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Factors associated with preterm delivery among women with rheumatoid arthritis and juvenile idiopathic arthritis

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Abstract

Objective: Pregnant women with inflammatory arthritis may be at increased risk for preterm delivery (PTD), yet it is unclear what drives this risk. This prospective cohort study of pregnant women with rheumatoid arthritis (RA), juvenile idiopathic arthritis (JIA), or healthier comparison women analyzed the independent effects of maternal disease activity, medication use, and comorbid pregnancy conditions on PTD risk.

Methods: Women were enrolled before 19 weeks' completed gestation as part of the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project. Data on pregnancy events, medications, disease activity, and outcomes were obtained by maternal report and validated by medical records. Poisson regression with robust standard errors estimated risk ratios (RR), multivariable adjusted risk ratios (aRR) and 95% Confidence Intervals (CI).

Results: A total of 657 women with RA, 170 with JIA, and 564 comparison women without autoimmune disease who delivered live-born infants from 2004–2017 were included for analysis. Both RA and JIA groups had an increased risk of PTD versus the comparison group (RR 2.09, 95% CI 1.50–2.91; and RR 1.81, 95% CI 1.14–2.89, respectively). Active RA at enrollment (aRR 1.58, 95% CI 1.10–2.27) and anytime during pregnancy (aRR 1.52, 95% CI 1.06–2.18) was associated with PTD. Corticosteroid use in every trimester was associated with an approximate 2 to 5-fold increased risk for PTD for both arthritis groups, independent of disease activity.

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Conclusion: Women with RA and JIA are at increased risk for PTD. Maternal disease activity and corticosteroid use may contribute to some of this excess risk.

Introduction

Chronic forms of inflammatory arthritis may be associated with adverse pregnancy outcomes such as preterm delivery (PTD). This higher risk of PTD has been demonstrated for pregnant women with rheumatoid arthritis (RA) in both prospective and retrospective analyses(1–4). Few, however, have analyzed the contribution of disease activity and medication use on PTD in women with RA. One study from 2014 showed no association between active disease and PTD in 46 RA pregnancies, but did find that medication discontinuation conferred a higher odds of earlier gestational age at delivery(3). A 2015 cohort analysis from our group found that disease activity in early pregnancy did predict PTD, although medication use was not considered(4). The Dutch PARA study from 2009 found that the effect of prednisone on lower birth weight was mediated through a lower gestational age at delivery, but this study did not analyze risk factors for PTD specifically(5). Similarly, only a handful of studies have looked at birth outcomes dedicated to the juvenile idiopathic arthritis (JIA) population. Retrospective and prospective cohort analyses have shown an increased risk of PTD, but none have been able to adjust for medication use or disease activity(6–9).

The purpose of this study was to assess the risk of pregnancy complications in women with RA and JIA in comparison to a healthier cohort, and to examine the independent effects of these pregnancy complications, medications, and disease activity on the risk for PTD in women with inflammatory arthritis.

Materials and methods

Source of the sample

Data for this analysis were obtained from the Organization of Teratology Information Specialists (OTIS) Autoimmune Disease in Pregnancy Project, a prospective cohort study of pregnancy outcomes among women in the U.S. and Canada. Participants were recruited from pregnant callers who initiated contact with an OTIS service as well as from direct marketing to consumers through social media and the OTIS MotherToBaby study website. Participants were also recruited through direct marketing to health care professionals and specialists through mail, professional meetings, and the website. Women were eligible for the cohort study if they enrolled prior to 19 completed weeks' gestation and had not enrolled in this study with a previous pregnancy. Pregnant women who enrolled in the study between 2004 and 2017 and delivered at least one live born infant were eligible for the analysis. The study sample was further limited to those participants for whom the gestational age at delivery was recorded. The protocol was approved by the institutional review board at the University of California, San Diego. Women in the study provided oral consent for interview data and written consent for release of medical records.

