placebo (HR =2.06, 95% CI 1.6-2.7 (1).

- The rates of VTE were 3.5 and 1.7 per 1000 person-years in the estrogen-progestin and placebo groups, respectively.

Systematic review / meta-analysis of 22 randomized trials of HRT: risk of VTE increased. After one year, VTE risk increased from 2 per 1000 to 2-10 per 1000 for combined estrogen-progestin therapy and to 4-11 per 1000 for unopposed estrogen therapy (2).

Factors affecting VTE risk include:

1. Type of oral estrogen: In a population-based, case-control study (586 with VTE, 2268 healthy women), women taking conjugated estrogens, but not esterified (plant-derived) estrogens, were at increased risk of VTE when compared with non-estrogen users (OR= 1.7) (3).

2. Route of estrogen: ***Transdermal estrogen has little effect on hemostasis and seems associated with a lower VTE risk***. A case-control study included 271 VTE cases of and 610 matched controls. OR's for VTE in current users of oral or transdermal estrogen compared with nonusers were 4.2 (95% CI 1.5-11.6) and 0.9 (95% CI 0.4-2.1), respectively (4). In a meta-analysis, no excess risk of VTE was observed in women taking transdermal estrogen (OR 1.2, 95% CI 0.1-1.7), even in those with prothrombotic mutations or high body mass index (BMI) (5).

3. Type of progestin: Type of progestin also affects risk of VTE. In a study of over one million postmenopausal women that included 2200 VTE events, the relative risk of VTE in current hormone users versus nonusers was higher for women taking oral estrogen-progestin than unopposed estrogen regimens (RR 2.07 versus 1.42) (6). Transdermal estrogen users had no excess risk.

Among the oral estrogen-progestin users, risk was greater for regimens containing DMPA than other progestins (RR 2.67 versus 1.91). The estimated absolute risk of being admitted to the hospital (or mortality from) pulmonary embolism was:

1 in 660 for never users of HRT
1 in 475 for current users of oral estrogen-only HRT
1 in 390 for users of estrogen-progestin HRT containing norethisterone/norgestrel
1 in 250 for users of estrogen-progestin HRT containing DMPA

Prothrombotic mutations increase risk of VTE with HRT:

In a case-control study of 235 postmenopausal women with documented VTE and 554 control subjects without VTE, Factor V Leiden was associated with a 3.4-fold-increased risk of VTE (CI 2.0 to 5.8), and a prothrombin mutation was associated with a 4.8-fold-increased risk of VTE (CI 2.5 to 9.4). Oral but not transdermal estrogen was associated with an increased risk of VTE (OR 4.3; CI, 2.6 to 7.2; and OR, 1.2; CI, 0.8 to 1.7, respectively). After adjustment for potential confounding factors, the combination of either factor V Leiden or prothrombin G20210A mutation and oral estrogen gave a 25-fold-increased risk of VTE compared with nonusers without mutation (95% CI, 6.9 to 95.0). However, the risk for women with prothrombotic mutation using transdermal estrogen was similar to that of women with a mutation who were not using estrogen (OR, 4.4; CI, 2.0 to 9.9; and OR, 4.1; CI, 2.3 to 7.4, respectively) (7).

In the WHI study, the presence of factor V Leiden further increased the risk of VTE in women receiving HRT compared with placebo (HR 6.7, 95% CI 3.1-14.5). Other genetic variants did not modify the risk of VTE with estrogen therapy (1).

Another study investigated the two most common prothrombotic mutations, factor V Leiden and prothrombin 20210A in women who participated in a case–control study on venous thrombosis. Among 77 post-menopausal women with a first VTE, 51% were receiving HRT at the time of thrombosis, compared with 24% of control women (OR = 3·3, CI95 1·8–5·8). Among the patients, 23% had a prothrombotic defect, versus 7% among the control women (OR=3.8, CI 95 1.7–8.5). Women who had factor V Leiden and used HRT had a 15-fold increased risk (OR=15.5, CI 95 3.1–77) (8).

References:

1. Cushman M, Kuller LH, Prentice R, Rodabough RJ, Psaty BM, Stafford RS, Sidney S, Rosendaal FR, Women's Health Initiative Investigators. Estrogen plus progestin and risk of venous thrombosis. JAMA. 2004;292(13):1573.
2.. Marjoribanks J, Farquhar C, Roberts H, Lethaby A, Lee J Long-term hormone therapy for perimenopausal and postmenopausal women. Cochrane Database Syst Rev. 2017;1:CD004143. Epub 2017 Jan 17.
3. Smith NL, Heckbert SR, Lemaitre RN, Reiner AP, Lumley T, Weiss NS, Larson EB, Rosendaal FR, Psaty BM. Esterified estrogens and conjugated equine estrogens and the risk of venous thrombosis. JAMA. 2004;292(13):1581.
4. Canonico M, Oger E, Plu-Bureau G, Conard J, Meyer G, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY, Estrogen and Thromboembolism Risk (ESTHER) Study Group Hormone therapy and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration and progestogens: the ESTHER study. Circulation. 2007;115(7):840.
5. Canonico M, Plu-Bureau G, Lowe GD, Scarabin PY. Hormone replacement therapy and risk of venous thromboembolism in postmenopausal women: systematic review and meta-analysis. BMJ. 2008;336(7655):1227.
6. Sweetland S, Beral V, Balkwill A, Liu B, Benson VS, Canonico M, Green J, Reeves GK, Million Women Study Collaborators Venous thromboembolism risk in relation to use of different types of postmenopausal hormone therapy in a large prospective study. J Thromb Haemost. 2012;10(11):2277.
7. Straczek C, Oger E, Yon de Jonage-Canonico MB, Plu-Bureau G, Conard J, Meyer G, Alhenc-Gelas M, Lévesque H, Trillot N, Barrellier MT, Wahl D, Emmerich J, Scarabin PY, Estrogen and Thromboembolism Risk (ESTHER) Study Group. Prothrombotic mutations, hormone therapy, and venous thromboembolism among postmenopausal women: impact of the route of estrogen administration. Circulation. 2005;112(22):3495.
8. Rosendaal FR, Vessey M, Rumley A, Daly E, Woodward M, Helmerhorst FM, Lowe GD. Hormonal replacement therapy, prothrombotic mutations and the risk of venous thrombosis. British journal of haematology. 2002 Mar 1;116(4):851-4.

