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. Supraphysiologic 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).


**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 increased risk for osteoporosis (11).

References:


**Thrombotic Risk of Hormone Replacement Therapy (HRT):**

Risk of VTE is increased with HRT use:

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, CI 95 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:

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.¹ ²

*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. ³ ⁴ ⁵

**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.⁶ Lifestyle interventions may reduce cardiovascular disease risk by 4-13%.

¹

No data specific to patients with rheumatic illnesses are available.


ACEi and ARBs During Pregnancy

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

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

**Aspirin for Pre-Eclampsia**

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


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

<table>
<thead>
<tr>
<th>Reference</th>
<th>Study period</th>
<th>No. of pregnancies</th>
<th>Indication for colchicine</th>
<th>Daily dose of colchicine</th>
<th>Details of control groups</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Chetrit et al. [10]</td>
<td>2004–08</td>
<td>179</td>
<td>FMF</td>
<td>1–1.5 mg</td>
<td>197 pregnancies with FMF, 312 healthy pregnancies</td>
</tr>
<tr>
<td>Rabinovitch et al. [12]</td>
<td>1973–92</td>
<td>91*</td>
<td>FMF</td>
<td>1–2 mg</td>
<td>94 pregnancies with FMF</td>
</tr>
<tr>
<td>Yazicioglu et al. [13]</td>
<td>2002–12</td>
<td>42</td>
<td>FMF</td>
<td>NR</td>
<td>8 pregnancies with FMF</td>
</tr>
</tbody>
</table>

*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:**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>No Colchicine</th>
<th>Colchicine</th>
<th>Total</th>
<th>Event Weight</th>
<th>M-H</th>
<th>Random</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Chetrit 2010</td>
<td>18</td>
<td>31</td>
<td>197</td>
<td>58.6%</td>
<td>0.60 [0.49, 1.11]</td>
<td>0.48</td>
<td>1 (P = 0.49)</td>
<td>I² = 0%</td>
</tr>
<tr>
<td>Rabinovitch 1992</td>
<td>16</td>
<td>91</td>
<td>19</td>
<td>41.4%</td>
<td>0.84 [0.40, 1.76]</td>
<td>0.48</td>
<td>1 (P = 0.49)</td>
<td>I² = 0%</td>
</tr>
<tr>
<td>Yazicioglu 2014</td>
<td>0</td>
<td>42</td>
<td>0</td>
<td>0</td>
<td>Not estimable</td>
<td>0.48</td>
<td>1 (P = 0.49)</td>
<td>I² = 0%</td>
</tr>
</tbody>
</table>

Total (95% CI) 312, 299, 100.00%

**MISCARRIAGE for any woman with and without Colchicine:**
Major malformations for woman with FMF with and without Colchicine:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colchicine Events Total</th>
<th>No Colchicine Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Chetrit 2010†</td>
<td>1 179 4 509 8.7%</td>
<td>2 179 5 509 8.7%</td>
<td></td>
<td>0.57 [0.33, 0.99]</td>
</tr>
<tr>
<td>Diav-Citrin 2010†</td>
<td>10 235 35 908 81.7%</td>
<td>11 235 35 908 81.7%</td>
<td></td>
<td>1.18 [0.58, 2.43]</td>
</tr>
<tr>
<td>Rabinovitch 1992†</td>
<td>2 131 0 94 4.5%</td>
<td>3 131 0 94 4.5%</td>
<td></td>
<td>3.65 [0.17, 76.88]</td>
</tr>
<tr>
<td>Yazicioglu 2014†</td>
<td>1 42 1 8 5.1%</td>
<td>2 42 1 8 5.1%</td>
<td></td>
<td>0.17 [0.01, 3.06]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>312 299 100.0%</td>
<td>309 299 100.0%</td>
<td></td>
<td>0.59 [0.12, 2.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>3 3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 1.80, df = 2 (P = 0.41); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.65 (P = 0.52)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Major malformations for any woman with and without Colchicine:

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Colchicine Events Total</th>
<th>No Colchicine Events Total</th>
<th>Weight</th>
<th>Odds Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ben-Chetrit 2010†</td>
<td>1 179 4 509 8.7%</td>
<td>2 179 5 509 8.7%</td>
<td></td>
<td>0.71 [0.08, 6.39]</td>
</tr>
<tr>
<td>Diav-Citrin 2010†</td>
<td>10 221 35 908 81.7%</td>
<td>11 231 35 908 81.7%</td>
<td></td>
<td>1.18 [0.58, 2.43]</td>
</tr>
<tr>
<td>Rabinovitch 1992†</td>
<td>2 131 0 94 4.5%</td>
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<td></td>
<td>3.65 [0.17, 76.88]</td>
</tr>
<tr>
<td>Yazicioglu 2014†</td>
<td>1 42 1 8 5.1%</td>
<td>2 42 1 8 5.1%</td>
<td></td>
<td>0.17 [0.01, 3.06]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>573 1519 100.0%</td>
<td>573 1519 100.0%</td>
<td></td>
<td>1.08 [0.56, 2.07]</td>
</tr>
<tr>
<td>Total events</td>
<td>14 40</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Tau² = 0.00; Chi² = 2.39, df = 3 (P = 0.50); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.23 (P = 0.62)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**TABLE 2**
Comparison A: Colchicine vs no colchicine in FMF
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Estimate</th>
<th>OR/MD (95% CI)</th>
<th>P-value</th>
<th>I²(%)</th>
<th>Raw values (colchicine vs no colchicine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage</td>
<td>3ᵃ</td>
<td>OR</td>
<td>0.69 (0.43, 1.11)</td>
<td>0.12</td>
<td>0</td>
<td>34/312 (10.9%) vs 50/299 (16.7%)</td>
</tr>
<tr>
<td>Major malformations</td>
<td>3</td>
<td>OR</td>
<td>0.59 (0.12, 2.93)</td>
<td>0.52</td>
<td>0</td>
<td>3/312 (1.0%) vs 3/299 (1.0%)</td>
</tr>
<tr>
<td>Pre-term birth</td>
<td>1</td>
<td>OR</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>2</td>
<td>OR</td>
<td>1.61 (0.65, 4.03)</td>
<td>0.31</td>
<td>64</td>
<td>37/270 (13.7%) vs 27/291 (9.3%)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>1</td>
<td>MD</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Birthweight, g</td>
<td>2</td>
<td>MD</td>
<td>−96.72 (−218.90, 25.46)</td>
<td>0.12</td>
<td>0</td>
<td>2956.03 ± 661.87 vs 3104.52 ± 451.55</td>
</tr>
</tbody>
</table>

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)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>No. of Studies</th>
<th>Estimate</th>
<th>OR/MD (95% CI)</th>
<th>P-value</th>
<th>I²(%)</th>
<th>Raw values (colchicine vs no colchicine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage</td>
<td>4ᵃ</td>
<td>OR</td>
<td>0.65 (0.45, 0.93)</td>
<td>0.02</td>
<td>0</td>
<td>46/590 (7.8%) vs 157/1575 (10.0%)</td>
</tr>
<tr>
<td>Major malformations</td>
<td>4</td>
<td>OR</td>
<td>1.08 (0.56, 2.07)</td>
<td>0.82</td>
<td>0</td>
<td>14/573 (2.4%) vs 40/1519 (2.6%)</td>
</tr>
<tr>
<td>Pre-term birth</td>
<td>2</td>
<td>OR</td>
<td>2.48 (1.65, 3.71)</td>
<td>&lt;0.001</td>
<td>1</td>
<td>57/345 (16.5%) vs 62/961 (6.5%)</td>
</tr>
<tr>
<td>Cesarean section</td>
<td>3</td>
<td>OR</td>
<td>1.47 (0.96, 2.26)</td>
<td>0.07</td>
<td>38</td>
<td>99/527 (18.8%) vs 196/1178 (16.6%)</td>
</tr>
<tr>
<td>Gestational age, weeks</td>
<td>2</td>
<td>MD</td>
<td>−1.00 (−1.05, −0.95)</td>
<td>&lt;0.001</td>
<td>0</td>
<td>38.57 ± 1.88 vs 39.98 ± 0.55</td>
</tr>
<tr>
<td>Birthweight, g</td>
<td>3</td>
<td>MD</td>
<td>−209.62 (−381.58, −37.66)</td>
<td>0.02</td>
<td>80</td>
<td>2985.12 ± 413.96 vs 3281.30 ± 186.96</td>
</tr>
</tbody>
</table>