Study design and data collection

Women who consented to participate were interviewed by telephone two to three times during pregnancy using a standard questionnaire about their personal medical history, prescription and non-prescription medication exposures during pregnancy, history of previous pregnancies, family medical history, pre-pregnancy body mass index (BMI), and socioeconomic and demographic characteristics of the woman and her partner. Exposure history included start and stop dates of each prescription and over-the-counter medication, as well as indications, dosage changes and frequencies, use of caffeine, dietary supplements, occupational exposures, infections, prenatal testing or other medical procedures, and use of recreational drugs, tobacco, and alcohol.

Birth outcomes were obtained using a standard interview form completed by telephone shortly after delivery. Women were asked about exposure information during pregnancy, gestational age at delivery, mode of delivery, and any pregnancy complications. Medical records from the prenatal care provider, delivery hospital, any specialty providers that managed the woman's care in pregnancy, and the pediatrician were collected and data abstracted for additional exposure and outcome information, including validation of maternal self-report of autoimmune disease diagnosis. If a discrepancy existed between information in the medical record and maternal report, the medical record data was used in the analysis.

Classification of Exposure Groups

Inflammatory arthritides considered in the analysis included RA and JIA. Maternal report validated by medical records was used to classify maternal autoimmune disease. Women who were enrolled in the study, met criteria for inclusion in this analysis, and had no history of any of the aforementioned autoimmune diseases or any other chronic disease were selected as a comparison cohort.

Medication treatments for autoimmune diseases were grouped by class and defined as treatment at any dose for any length of time in pregnancy. The specific classes of medications considered included disease modifying anti-rheumatic drugs (DMARDs), non-DMARD biologic medications, oral corticosteroids, and non-steroidal anti-inflammatory drugs (NSAIDs).

Disease activity for autoimmune subjects was documented at intake and 32 weeks' gestation using patient-reported assessments, including the Health Assessment Questionnaire (HAQ) on a scale from 0–3, as well as pain score and patient global disease activity assessment on a scale from 0–100. These three markers of disease activity were used to calculate the Patient Activity Scale (PAS) score, with resulting values ranging from 0–10. High disease activity was defined as PAS score >3.70 and low disease activity as ≤3.70 based on standard interpretation(10).

Covariates and Outcomes

Baseline covariates considered in the analysis included the following: maternal age in years at the estimated due date; parity and gravidity at the time of conception; pre-pregnancy BMI;

maternal race; socioeconomic status (SES) as defined by Hollingshead categories; tobacco and alcohol use; prior adverse pregnancy outcome such as preterm delivery, preeclampsia, or intrauterine growth restriction; comorbid conditions such as thyroid dysfunction, diabetes mellitus type 1 and 2, or hypertension; and the presence of other autoimmune diseases such as psoriasis, inflammatory bowel disease, lupus, Sjögren's syndrome, undifferentiated connective tissue disease and antiphospholipid syndrome(11). Pregnancy events considered as covariates in the analysis included the following: preeclampsia, pregnancy-induced hypertension (PIH), placenta previa and/or placental abruption, gestational diabetes mellitus (GDM), and fever anytime during pregnancy. Fever during pregnancy was defined to include any documented fever over the course of the pregnancy, and preterm labor was defined as the onset of labor prior to 37 weeks' gestation. Preterm delivery as an outcome was defined as delivery at less than 37 completed weeks' gestation regardless of mode of delivery or indication, very preterm was defined as delivery at less than 32 weeks' completed gestation, and early term was defined as delivery at less than 39 weeks and at least 37 weeks' completed gestation. Multiple pregnancy was defined as twin or higher order multiple with more than one fetus identified during prenatal care, regardless of whether all fetuses resulted in live births.

Statistical analyses

Maternal and obstetric characteristics were compared among those with inflammatory arthritis to those in the healthier comparison group using two-tailed univariate comparisons with Student's t-test for continuous variables and Fisher's Exact Test or chi-square tests for categorical variables, depending on the cell size. Poisson regression with robust standard errors was utilized to calculate unadjusted risk ratios (RR) and 95% Confidence Intervals (CI) for obstetric outcomes and pregnancy complications among women with RA and JIA versus women in the comparison group.