Medication use before and during pregnancy:

LOW DOSE ASPIRIN

What is impact of low dose aspirin (LDA, 75-100 mg/d) long term on thrombosis or CVD risk in women with history of (non-aPL associated) adverse pregnancy outcomes, specifically preeclampsia?

Pre-eclampsia is a major risk factor for development of cardiovascular disease and renal disease

A systematic review of >6.4 million women, of whom >258,000 had preeclampsia, relative risk for heart failure was 4.19, coronary heart disease 2.50, death from cardiovascular disease 2.2, and stroke 1.81. Women with preeclampsia in their first pregnancy had a relative risk of 4.7 for ESRD, but the absolute risk was <1% within 20 years.[i] [ii]

The risk is related to the severity of pre-eclampsia, the gestational age at which it occurs, and the number of recurrences

In systematic reviews, mild preeclampsia increases risk of future cardiac disease, RR 2.00, moderate increases the risk, RR 2.99, and severe increases the risk, RR 5.36. [iii] [iv] [v]

Lifestyle interventions (largely to prevent obesity and diabetes) after pre-eclampsia can reduce a woman's cardiovascular disease risk; whether LDA reduces overall risk is controversial.

A review of two randomized controlled trials, encompassing about 47,000 healthy women, concluded that aspirin lowered the risk of stroke (RR 0.73-0.83) but not that of myocardial infarction in women under 65, that statins markedly reduced the risk of myocardial infarction (RR 0.46), stroke (0.52), and unstable angina (0.53). A metaanalysis of almost 12,000 women without cardiovascular disease concluded that lipid lowering did not reduce total or coronary heart disease mortality.[vi] Lifestyle interventions may reduce cardiovascular disease risk by 4-13%.

1

No data specific to patients with rheumatic illnesses are available.

[i] Mosca L, Benjamin EJ, Berra K, et al. Effectiveness-based guidelines for the prevention of cardiovascular disease in women--2011 update: a guideline from the American Heart Association. J Am Coll Cardiol 2011; 57:1404.

[ii] Vikse BE, Irgens LM, Leivestad T, et al. Preeclampsia and the risk of end-stage renal disease. N Engl J Med 2008; 359:800.

[iii] McDonald SD, Malinowski A, Zhou Q, et al. Cardiovascular sequelae of preeclampsia/eclampsia: a systematic review and meta-analyses. Am Heart J 2008; 156:918

[iv] Kessous R, Shoham-Vardi I, Pariente G, et al. Long-term maternal atherosclerotic morbidity in women with pre-eclampsia. Heart 2015; 101:442.

[v] Wu P, Haththotuwa R, Kwok CS, et al. Preeclampsia and Future Cardiovascular Health. A Systematic Review and Meta-Analysis. Circ Cardiovasc Qual Outcomes 2017; 10

[vi] Lee SK, Khambhati J, Varghese T, et al. Comprehensive primary prevention of cardiovascular disease in women. Clin Cardiol 2017;40:832.

[111] Berks D, Hoedjes M, Raat H, et al. Risk of cardiovascular disease after pre-eclampsia and the effect of lifestyle interventions: a literature-based study. BJOG 2013; 120:924

ACEi and ARBs During Pregnancy

Outcome	Author/year	Study type	Duration	Population description	Treatment given to relevant population	Results
CBD	Batemen Obstet Gynecol 2017	Medicaid claims data		4107 exposed ACE first trimester	7.9-8.7 mg/prednisone all three trimesters	RR of malformation 1.82 (5.9% vs 3.3% exposed verses unexposed), RR cardiac malformation 2.95;however, once controlling for hyptertension and other confounders no increased risk.
CBD	Ruys International Journal of Cardiology 2014	Prospective Cohort		1321 pregnant women with heart disease, 38 on ACEi, 7.9% fetal anomaly		Highest rate of fetal anomaly amongst treatment but numbers are small
CBD	Cooper 2006	Cohort study		Increased risk of CBD in infants with first trimester exposure to ACEi RR 2.71		Study criticized for not controlling of obesity or diabetes.
CBD	Moretti 2011	Prospective cohort mother-risk		138 pregnancies exposed to ACE or ARB 90% first trimester		No increase in CBD, higher miscarriage rate in ACE/ARB group
Fetal RAS blockade Oligohydranios Neonatal renal failure	Bullo 2012	Meta analysis		118 ACEi (11 –second trimester 18 third, 31 throughout)		48% fetal RAS-blockade: Decreased risk with first trimester exposure and with captopril

PDA Pulmonary hypoplasia Fetal growth restriction Hypotension Joint contractures				68 ARBs (50 with exposure second or third trimester)		87% of those with ARB exposure fetal RAS-blockade
Fetal RAS blockade	Nadeem 2015	Retrospecitve study		24 cases		47% of those with exposure after the first trimester required dialysis or transplant,) None of those with first trimester exposure

The issues regarding the use of ACEi and ARBs during pregnancy are two-fold. First, is the issue of teratogenicity. The second is fetal RAS blockade, a serious side effect of ACEi and ARB exposure that can lead to oligohydramnios, neonatal renal failure (often leading to dialysis and/or transplant), pulmonary hypoplasia, fetal growth restriction, hypotension and joint contractures. In terms of teratogenicity, some early studies (e.g. Cooper) suggested that there was an increased risk of CBD in infants exposed to ACEi and ARBs during the first trimester. Studies such as this one however have been criticized because either they did not control for the underlying hypertension or co-morbidities. Subsequent studies (Bateman, Ruys, and Morretti) suggest that there is no increased risk of CBD and any increase seen is due to the underlying hypertension or co-morbidities such as obesity or diabetes. Therefore the data suggest that these agents do not increase the risk of CBD.

The second issue is the high risk of fetal RAS blockade, a complication with high morbidity. Exposure during the second and third trimester pose the largest risk, although there have been cases reported with first trimester exposure. Captopril seems to carry the lowest risk for this complication.