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.
<table>
<thead>
<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>
</thead>
<tbody>
<tr>
<td>CBD</td>
<td>Schatz 1976 JAMA</td>
<td>Case series</td>
<td></td>
<td>70 pregnancies in 55 asthmatics</td>
<td>7.9-8.7 mg/prednisone all three trimesters</td>
<td>1 termination 71 births (two sets of twins) 10 premature &lt;37 weeks One cleft palate</td>
</tr>
<tr>
<td>Adverse preg outcome</td>
<td>Park Wyllie 2000 /Teratology</td>
<td>Prospective Cohort and meta analysis</td>
<td></td>
<td>184 women prospective Meta- analysis</td>
<td></td>
<td>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)</td>
</tr>
<tr>
<td>Cleft lip+palate</td>
<td>Carmichael 2007 AJOG</td>
<td>Case-control</td>
<td></td>
<td>1141 cleft lip + palate, 628 cleft palate 4143 control</td>
<td></td>
<td>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</td>
</tr>
<tr>
<td>Cleft palate</td>
<td>Gur Reprod Toxicol 2004</td>
<td>Israeli Teratogen Information Services Prospective Case control</td>
<td></td>
<td>311 exposed 790 controls</td>
<td></td>
<td>No increase in major anomalies and no pattern, no CP Higher rates of miscarriage, preterm birth amongst exposed group, lower birth weight P&lt;.001</td>
</tr>
<tr>
<td>Gestational age</td>
<td>Palmsten Pharmacoepidemiol Drug Safety 2018</td>
<td>Mother to baby observational cohort study</td>
<td></td>
<td>254 exposed /mult diagnosis</td>
<td></td>
<td>Higher total cumulative prednisone dose was associated with shorter gestation even when adjusting for disease activity</td>
</tr>
<tr>
<td>IBD pregnancy outcomes</td>
<td>Boyd et. al 2015, PLOS 1</td>
<td></td>
<td></td>
<td>666 pregnancies IBD</td>
<td></td>
<td>Increased rate of severe pre-eclampsia amongst patients using OCS H.R. 17.4 Prematurity H.R. 6.32</td>
</tr>
<tr>
<td>Danish National registry</td>
<td>Hviid, 2011</td>
<td>Study type</td>
<td></td>
<td>51,973 exposures to corticosteroids (84 first trimester)</td>
<td></td>
<td>Results RRCLP 1.05, CP 1.23 Not statistically significant</td>
</tr>
<tr>
<td>Infection rheumatic diseases</td>
<td>Desai, 2017</td>
<td>Claims data</td>
<td>4961 pregnant women treated with immunosuppressive drugs</td>
<td>Increased dose of steroids associated with an increased risk of serious infection</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CBD</td>
<td>Garne E</td>
<td>Prospective Cohort and meta analysis 519242 pregnancies from Norway, Wales and Denmark</td>
<td>Inhaled steroids</td>
<td>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.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ADD</td>
<td>Laugessen et. al BMJ 2017</td>
<td>Case-control National birth defects prevention</td>
<td>5319 exposures to systemic GC</td>
<td>No association to ADHD found Slight increase in hazard ratio thought to be due to confounding</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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 1.7 for 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 glucocorticoids 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.


Cox II Inhibitors
Data pulled from REPROTOX on 5/30/2018. https://reprotox.org/login
<table>
<thead>
<tr>
<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>
</thead>
<tbody>
<tr>
<td>Nakhai-Pour HR</td>
<td>nested case-control study design</td>
<td>1997-2010</td>
<td>Any pregnant women (some typical exclusion criteria).</td>
<td>Non-aspirin NSAIDS: filling a prescription between months prior to and throughout pregnancy.</td>
<td>Spontaneous abortion: varies by NSAID</td>
</tr>
<tr>
<td></td>
<td>Quebec Pregnancy Registry</td>
<td></td>
<td></td>
<td>Rofecoxib: 1.83 (1.24-2.7)</td>
<td>Celexocib: 2.21 (1.42-3.45)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>(all adjusted for maternal disease, etc.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All NSAIDs for women with rheumatic disease: SLE: aOR 0.54 (0.06-5.01)</td>
<td>RA: aOR 1.12 (0.52-2.41)</td>
</tr>
</tbody>
</table>


**Cyclophosphamide**

Data pulled from REPROTOX on 5/30/2018. [https://reprotox.org/login](https://reprotox.org/login)


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/m2) intravenously on Day 1), doxorubicin (50 mg/m2) by continuous infusion over 72 hours), and 2 bolus doses of 5-fluorouracil (500 mg/m2) 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


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


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%).
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]).
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

**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.

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**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](https://reprotox.org/login)

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

<table>
<thead>
<tr>
<th>TCZ Exposure</th>
<th>Prospective (n = 180)</th>
<th>Retrospective (n = 108)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Live birth</td>
<td>68 (n = 112)</td>
<td>55 (n = 108)</td>
</tr>
<tr>
<td>Liveborn children</td>
<td>68 (n = 34)</td>
<td>56</td>
</tr>
<tr>
<td>Spontaneous abortion</td>
<td>20 (n = 6)</td>
<td>31 (n = 28.7%)</td>
</tr>
<tr>
<td>Stillbirth</td>
<td>0 (n = 14)</td>
<td>22 (n = 20.4%)</td>
</tr>
</tbody>
</table>

*All except one were exposed at least in the first trimester.