To determine the effect of disease activity and medication use on the risk of PTD, Poisson regression with robust standard errors was conducted. Active disease was defined as PAS score >3.70, as compared to inactive disease, defined as PAS score ≤3.70. Multivariable adjustment was made for pertinent maternal factors, including age, race, SES, tobacco use, parity, preexisting medical condition and history of adverse pregnancy outcome, as well as corticosteroid use in the first trimester. The effect of biologic, DMARD, NSAID, and corticosteroid use during each trimester on PTD was then calculated for both RA and JIA. Multivariable adjustment was made for the aforementioned maternal factors as well as for maternal disease activity, defined by PAS score at intake.

Finally, Poisson regression analysis was performed for all three groups to compare and contrast the independent effects of pregnancy complications traditionally associated with PTD. These covariates included preeclampsia, placental complications, GDM, and maternal fever. Multivariable adjustment was made for maternal factors as well as all other variables in the models. Additionally, in the RA and JIA groups, further adjustment for corticosteroid use in the first trimester and PAS score at intake was included.

A p-value cut-off of 0.05 was considered statistically significant for all analyses. All analyses were conducted using Statistical Package for the Social Science (SPSS) statistical software Version 23.0, 2015, Armonk, NY.

Results

After exclusion of 2 stillbirth cases and 4 cases without information on gestational age at delivery, a total of 1391 women were eligible for analysis, including 657 in the RA group, 170 in the JIA group, and 564 in the comparison group. Baseline characteristics of the three groups are outlined in Table 1. All subjects were predominantly White with a higher SES score defined as Hollingshead score between 1 and 3 on a scale of 1 to 5. The mean maternal age at estimated due date was significantly higher in the RA group and lower in the JIA group than the comparison group. The RA and JIA groups had significantly more women with a history of at least 3 prior spontaneous abortions versus comparison women, and significantly fewer patients with RA were first-time mothers than in the comparison group. Women in both arthritis groups reported significantly more tobacco use as well as history of pre-gestational hypertension compared to the healthier group of women (Table 1).

In univariate analyses, mothers with RA and JIA each had a significantly higher risk of preterm labor, early term delivery, moderate preterm delivery, and caesarian section versus comparison women. Women with RA additionally had a significantly higher risk of very preterm delivery before 32 weeks' gestation and GDM, and women with JIA had a higher risk of preeclampsia versus the comparison group (Table 2).

Active disease (PAS score >3.70) was significantly associated with PTD among women with RA both at intake and anytime during pregnancy. This association remained after multivariable adjustment for maternal age, race, SES, pre-pregnancy BMI, tobacco use, parity, pre-existing medical disease, prior adverse pregnancy outcome, as well as first trimester corticosteroid use (aRR 1.58, 95%CI 1.10–2.27 at intake; aRR 1.52, 95% CI 1.06–2.18 anytime in pregnancy). Disease activity was not significantly associated with PTD among JIA women (Table 3). After multivariable adjustment for factors including high disease activity, corticosteroid use in any of the three trimesters was significantly associated with PTD among women with both RA and JIA. In addition, use of NSAIDs in the first trimester was significantly associated with PTD in women with JIA. However, neither DMARDs nor biologics in any trimester were associated with increased risks for PTD (Table 4).

Preeclampsia, PIH without preeclampsia, and GDM were independently associated with a significantly higher risk for PTD in the RA group, but not in the comparison or JIA groups, after multivariable adjustment. Fever during pregnancy independently increased the risk for PTD among JIA women in multivariable analysis (Table 5).

Discussion

Our findings suggest that women with RA and JIA are at an increased risk for preterm delivery and early term delivery. Women with RA also have a higher risk of very preterm delivery that was not noted in JIA in our sample. Interestingly, prior studies suggest the

opposite, with a 2010 prevalence study showing a higher odds of moderate but not very preterm delivery for RA, and another analysis noting a higher risk for very preterm delivery in JIA (1,7).