1. Bateman Bt, Patorno E, Desai RJ, et. al: Angiotensin-converting enyem inhibitors and the risk of congenital Malformations. Obstet Gynecol 2017; 129:174-184.
2. Ruys TPE, Maggioni A, Johnson MR, et. al: Cardiac medication during pregnancy, data from the RPAC. International Journal of Cardiology 2014. 124-128.
3. Cooper WO, Hernandez-Diaz S, Arbogast PG, et al. Major congenitl malformations after first-trimester exposure to ACE inhibitors. NEJM 2006; 354:2443-51.
4. Bullo M, Tschumi S, Bucher BS, Bianchetti MG,Simonetti GD. Pregnancy outcome following exposure to angiotensin-converting enzyme inhibitors or angiotensin receptor antagonists: a systematic review. Hypertension 2012;60:444_50.
5. Moretti ME, Caprara D, Drehuta I et al. The fetal safety of angiotensin converting enzyme inhibitors and angiotensin

II receptor blockers. Obstet Gynecol Int 2012;2012:658310
6. Nadeem S, Hashmat S, Deefreitas MJ, et. al: Renin Angiotensin System Blocker Fetopathy: A Midwest Pediatric Nephrology Consortium Report J Pediatr 2015, 881-5.

Aspirin for Pre-Eclampsia

Outcome	Author/year	Study type	Duration	Population description	Treatment given to relevant population	Results
LOS Neonatal ICU	Wright et. al Am J Ob gyn	Randomized controlled trial in women with estimated risk for preterm PE of >1:100		822 placebo 798 aspirin	150mg asa wks 11-14 up to 36 weeks	Aspirin group had shorter LOS in the NICU Lower percentage of infants born at less than 37 weeks in the treatment group
Reduce incidence of preterm pre-eclampsia	Rolnik NEJM 2017	Randomized controlled trial in women with estimated risk for preterm PE >1:100		822 placebo 798 aspirin	150mg asa wks 11-14up to 36 weeks	Pre-eclampsia in 13 of the aspirin group(1.6%) compared with 35 (4.3%) placebo group. Odds ratio 0.2
Fetal growth	Adkins: Am J Obstet Gynecol 2017	Secondary analysis MFMU (cohort of diabetes patients) randomized controlled trial of aspirin 60mg for the prevention of preeclampsia		Two groups: nonvascular (391)or vascular(52) (highest risk for SGA infants)		Aspirin associated with higher birthweight in the nonvascular group only – LGA Did not decrease SGA infants in the vascular group. Not what they expected.
Reduction in pre-eclampsia	Duley L, 2007	Cochrane review		59 trials 37,560 women		17% reduction in the risk of pre-eclampsia, 8% reduction in the risk of preterm birth and 14%

						reduction in fetal or neonatal deaths

Data suggest that women at increased risk for pre-eclampia can reduce that risk during pregnancy by taking low dose aspirin. (80-160mg/day).(Rolnik, Duley). Low dose aspirin also decreases the length of stay in the NICU for infants born pre-maturely Most of that reduction in length of stay is due to the fact that fewer infants of mother who received aspirin for pre-eclampsia prevention were born prior to 37 weeks gestation (Wright). In women with diabetes however, aspirin did not improve outcome and in women with non-vascular diabetes there was a trend towards LGA infants in those women who received aspirin during pregnancy.

1. Wright D, Rolnik DL, Syngelaki A et. al: Aspirin for evidence-based pre-eclampsia prevention trial: effect of aspirin on length of stay in the neonatal intensive care unit. Am J Obstet Gynecol 2018. [epub]
2. Rolnik DL, Wright D, Poon LC., et. al: Aspirin verseus placebo in pregnancies at high risk for preterm preeclampsia. NEJM 2017; 377:613-622
3. Adkins K, Allshous AA, Metz TD, Heyborne KD: Impact of aspirin on fetal growth in diabetic pregnancies according to white classification. Am J Obstet Gynecol 2017; 465
4. Duley L, Henderson-Smart, DJ, Meher S, King JF: Antiplatelet agents for preventing pre-eclampsia and its complications 2007

AZATHIOPRINE:

ALL DATA PULLED FROM REPROTOX ON 5/30/2018. HTTPS://REPROTOX.ORG/LOGIN

Colchicine:

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

The following data tables and figures from: **Indraratna PL, Virk S, Gurram D, Day RO. Use of colchicine in pregnancy: a systematic review and meta-analysis. Rheumatology (Oxford). 2018 Feb 1;57(2):382-387. doi: 10.1093/rheumatology/kex353. Review. PMID: 29029311**

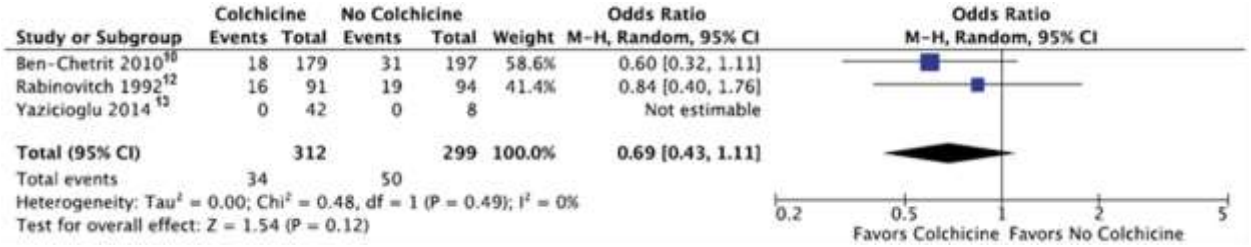
TABLE 1

Study characteristics

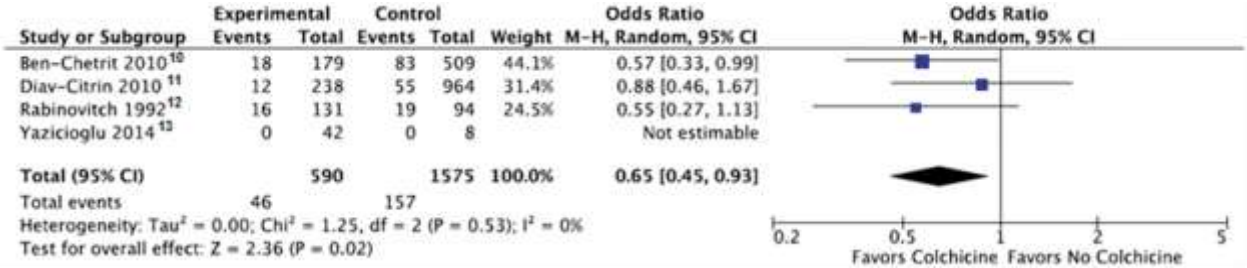
Reference	Study period	No. of pregnancies	Indication for colchicine	Daily dose of colchicine	Details of control groups
Ben-Chetrit *et al.* [10]	2004–08	179	FMF	1–1.5 mg	197 pregnancies with FMF, 312 healthy pregnancies
Diav-Citrin *et al.* [11]	1994–2006	238	FMF, Behçet's disease and other	1 mg (median)	964 healthy pregnancies
Rabinovitch *et al.* [12]	1973–92	91[a]	FMF	1–2 mg	94 pregnancies with FMF
Yazicioglu *et al.* [13]	2002–12	42	FMF	NR	8 pregnancies with FMF

[a] Does not include a separate subgroup of 40 patients who ceased colchicine therapy during pregnancy. NR: not reported.