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

<table>
<thead>
<tr>
<th>Exposure</th>
<th>Prospective (n = 111)</th>
<th>Retrospective (n = 56)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Pregnancy (n = 68)</td>
<td>All (n = 56)</td>
</tr>
<tr>
<td></td>
<td>Preconception (n = 34)</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Unknown (n = 0)</td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gestational age at birth (weeks)*</th>
<th>n = 55</th>
<th>n = 32</th>
<th>n = 6</th>
<th>n = 10</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>39.0 (IQR: 36.7–40.0; R: 29.3–42.0)</td>
<td>37.5 (IQR: 36.1–38.9; R: 27.7–40.9)</td>
<td>38.9 (IQR: 36.7–39.8; R: 36.1–41.0)</td>
<td>38.5 (IQR: 37.4–39.0; R: 33.0–41.0)</td>
</tr>
<tr>
<td>Preterm</td>
<td>16 (23.0%)</td>
<td>11 (33.3%)</td>
<td>2 (33.3%)</td>
<td>2 (20.0%)</td>
</tr>
<tr>
<td>Sex</td>
<td>n = 42</td>
<td>n = 30</td>
<td>n = 5</td>
<td>n = 15</td>
</tr>
<tr>
<td>Female</td>
<td>19 (45.2%)</td>
<td>15 (49.0%)</td>
<td>2 (40.0%)</td>
<td>9 (60.0%)</td>
</tr>
<tr>
<td>Male</td>
<td>23 (54.8%)</td>
<td>15 (51.0%)</td>
<td>3 (60.0%)</td>
<td>6 (40.0%)</td>
</tr>
<tr>
<td>Weight (g)*</td>
<td>n = 39</td>
<td>n = 26</td>
<td>n = 3</td>
<td>n = 13</td>
</tr>
<tr>
<td>Length (cm)*</td>
<td>n = 23</td>
<td>n = 20</td>
<td>n = 3</td>
<td>n = 6</td>
</tr>
<tr>
<td></td>
<td>48 (IQR: 45.5–54; R: 36–55)</td>
<td>47.5 (IQR: 45.5–50; R: 39–52)</td>
<td>51 (IQR: 50–51.5; R: 49–52)</td>
<td>49 (IQR: 48–50; R: 47–51)</td>
</tr>
</tbody>
</table>

* Median (interquartile range, IQR; range, R).

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

Tofacitinib
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](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](https://reprotox.org/login)

Warfarin

**Data pulled from REPROTOX on 5/30/2018.** [https://reprotox.org/login](https://reprotox.org/login)

**New oral anticoagulants:**

Rivaroxaban

**Data pulled from REPROTOX on 5/30/2018.** [https://reprotox.org/login](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

**Folic acid antagonists during pregnancy and the risk of birth defects.**  
Hernández-Díaz S¹, 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.**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cardiovascular Defects</th>
<th>Oral Clefts</th>
<th>Urinary Tract Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>relative risk (95% confidence interval)*</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any folic acid antagonist</td>
<td>2.1 (1.5–3.0)</td>
<td>2.1 (1.4–3.2)</td>
<td>2.1 (1.2–3.7)</td>
</tr>
<tr>
<td>Dihydrofolate reductase inhibitors†</td>
<td>3.4 (1.8–6.4)</td>
<td>2.6 (1.1–6.1)</td>
<td>—‡</td>
</tr>
<tr>
<td>Antiepileptic drugs§</td>
<td>2.2 (1.4–3.5)</td>
<td>2.5 (1.5–4.2)</td>
<td>2.5 (1.2–5.0)</td>
</tr>
</tbody>
</table>

*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, trimethoprime, 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.

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Tacrolimus

Data pulled from REPROTOX on 5/30/2018. [https://reprotox.org/login](https://reprotox.org/login)
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Author, year</th>
<th>Study type</th>
<th>Population Description</th>
<th>Treatment given to relevant population</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Preterm birth SGA</td>
<td>Ichinose 2018</td>
<td>Retrospective chart review</td>
<td>54 SLE pregnancies</td>
<td>15 preg with tacrolimus</td>
<td>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</td>
</tr>
<tr>
<td>Preterm birth</td>
<td>Webster 2014</td>
<td>Retrospective</td>
<td>9 SLE pregnancies</td>
<td>9 preg with tacrolimus</td>
<td>No pregnancy loss, no birth defects 4/9 preterm births</td>
</tr>
</tbody>
</table>


**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.


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