Existing data are conflicting on the effect of disease activity in RA on gestational age at delivery, with one retrospective study from 2014 showing no association between PTD and active disease at conception or throughout pregnancy and another prospective trial identifying disease activity in early pregnancy as predictive of PTD (3,4). In our study, active disease both at intake and anytime during pregnancy was associated with a higher risk for PTD in RA. One might expect that the increased rate of PTD is mediated through more corticosteroid use to control disease flares, as this relationship has previously been documented in the literature (5). However, in our study, the significant association between disease activity and PTD remained even after multivariate adjustment for first trimester corticosteroid use, implying that active disease in RA may contribute to PTD independent of medications. Indeed, inflammation such as that seen in conditions like RA has been linked to PTD; pro-inflammatory cytokines have been noted in higher concentrations in women with preterm labor, and have been theorized to stimulate prostaglandins, thereby promoting uterine contractions (12). While it seems that this idea of unchecked inflammation leading to PTD may be applicable to all chronic diseases, it does not explain the fact that, in our study, active disease did not confer a higher risk of PTD in the JIA group.

The JIA group had a very high incidence of pre-pregnancy hypertension (Table 1). This may have contributed to the elevated incidence of preeclampsia seen in this group (Table 2), as pre-pregnancy hypertension has previously been demonstrated to be highly predictive of preeclampsia (13). The JIA group had a higher incidence of fever during pregnancy, which was independently associated with PTD; there was also an association between first trimester NSAID use and PTD exclusively among women in this group. Fever may be a sign of active disease in JIA, particularly the systemic subtype, and NSAID use may also reflect higher disease activity (14). Even though our analysis adjusted for disease activity in these models, disease activity may not have been adequately captured for JIA by the PAS or other patient-reported outcome measures, as our sample of JIA patients was quite heterogeneous with an unknown breakdown of disease subtypes. Therefore, these findings may still be influenced by disease activity despite the multivariable adjustment.

While neither DMARD nor biologic use conferred a higher risk for PTD, corticosteroid use was strongly associated with PTD in all three trimesters for both RA and JIA, independent of underlying disease activity (Table 4). It is often difficult to distinguish between the contributions of corticosteroid use and disease activity to the risk for PTD, and prior investigators have highlighted disease activity as the likely contributing factor (15). One prior study in pregnant women with Crohn’s disease adjusted for disease activity when analyzing the effect of corticosteroid use on PTD, and found that the effect of corticosteroids was attenuated after multivariable analysis (16). Our study, however, highlights that there is an excess risk associated with corticosteroid use on PTD in both RA and JIA even after adjustment for disease activity measures at intake. Further studies are warranted to confirm the independent contributions of corticosteroids and disease activity on gestational age of delivery.

We noted differences in the risks of pregnancy complications across the three groups, (Table 2), and we noted differences in the independent effects of these factors for PTD by group (Table 5). For example, preeclampsia was associated with a significantly elevated risk for PTD in the RA group, but not in the comparison group. We also noted a significantly higher incidence of GDM in RA than in the JIA or comparison groups (Table 2). The presence of GDM in the RA group was associated with a significant increased risk for PTD, independent of underlying corticosteroid use; no such associations were found in the JIA or comparison groups (Table 5). GDM has previously been associated with preeclampsia, hypertension, polyhydramnios, and macrosomia, but not directly with PTD (17–19). Our multivariable adjustment accounted for preeclampsia and hypertension, so it is unlikely that the higher risk for PTD associated with GDM in the RA group was attributable to higher rates of these complications. However, in our multivariable adjustment we were not able to account for polyhydramnios, which may have influenced PTD particularly in the RA group. Additionally, given that women with both RA and GDM are at a particularly high risk for perinatal complications, we can speculate that the obstetricians in this group were perhaps more aggressive about inducing at an earlier gestational age than in other groups, but this information was not available in the dataset.