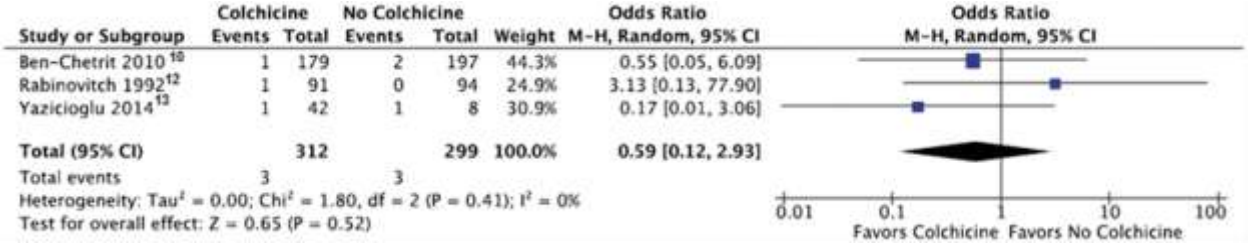
MISCARRIAGE for women with FMF with and without Colchicine:



MISCARRIAGE for any woman with and without Colchicine:



Major malformations for woman with FMF with and without Colchicine:



Major malformations for any woman with and without Colchicine:

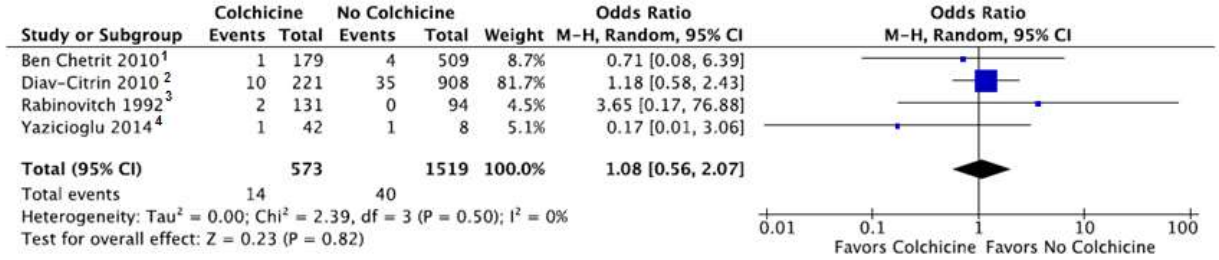


TABLE 2

Comparison A: Colchicine *vs* no colchicine in FMF

Outcome	No. of Studies	Estimate	OR/MD (95% CI)	P-value	I^2(%)	Raw values (colchicine *vs* no colchicine)
Miscarriage	3[a]	OR	0.69 (0.43, 1.11)	0.12	0	34/312 (10.9%) *vs*50/299 (16.7%)
Major malformations	3	OR	0.59 (0.12, 2.93)	0.52	0	3/312 (1.0%) *vs* 3/299 (1.0%)
Pre-term birth	1	OR	—	—	—	—
Cesarean section	2	OR	1.61 (0.65, 4.03)	0.31	64	37/270 (13.7%) *vs*27/291 (9.3%)
Gestational age, weeks	1	MD	—	—	—	—
Birthweight, g	2	MD	−96.72 (−218.90, 25.46)	0.12	0	2956.03 ± 661.87 *vs*3104.52 ± 451.55

a
Includes one study with zero event rate. MD: mean difference; OR, odds ratio.

TABLE 3
Comparison B: colchicine *vs* no colchicine (in any women, not just FMF)

Outcome	No. of Studies	Estimate	OR/MD (95% CI)	P-value	I^2(%)	Raw values (colchicine *vs* no colchicine)
Miscarriage	4[a]	OR	0.65 (0.45, 0.93)	0.02	0	46/590 (7.8%) *vs*157/1575 (10.0%)
Major malformations	4	OR	1.08 (0.56, 2.07)	0.82	0	14/573 (2.4%) *vs*40/1519 (2.6%)
Pre-term birth	2	OR	2.48 (1.65, 3.71)	<0.001	1	57/345 (16.5%) *vs*62/961 (6.5%)
Cesarean section	3	OR	1.47 (0.96, 2.26)	0.07	38	99/527 (18.8%) *vs*196/1178 (16.6%)
Gestational age, weeks	2	MD	−1.00 (−1.05 −0.95)	<0.001	0	38.57 ± 1.88 *vs* 39.98 ± 0.55
Birthweight, g	3	MD	−209.62 (−381.58, −37.66)	0.02	80	2985.12 ± 413.96 *vs*3281.30 ± 186.96

a
Includes one study with zero event rate. MD: mean difference; OR, odds ratio.

Corticosteroids

Literature Search: Non-fluorinated glucocorticoids and pregnancy.
Focused on large data base studies, National registries, Teratology registries.
Focused on IBD and Asthma.

Outcome	Author/year	Study type	Duration	Population description	Treatment given to relevant population	Results
CBD Adverse preg outcome	Schatz 1976 JAMA	Case series		70 pregnancies in 55 asthmatics	7.9-8.7 mg/prednisone all three trimesters	1 termination 71 births (two sets of twins) 10 premature <37 weeks One cleft palate
CBD	Park Wyllie 2000 /Teratology	Prospective Cohort and meta analysis		184 women prospective Meta- analysis		184 women exposed prednisone (prospective)No diff Meta-analysis Any anomaly 3.03 Cleft palate 3.4 fold increase (six cohort studies (51470pts) and four case-control studies (71,705)
Cleft lip+palate Cleft palate	Carmichael 2007 AJOG	Case-control National birth defects prevention		1141 cleft lip +palate, 628 cleft palate 4143 control		2.9% of infants with CLP and 1% of infants with CP and 1.7% controls reported corticoid steroid use 4 weeks before to 12 weeks conception Crude odds ratio for any use for CLP 1.7% and 0.5 for CP
CBD	Gur Reprod Toxicol 2004	Israeli Teratogen Information Services Prospective Case control		311 exposed 790 controls		No increase in major anomalies and no pattern, no CP Higher rates of miscarriage, preterm birth amongst exposed group, lower birth weight P<).001
Gestational age	Palmsten Pharmacoepidemiol Drug Safety 2018	Mother to baby observational cohort study		254 exposed /mult diagnosis		Higher total cumulative prednisone dose was associated with shorter gestation even when adjusting for disease activity
IBD pregnancy outcomes	Boyd et. al 2015, PLOS 1			666 pregnancies IBD		Increased rate of severe pre-eclampsia amongst patients using OCS H.R. 17.4 Prematurity H.R. 6.32
Danish National registry	Hviid, 2011	Study type	Duration	51,973 exposures to corticosteroids (84 first trimester)		Results RRCLP 1.05, CP 1.23 Not statistically significant

Infection rheumatic diseases	Desai, 2017	Claims data		4961 pregnant women treated with immunosuppressive drugs		Increased dose of steroids associated with an increased risk of serious infection
CBD	Garne E	Prospective Cohort and meta analysis 519242 pregnancies from Norway, Wales and Denmark		Inhaled steroids		Increased OR anal atresia 3.40, and for severe congenital heart defects OR 1.97 in those treated with combination inhaled steroids and beta 2 agonists.
ADD	Laugessen et. al BMJ 2017	Case-control National birth defects prevention		5319 exposures to systemic GC		No association to ADHD found Slight increase in hazard ratio thought to be due to confounding

Concern regarding congenital birth defects including cleft lip +/- palate in infants exposed to corticosteroids in utero stems from animal studies. A large meta-analysis in 2000 (Park-Wyllie et. al), found a 3.4 fold increase in cleft palate amongst infants exposed in utero to steroids. However, amongst their own cohort of 184 patients followed prospectively there were no cases of CP+/- lip. On the other hand, Carmichael found a crude odds ratio for any use of steroids during pregnancy to be 1.7for CLP 1. But 0.5 for CP. In a large series from Denmark in which there were 51,973 exposures to corticosteroids (84 first trimester) but no statistically significant increase in risk of cleft palate +/- lip. Similarly, in the Israeli Teratogen information service, there was no increase in any CBD amongst 311 in utero exposed infants. This group did find an increased risk of miscarriage, preterm birth amongst exposed group, and lower birth weight P<).001 (Gur). Similarly, shorter gestational age was found in pregnancies exposed to higher cumulative corticosteroids. Boyd similarly found increased rates of severe pre-eclampsia and prematurity amongst 666 pregnancies in IBD patients in which they were exposed to steroids. Desai found that increased doses of steroids during pregnancy also increases infection risk. In asthma patients, inhaled steroids increased OR of anal atresia 3.40, and for severe congenital heart defects OR 1.97 in those treated with combination inhaled steroids and beta 2 agonists. Laugesen and others did not find an increased risk of ADHD amongst 5319 offspring who were exposed to steroids in utero.

In conclusion: Data do not substantiate the finding that exposure to glucococorticoids in utero increases the risk of CBD including cleft palate +/- lip. Increasing doses of steroids during pregnancy appear to increase the risk of miscarriage, preterm birth, lower birth weight, and infection.

1.Schatz M, Patterson R, Zeitz S, et al. Corticosteroid therapy for the pregnant asthmatic patient. JAMA 1975; 233:804–807.

2.. Park-Wyllie L, Mazzotta P, Pastuszak A, et al. Birth defects after maternal exposure to corticosteroids: prospective cohort study and meta-analysis of epidemiological studies. Teratology 2000; 62:385–392.

3. Carmichael SL, Shaw GM, Ma C, et al. Maternal corticosteroid use and orofacial clefts. Am J Obstet Gynecol 2007; 197:585.

4.. Gur C, Diav-Citrin O, Shechtman S, et al. Pregnancy outcome after first trimester exposure to corticosteroids: a prospective controlled study. ReprodToxicol 2004; 18:93–101.

5. Palmsten K, Rolland M, Herbert M et. al Patterns of prednisone use during pregnancy in women with rheumatoid arthritis: Daily and cumulative dose. Pharmacoepidemiol Drug Saf 2018: 25: 430-8.

6. Boyd H, Basit S, Harpsoe MC et. al. Inflammatory Bowel Disease and Risk of Adverse Pregnancy Outcomes. 2015

7. Hviid A, Molgaard-Nielsen D: Corticosteroid use during pregnancy and risk of orofacial clefts. CMAJ 2001; 183: 796-804.

8. Garne E, Vinkel Hansen A, Morris J: Risk of congenital anomalies after exposure to asthma medication in the first trimester of pregnancy- a cohort linkage study. BJOG, 2016

9. Lugesen K, Byrjalsen a, FroslevT et. al: Use of glucocorticoids during pregnancy and risk of attention-deficit hyperactivity disorder in offspring: a nationwide Danish cohort study.

Cox II Inhibitors
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Author, year	Study type	Duration	Population Description	Treatment given to relevant population	Results
Nakhai-Pour HR	nested case-control study design Quebec Pregnancy Registy	1997-2010	Any pregnant women (some typical exclusion criteria).	Non-aspirin NSAIDS: filling a prescription between months prior to and throughout pregnancy.	Spontaneous abortion: varies by NSAID Rofecoxib: 1.83 (1.24-2.7) Celexocib: 2.21 (1.42-3.45) (all adjusted for maternal disease, etc.) All NSAIDs for women with rheumatic disease: SLE: aOR 0.54 (0.06-5.01) RA: aOR 1.12 (0.52-2.41)

Nakhai-Pour HR1, Broy P, Sheehy O, Bérard A. Use of nonaspirin nonsteroidal anti-inflammatory drugs during pregnancy and the risk of spontaneous abortion. CMAJ. 2011 Oct 18;183(15):1713-20. doi: 10.1503/cmaj.110454. Epub 2011 Sep 6.

Cyclophosphamide

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Murthy RK[1], Theriault RL[2], Barnett CM[3], Hodge S[4], Ramirez MM[5], Milbourne A[6,7], Rimes SA[8], Hortobagyi GN[9], Valero V[10], Litton JK[11]. **Outcomes of children exposed in utero to chemotherapy for breast cancer.** Breast Cancer Res. 2014 Dec 30;16(6):500.