Strengths of this study include the prospective cohort design and multivariable adjustment analyses. Adjustment was made for PAS score at intake and corticosteroid use in the first trimester, as opposed to anytime in pregnancy, to avoid adjustment for a mediator, as disease activity and corticosteroid use throughout pregnancy have the potential to mediate the effect of PTD. Furthermore, the utilization of these measures early in pregnancy avoided potential reverse causation bias. That is, in women with PTD, the pro-inflammatory immune state surrounding the delivery period may be initiated well before the actual delivery, with the capacity to influence maternal disease activity and corticosteroid intake (12). This is a theoretical situation in which the immune system changes surrounding the event of PTD occur first, subsequently leading to the exposure (corticosteroid use), as opposed to the exposure preceding the outcome. By excluding corticosteroid use later in pregnancy from our analysis, we avoid this potential bias. Unfortunately, using baseline disease activity measures and first trimester corticosteroid use may also have limited our conclusions, given we did not analyze the influence of disease activity or corticosteroid use later in pregnancy on PTD in the multivariable models.

These results should be viewed in light of the limitations. The sample had a relatively small number of subjects with the primary outcome of preterm delivery and a small number with JIA, thereby limiting the confidence in our conclusions. Another limitation was the potential for overfitting of our models due to the number of variables included in the analysis. Also, we did not have information on the timing of onset of preeclampsia, which in some individuals, may have occurred after 37 weeks of gestation. If this misclassification was differential by group, effect estimates for preeclampsia may have been biased.

The heterogeneous nature of our JIA cohort may have rendered the disease activity measures less reliable. Because the diseased cohort included women who may have chosen to participate in the study as a result of their arthritis, the sample may have included women with more severe disease, more medication use, or a higher number of comorbid conditions

than other national record-based studies. On the other hand, the volunteers who comprised our comparison cohort may have been healthier than the general population, as evidenced by the low rate of comorbid conditions and tobacco use seen in this group. Indeed, the rate of preterm birth in the comparison cohort (7.8%) was lower than the national average (9.6% in 2015), and this disparity has the potential to bias the effects seen in the arthritis groups away from the null.(20) Lastly, the entire cohort was predominantly White and with a high SES level, and thus these results may not be generalizable to the entire population.

In conclusion, this study highlights the factors driving PTD for pregnant women with inflammatory arthritis. Active disease was significantly associated with PTD among RA women even when measured in the first half of pregnancy, and corticosteroid use was a strong risk factor of PTD for both RA and JIA, independent of disease activity. Additional factors, such as GDM, fever during pregnancy, first trimester NSAID use, and preeclampsia may have differential influence on PTD risk in the inflammatory arthritis population compared to the general population of pregnant women. Reassuringly, neither DMARDs nor biologic medications used in any trimester were independently linked to higher risk of PTD. Further analyses are necessary to look at other categories of arthritis affecting women of childbearing age, racial disparities in these populations, as well as the influence of disease activity in the later stages of pregnancy on other perinatal factors that may contribute to PTD risk.

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Significance and Innovations

- Women with rheumatoid arthritis and juvenile idiopathic arthritis have an increased risk for preterm delivery.
- Active disease in rheumatoid arthritis may be associated with an increased risk for preterm delivery.
- Corticosteroid use in any trimester may increase the risk for preterm delivery in both rheumatoid arthritis and juvenile idiopathic arthritis, independent of disease activity.

Table 1.