1992-2010 at MD Anderson. 81 pregnancies in women with breast cancer during pregnancy.

"The patients received outpatient combination chemotherapy (FAC) with **cyclophosphamide (500 mg/m [2] intravenously on Day 1**), doxorubicin (50 mg/m [2] by continuous infusion over 72 hours), and 2 bolus doses of 5-fluorouracil (500 mg/m [2] intravenously on Days 1 and Day 4 [18]. **Each cycle was given every 21 to 28 days**, and **therapy lasted through gestational week 35**."

Delivery outcomes for children exposed to chemotherapy in utero

Mean Range Gestational age at delivery: 37wks (range 29-41)

Mean Birth weight: 2.9kg (range 1.3-3.9)

Preterm (<37wks) 28/81 with just 1 delivery <32 weeks.

NICU: 14%

Cesarean section 27 (33.3%)

Chemotherapy Exposure: >4 cycles of FAC: 86.0%

Long-term follow-up of the offspring: 63
7 year follow-up for 50 children:
'child considered healthy': 98%
Developmental delay: 12%
School difficulties: 11%
"Our data indicate that treating women with anthracycline based systemic chemotherapy for breast cancer during the second and third trimesters of pregnancy can be done without significant impairment of the health for their offspring at delivery or into childhood compared with children in the general population."
Treatment of breast cancer during pregnancy: an observational study

Cyclosporin

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Tables and text from: Paziana K, Del Monaco M, Cardonick E, Moritz M, Keller M, Smith B, Coscia L, Armenti V. Ciclosporin use during **pregnancy**. Drug Saf. 2013 May;36(5):279-94. doi: 10.1007/s40264-013-0034-x. Review. PMID: 23516008

Table 3 Literature review of pregnancy outcomes for kidney transplant recipients taking ciclosporin (cyclosporine) during pregnancy

Outcomes	NTPR: kidney		NTPR: liver		Ghafari and Sanadgol [61]	Al-Khader et al. [62]	Ghanem et al. [63]
	CsA	Neoral®	CsA	Neoral®			
No. of pregnancies	514	199	96	44	61	113	67
Maternal factors (%)							
Hypertension in pregnancy	62	68	39	44	21	43	19.2
Gestational diabetes mellitus	12	2	2	0	–	21	5.7
Pre-eclampsia	29	28	25	29	26.4	–	–
Infection	23	19	33	33	34	17	13.4
Perinatal outcomes (%)							
Premature (<37 weeks)	52	48	37	28	26.4	64	40.9
Low birthweight (<2,500 g)	46	43	34	41	20.7	–	19.2

CsA ciclosporin, *NTPR* National Transplantation Pregnancy Registry

CsA is generic cyclosporine. Neoral is a modified version of cyclosporine that this is more consistently absorbed.

Table 5 Overview of literature concerning pregnancy outcomes in women using ciclosporin (cyclosporine) during pregnancy for indications other than transplant

Disease	No. of patients	Age (years)	Additional medications	Known comorbidities	Pregnancy outcome (%)	Premature birth (%)	Low birthweight (%)
Psoriasis [89–94, 97]	19	20–38	High-dose prednisone (5)	Smoker and chronic inflammatory disease (1); MS and recurrent spontaneous abortions	95	21	21
SLE [43, 98–103]	18	28–32	All prednisone; hydroxychloroquine, IV immunoglobulin (1); immunoadsorption therapy (1)	Lupus nephritis (1), polymyositis (1)	94	22	22
IBD [105, 108–110]	5	21–36	Prednisolone (2); azathioprine, thioguanine, mesalamine, sertraline (1)	Not available	100	100	80
Other[a]	5	26–30	Not available	Not available	100	60	80

IBD inflammatory bowel disease, *IV* intravenous, *MS* multiple sclerosis, *SLE* systemic lupus erythematosus

[a] Aplastic anaemia (2) [116, 117], impetigo herpetiformis (2) [118, 119], systemic sclerosis (1) [120], hemophagocytic lymphohistiocytosis (1) [121]

"Overall, based on case, centre and registry reports, ciclosporin exposure during pregnancy in the transplant population does not appear to be associated with an increased risk of congenital malformations. However, ciclosporin use does appear to be associated with premature delivery and low birthweight infants, but no reports distinguish between mothers that are induced prematurely to minimize the burden of pregnancy on the transplanted organ, or those that go naturally into preterm labour or are induced secondary to a maternal comorbidity or complication of ciclosporin use. Furthermore, comorbidities such as drug-related hypertension, pre-eclampsia and gestational diabetes are reported at higher incidences than the general population but also appear to be organ specific."

"Overall, the literature reports a lower mean gestational age and mean birthweight for women exposed to ciclosporin during pregnancy across all indications than in the general population. However, it is not clear if the maternal complications are related to ciclosporin exposure during pregnancy or to maternal disease."

"In conclusion, ciclosporin use during pregnancy may be a safe alternative for patients with autoimmune disease refractory to conventional treatment. Continued monitoring of this patient population remains a key component to understanding the risk factors associated with ciclosporin exposure during pregnancy."

Leflunomide

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Methotrexate

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Figure and table from: Weber-Schoendorfer C, **Chambers** C, Wacker E, Beghin D, Bernard N; Network of French Pharmacovigilance Centers, Shechtman S, Johnson D, Cuppers-Maarschalkerweerd B, Pistelli A, Clementi M, Winterfeld U, Eleftheriou G, Pupco A, Kao K, Malm H, Elefant E, Koren G, Vial T, Ornoy A, Meister R, Schaefer C. **Pregnancy** outcome after **methotrexate** treatment for rheumatic disease prior to or during early **pregnancy**: a prospective multicenter cohort study. Arthritis Rheumatol. 2014 May;66(5):1101-10. doi: 10.1002/art.38368. PMID: 24470106
In a prospective study of pregnancies with and without methotrexate (rheumatic doses), methotrexate was associated with an estimated doubling of the risk of pregnancy loss (to ~40%) and major birth defects (to ~10%).

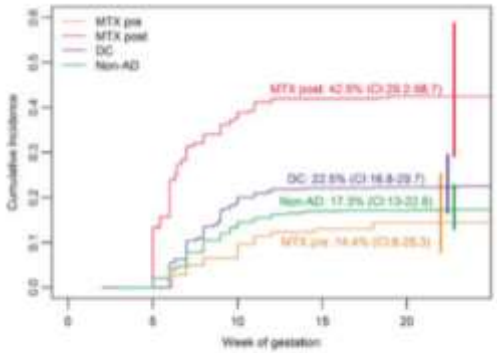


Figure 1. Cumulative incidence rates of spontaneous abortion stratified by cohort. Cumulative incidences of spontaneous abortion are plotted for the cohort of women exposed to methotrexate (MTX) before conception (MTX pre), the cohort of women exposed to MTX after conception (MTX post), the disease-matched cohort (DC), and the cohort of women without autoimmune diseases (non-AD). The adjusted hazard ratio (HR) for post-conception exposure was 2.1 (95% confidence interval [95% CI] 1.3–3.2) relative to the disease-matched cohort and 2.5 (95% CI 1.4–4.3) relative to the cohort of women without autoimmune diseases. The HR for pre-conception exposure was 0.8 (95% CI 0.4–1.4) relative to the disease-matched cohort and 1.3 (95% CI 0.6–3.0) relative to the cohort of women without autoimmune disease. Vertical lines show the 95% CI for each incidence rate.

Data Source: European Network of Teratology Information Services (EN-TIS) (Finland [n 49], France [n 596], Germany [n 555], Israel [n 237], Italy [n 120], The Netherlands [n 71], and Switzerland [n 35]), as well as from the Organization of Teratology Information Specialists (OTIS) (US and Canada [n 227]).

Table 4. Birth defects by cohort

	MTX-exposed		Disease-matched comparison (n = 459)	Non-autoimmune disease comparison (n = 1,107)
	Pre-conception (n = 136)	Post-conception (n = 188)		
No. of live births, including twins	113	103	392	997
Major birth defects, no./total assessed (%)	4/114 (3.5)*	7/106 (6.6)†	14/393 (3.6)‡	29/1,001 (2.9)§
Minor birth defects, no./total assessed (%)	5/113 (4.4)	2/104 (1.9)¶	22/392 (5.6)	23/997 (2.3)
Genetic birth defects, no./total assessed (%)	1/114 (0.9)*	0	2/394 (0.5)#	7/1,003 (0.7)**

* One hundred thirteen liveborn infants and 1 elective termination of pregnancy.
† One hundred three liveborn infants (excluding 2 cases with methotrexate [MTX] exposure started after the first trimester) and 5 elective terminations.
‡ Three hundred ninety-two liveborn infants and 1 elective termination.
§ Nine hundred ninety-seven liveborn infants, 3 elective terminations, and 1 stillbirth.
¶ One hundred three liveborn infants and 1 elective termination.
# Three hundred ninety-two liveborn infants and 2 elective terminations.
** Nine-hundred ninety-seven liveborn infants and 6 elective terminations.

Mycophenolate

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

NSAIDs:

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Other Medications

Anakinra
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Smith CJF[1], Chambers CD[2]. **Five successful pregnancies with antenatal anakinra exposure.** Rheumatology (Oxford). 2018 Apr 12.

Abstract: Our aim is to add to the limited existing prospective data on IL-1 inhibitor use in pregnancy.
METHODS: Data were obtained from the Organization of Teratology Information Specialists Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes in the USA and Canada. Eligible women were enrolled prior to 19 weeks' gestation between 2004 and 2017. Outcomes were obtained by maternal interview and medical record abstraction.
RESULTS: Five pregnancies with anakinra exposure were identified, all resulting in full-term singleton live births with no major or long-term complications. Three maternal subjects used anakinra for adult-onset Still's disease and two for systemic JIA. For all individuals who discontinued anakinra, some amount of steroid medication was necessary for treatment of disease flare. Two maternal subjects developed oligohydramnios, one also with pregnancy-induced hypertension. Two women had Caesarian sections, one medically indicated and one scheduled. One infant had low birth weight, but follow-up records indicated normal adjusted weight at 1 year. Three women successfully breastfed their infants, at least two of whom continued anakinra while breastfeeding.
CONCLUSION: Anakinra was used successfully in five full-term pregnancies; however, two subjects developed oligohydramnios, a process that can be linked to fetal renal anomalies. Given previously reported cases of congenital renal anomalies associated with both antenatal anakinra use and maternal hyperthermia, the relationship between maternal IL-1 inhibitor use, uncontrolled maternal febrile disease and fetal outcomes should be further explored.

Rituximab:
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Belimumab:
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Abatacept:
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Kumar M, Ray L, Vemuri S, Simon TA. **Pregnancy** outcomes following exposure to **abatacept** during **pregnancy**. Semin Arthritis Rheum. 2015 Dec;45(3):351-6. PMID: 26210783

Tocilizumab
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Hoeltzenbein M, Beck E, Rajwanshi R, Gøtestam Skorpen C, Berber E, Schaefer C, Østensen M. **Tocilizumab** use in **pregnancy**: Analysis of a global safety database including data from clinical trials and post-marketing data. Semin Arthritis Rheum. 2016 Oct;46(2):238-45. PMID:27346577

Table 2
Pregnancy outcomes of 180 prospectively and 108 retrospectively ascertained pregnancies classified by exposure to TCZ in relation to pregnancy

	Prospective (n = 180)				Retrospective (n = 108)
TCZ Exposure	Pregnancy[a] (n = 112)	Preconc. (n = 54)	Unknown (n = 14)	All (n = 180)	All (n = 108)
Live birth	68	33	8	109 (60.6%)	55 (50.9%)
Liveborn children	68	34	9	111	56
Spontaneous abortion	20	13	6	39 (21.7%)	31 (28.7%)
ETOP	24	7	0	31 (17.2%)	22 (20.4%)
Stillbirth	0	1	0	1	0

[a] All except one were exposed at least in the first trimester.