Maternal characteristics and exposures among women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) compared to women without inflammatory arthritis in OTIS cohort 2004–2017 (n = 1391)

		COMPARISON GROUP	RA	P value[a]	JIA	P value[a]
		N = 564	**N = 657**		**N = 170**	
Maternal age at estimated due date, years, mean (SD)		32.09 (4.7)	33.14 (4.67)	**<0.001**	30.55 (0.39)	**<0.001**
Pre-pregnancy BMI, kg/m2, mean (SD)		24.12 (5.4)	25.51 (6.15)	**<0.001**	24.06 (5.58)	0.907
Race, n (%)						
	White	430 (87.2)	508 (87.0)		145 (94.2)	
	Black	23 (4.7)	23 (3.9)		3 (1.9)	
	Asian /Pacific Islander	30 (6.1)	28 (4.8)	0.266	2 (1.3)	**0.028**
	Native American	3 (0.6)	11 (1.9)		3 (1.9)	
	Other	7 (1.4)	14 (2.4)		1 (0.6)	
SES[b], n (%)						
	High score (1–3)	505 (90.7)	585 (91.8)	0.779	150 (90.4)	0.631
Obstetric history, n (%)						
Primigravid		222 (39.4)	202 (30.7)	**0.002**	81 (47.6)	0.054
Parity						
	1	175 (31.0)	238 (36.2)	0.056	49 (28.8)	0.584
	≥2	100 (17.7)	124 (18.9)	0.607	18 (10.6)	**0.026**
Prior SAB						
	1–2	131 (23.2)	181 (27.5)	0.084	34 (20.0)	0.377
	≥3	6 (1.1)	19 (2.9)	**0.025**	6 (3.5)	**0.037**
Prior TAB, ≥1		44 (7.8)	78 (11.9)	**0.018**	6 (3.5)	0.053
Prior preterm delivery		44 (7.8)	60 (9.1)	0.406	20 (11.8)	0.108
Prior preeclampsia		18 (3.2)	24 (3.7)	0.659	9 (5.3)	0.202
Prior IUGR		12 (2.1)	15 (2.3)	0.854	4 (2.4)	0.772
Comorbid pre-gestational conditions, n (%)						
	Thyroid dysfunction	49 (8.7)	114 (17.4)	**<0.001**	13 (7.6)	0.669
	Diabetes mellitus (type 1 and 2)	0 (0.0)	12 (1.8)	**0.001**	0 (0.0)	--
	Hypertension	10 (1.8)	45 (6.8)	**<0.001**	21 (12.4)	**<0.001**
Tobacco use, any in pregnancy		10 (1.8)	40 (6.1)	**<0.001**	13 (7.6)	**<0.001**
Alcohol use, any in pregnancy		263 (46.6)	326 (49.6)	0.298	77 (45.3)	0.759
Other autoimmune diseases, n (%)						
	Psoriasis	NA	23 (3.5)		11 (6.5)	
	Inflammatory bowel disease	NA	18 (2.7)		11 (6.5)	
	Lupus	NA	19 (2.9)		4 (2.4)	
	Sjögren’s syndrome or UCTD	NA	25 (3.8)		3 (1.8)	
	Antiphospholipid syndrome	NA	6 (0.9)		1 (0.6)	

		COMPARISON GROUP	RA	P value[a]	JIA	P value[a]
		N = 564	N = 657		N = 170	
Disease characteristics						
Duration of arthritis, years, mean (SD)		NA	6.34 (4.67)		20.32 (7.32)	
Disease activity measures at enrollment						
	HAQ, mean (SD)	NA	0.55 (0.62)		0.51 (0.53)	
	Pain, mean (SD)	NA	29.29 (27.85)		29.90 (26.69)	
	Patient Global, mean (SD)	NA	26.08 (26.66)		25.92 (22.92)	
	PAS, mean (SD)	NA	2.45 (2.31)		2.43 (2.00)	
Medication use anytime during pregnancy, n (%)						
	Biologic agents	NA	470 (71.5)		130 (76.5)	
	DMARDs	NA	263 (40.0)		45 (26.5)	
	NSAIDs	NA	183 (27.9)		54 (31.8)	
	Corticosteroids	NA	351 (53.4)		93 (54.7)	

[a]P values calculated by t-test for continuous variables and by chi-square test for categorical variables; Fisher's exact test used for cells with expected count <5

[b]SES defined by Hollingshead categories; Race – data missing for 71 subjects in controls, 73 in RA, and 16 in JIA; SES – data missing for 7 subjects in controls, 20 in RA, 4 in JIA; BMI – data for 2 subjects missing in controls; 3 in RA; 1 in JIA; SES = socioeconomic status; UCTD = undifferentiated connective tissue disease; IUGR = intrauterine growth restriction; SAB = spontaneous abortion; TAB = terminal abortion; HAQ = health assessment questionnaire; PAS = patient activity scale; DMARDs = disease-modifying antirheumatic drugs; NSAIDs = non-steroidal anti-inflammatory drugs

Table 2.