Tocilizumab data:

Table 3
Neonatal characteristics of 111 live-born children including two pairs of twins (prospectively reported) and 56 live-born children including one pair of twins (retrospectively reported) classified by time of exposure

Exposure	Prospective (n = 111)			Retrospective (n = 56)
	Pregnancy (n = 68)	Preconception (n = 34)	Unknown (n = 9)	All (n = 56)
Gestational age at birth (weeks)[a]	n = 55 39.0 (IQR: 36.7–40.0; R: 29.3–42.0)	n = 32 37.5 (IQR: 36.1–38.9; R: 27.7–40.9)	n = 6 38.9 (IQR: 36.7–39.8; R: 36.1–41.0)	n = 10 38.5 (IQR: 37.6–39.0; R: 33.0–41.0)
Preterm	16 (29.0%)	11 (35.5%)	2 (33.3%)	2 (20.0%)
Sex	n = 42	n = 30	n = 5	n = 15
Female	19 (45.2%)	13 (43.3%)	2 (40.0%)	9 (60.0%)
Male	23 (54.8%)	17 (56.7%)	3 (60.0%)	6 (40.0%)
Weight (g)[a]	n = 39 2800 (IQR: 2300–3320; R: 1200–4500)	n = 26 2750 (IQR: 2330–3100; R: 1360–3600)	n = 3 2950 (IQR: 2875–3275; R: 2800–3600)	n = 13 2800 (IQR: 2645–3360; R: 2000–3600)
Length (cm)[a]	n = 22 48 (IQR: 45.5–49; R: 36–55)	n = 20 47.5 (IQR: 45.5–50; R 39–52)	n = 3 51 (IQRL: 50–51.5; R: 49–52)	n = 6 49 (IQR: 48–50; R: 47–51)

[a] Median (interquartile range, IQR; range, R).

Secukinumab

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Tofacitinib

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Baricitinib
No entry in Reprotox.

From label: The JAK/STAT pathway has been shown to be involved in cell adhesion and cell polarity which can affect early embryonic development. There are no adequate data from the use of baricitinib in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). Baricitinib was teratogenic in rats and rabbits. Animal studies indicate that baricitinib may have an adverse effect on bone development in utero at higher dosages.

Apremilast

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

From FDA Label: "Adequate and well-controlled studies with OTEZLA have not been conducted in pregnant women. In animal embryo-fetal development studies, the administration of apremilast to cynomolgus monkeys during organogenesis resulted in dose-related increases in abortion/embryo-fetal death at dose exposures 2.1-times the maximum recommended human therapeutic dose (MRHD) and no adverse effect at an exposure of 1.4-times the MRHD. In mice, there were no apremilast induced malformations up to exposures 4.0-times the MRHD. The incidences of malformations and pregnancy loss in human pregnancies have not been established for OTEZLA. However, all pregnancies, regardless of drug exposure, have a background rate of 2% to 4% for major malformations, and 15% to 20% for pregnancy loss. OTEZLA should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus."

IVIG:
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Warfarin

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

New oral anticoagulants:

Rivaroxaban
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Unfractionated Heparin
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Enoxaparin
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Aspirin
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Clopidogrel (Plavix)

Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Sulfasalazine:
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

N Engl J Med. 2000 Nov 30;343(22):1608-14.
Folic acid antagonists during pregnancy and the risk of birth defects.
Hernández-Díaz S[1], Werler MM, Walker AM, Mitchell AA.

- Data from 1976-1998
- Interviewed mothers within 6m of delivery of infants with malformations, stillbirths, or aborted for a malformation.
- Cases: women with babies with heart defects (3870), cleft lip/palate (1962), urinary tract defects (1100)
- DID NOT INCLUDE neural tube defects: "Infants with coexisting neural-tube defects were excluded because the risk of these defects is already known to be reduced by maternal folic acid supplementation."
- Controls: women with other defects (none of the 3 and no neural tube defect) (n=8387)

TABLE 2. RELATIVE RISKS OF CARDIOVASCULAR DEFECTS, ORAL CLEFTS, AND URINARY TRACT DEFECTS IN INFANTS WHOSE MOTHERS RECEIVED A FOLIC ACID ANTAGONIST DURING THE SECOND OR THIRD MONTH AFTER THE LAST MENSTRUAL PERIOD.

DRUG	CARDIOVASCULAR DEFECTS	ORAL CLEFTS	URINARY TRACT DEFECTS
	relative risk (95 percent confidence interval)*		
Any folic acid antagonist	2.1 (1.5–3.0)	2.1 (1.4–3.2)	2.1 (1.2–3.7)
Dihydrofolate reductase inhibitors†	3.4 (1.8–6.4)	2.6 (1.1–6.1)	—‡
Antiepileptic drugs§	2.2 (1.4–3.5)	2.5 (1.5–4.2)	2.5 (1.2–5.0)

*All relative risks were adjusted for the year of the interview, the geographic region, maternal age, and the presence or absence of diabetes mellitus, multivitamin supplementation, and urinary tract or other infections during the first trimester of pregnancy. The relative risk of oral clefts was also adjusted for race, and the relative risk of urinary tract defects was adjusted for maternal weight.

†This category included trimethoprim, triamterene, and sulfasalazine.

‡Fewer than five case infants or five control infants were exposed during the second or third month.

§This category included phenobarbital, phenytoin, primidone, and carbamazepine.

Outcome	Author, year	Study type	Population Description	Treatment given to relevant population	Results
Preterm birth SGA	Ichinose 2018	Retrospective chart review	54 SLE pregnancies	15 preg with tacrolimus	Tacro patients were sicker than other patients (more prednisone, lower GFR, more renal disease, more APS.) Pregnancy outcomes were essentially the same for pregnancies with and without Tacro
Preterm birth	Webster 2014	Retrospective	9 SLE pregnancies	9 preg with tacrolimus	No pregnancy loss, no birth defects 4/9 preterm births

Ichinose K, Sato S, Kitajima Y, Horai Y, Fujikawa K, Umeda M, Fukui S, Nishino A, Koga T, Kawashiri SY, Iwamoto N, Tamai M, Nakamura H, Origuchi T, Yasuhi I, Masuzaki H, Kawakami A. The efficacy of adjunct tacrolimus treatment in pregnancy outcomes in patients with systemic lupus erythematosus. Lupus. 2018 Jan 1:961203318770536. PMID: 29665758
Webster P, Wardle A, Bramham K, Webster L, Nelson-Piercy C, Lightstone L. Tacrolimus is an effective treatment for lupus nephritis in pregnancy. Lupus. 2014 Oct;23(11):1192-6. doi: 10.1177/0961203314540353. Epub 2014 Jun 13. PMID: 24928830

Thalidomide
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Lenalidomide
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login

Medication use during lactation:

Data on use of medications in non-RMD populations was pulled from LACTMED on 5/31/2018.

https://toxnet.nlm.nih.gov/newtoxnet/lactmed.htm

Each medication listed includes a summary of use during lactation, maternal and infant drug levels and effects in breastfed infants, where available.