Obstetric outcomes among women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) compared to women without inflammatory arthritis in OTIS cohort 2004–2017 (n = 1391)

	COMPARISON GROUP (N = 564)	RA (N = 657)		JIA (N = 170)	
	N (%)	N (%)	UNADJUSTED RISK RATIO (95% CI)	N (%)	UNADJUSTED RISK RATIO (95% CI)
Gestational age at delivery					
Preterm (<37 weeks' gestation)	44 (7.8)	107 (16.3)	**2.09 (1.50–2.91)**	24 (14.1)	**1.81 (1.14–2.89)**
Very preterm (<32 weeks)	6 (1.1)	17 (2.6)	**2.63 (1.04–6.67)**	3 (1.8)	1.77 (0.44–7.06)
Moderate preterm (≥32 weeks and <37 weeks)	38 (6.7)	90 (13.7)	**2.07 (1.41–3.02)**	21 (12.4)	**1.85 (1.08–3.15)**
Early term (≥37 weeks and <39 weeks)	146 (25.9)	212 (32.3)	**1.37 (1.11–1.70)**	62 (36.5)	**1.51 (1.12–2.04)**
Multiple pregnancy, n (%)	21 (3.7)	24 (3.7)	0.98 (0.55–1.74)	8 (4.7)	1.26 (0.57–2.80)
Obstetric complications, n(%)					
Preeclampsia	20 (3.6)	37 (5.7)	1.59 (0.94–2.71)	15 (8.8)	**2.48 (1.30–4.74)**
PIH without preeclampsia	19 (3.4)	35 (5.4)	1.58 (0.91–2.72)	10 (6.0)	1.75 (0.83–3.69)
Placenta previa and/or abruption	9 (1.6)	12 (1.9)	1.12 (0.48–2.64)	4 (2.5)	1.46 (0.46–4.68)
Preterm labor	41 (7.4)	106 (16.4)	**2.21 (1.57–3.12)**	25 (15.1)	**2.03 (1.27–3.23)**
Gestational diabetes mellitus	26 (4.7)	59 (9.1)	**1.94 (1.24–3.04)**	13 (7.8)	1.66 (0.87–3.16)
Fever during pregnancy	131 (23.2)	141 (21.5)	0.92 (0.75–1.14)	47 (27.6)	1.19 (0.89–1.58)
Delivery Mode, n(%)					
Caesarian section	150 (26.6)	276 (42.1)	**1.58 (1.34–1.86)**	70 (41.2)	**1.55 (1.23–1.94)**

Preeclampsia – data missing for 1 subject in controls, 3 for RA; PIH – data missing for 12 subjects in controls, 12 for RA, 4 for JIA; Placenta previa or abruption – data missing for 25 subjects in controls, 16 for RA, 6 for JIA; Preterm Labor – data missing for 12 subjects in controls, 12 for RA, 4 for JIA; Gestational diabetes – data missing for 12 subjects in controls, 12 for RA, 4 for JIA; Delivery mode – data missing for 1 subject in controls, 1 for RA; PIH = pregnancy-induced hypertension; Risk ratio computed using Poisson regression

Table 3.

Association of active disease (PAS>3.70) versus inactive disease (PAS≤3.70) on preterm delivery among women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) in OTIS cohort 2004–2017 (n = 827)

	RA N = 657			JIA N = 170		
	Number of events, n/total (%)	**ADJUSTED RISK RATIO[a] (95% CI)**	**ADJUSTED RISK RATIO[b] (95% CI)**	**Number of events, n/total (%)**	**ADJUSTED RISK RATIO[a] (95% CI)**	**ADJUSTED RISK RATIO[b] (95% CI)**
Active Disease						
Anytime during pregnancy	221/623 (35.5)	**1.72 (1.21–2.45)**	**1.52 (1.06–2.18)**	53/160 (33.1)	0.66 (0.27–1.64)	0.56 (0.23–1.35)
Intake	188/622 (30.2)	**1.77 (1.24–2.52)**	**1.58 (1.10–2.27)**	39/158 (24.7)	0.79 (0.29–2.15)	0.68 (0.26–1.79)
32 wks[c]	93/444 (20.9)	1.46 (0.83–2.55)	1.33 (0.76–2.33)	22/112 (19.6)	0.47 (0.10–2.18)	0.31 (0.04–2.46)

[a]Multivariable adjusted risk ratio computed using Poisson regression with robust errors for: Maternal age, Race (white), SES (high), Pre-pregnancy BMI, Smoking, Parity, Pre-existing medical disease (HTN, thyroid disease, diabetes), and previous adverse pregnancy outcome (preeclampsia, preterm, IUGR)

[b]Multivariable adjustment for the prior maternal factors with the addition of corticosteroid use in first trimester

[c]excluding 2 RA subjects who gave birth < 32 weeks from 32 week analysis; PAS = patient activity scale

Table 4.

Association of medications with preterm delivery among women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) in OTIS cohort 2004–2017 (n = 827) by trimester of use

	RA N = 657		JIA N = 170	
	Number of events, n (%)	**ADJUSTED RISK RATIO (95% CI)[a]**	**Number of events, n (%)**	**ADJUSTED RISK RATIO (95% CI)[a]**
Biologic use				
1T	402 (61.2)	0.93 (0.66–1.32)	119 (70.0)	0.93 (0.36–2.44)
2T	269 (40.9)	1.10 (0.77–1.56)	85 (50.0)	0.43 (0.17–1.05)
3T [b]	242 (37.0)	1.20 (0.84–1.73)	76 (44.7)	0.58 (0.25–1.35)
DMARDs				
1T	207 (31.5)	0.79 (0.54–1.17)	35 (20.6)	1.09 (0.46–2.59)
2T	141 (21.5)	0.79 (0.49–1.29)	24 (14.1)	0.91 (0.30–2.75)
3T [b]	133 (20.3)	0.94 (0.59–1.49)	23 (13.5)	1.56 (0.57–4.25)
NSAIDs				
1T	161 (24.5)	1.10 (0.73–1.65)	45 (26.5)	**2.31 (1.04–5.14)**
2T	76 (11.6)	0.94 (0.53–1.66)	25 (14.7)	1.31 (0.50–3.47)
3T [b]	48 (7.3)	0.91 (0.44–1.91)	16 (9.4)	1.85 (0.63–5.39)
Corticosteroids				
1T	270 (41.1)	**1.96 (1.36–2.83)**	65 (38.2)	**3.37 (1.53–7.43)**
2T	280 (42.6)	**1.86 (1.27–2.73)**	73 (42.9)	**4.64 (1.98–10.84)**
3T [b]	269 (41.1)	**2.13 (1.46–3.11)**	73 (42.9)	**4.90 (2.02–11.89)**

[a] Multivariable adjusted risk ratio computed using Poisson regression with robust errors for: Maternal age, Race (white), SES (high), Pre-pregnancy BMI, Smoking, Parity, Preexisting medical disease (HTN, thyroid disease, diabetes), and previous adverse pregnancy outcome (preeclampsia, preterm, IUGR), and disease activity defined by Patient Activity Scale at intake

[b] 2 RA subjects that delivered < 26 weeks were excluded from third trimester analysis

Table 5.

Risk of preterm delivery by covariates among comparison women and women with rheumatoid arthritis (RA) and juvenile idiopathic arthritis (JIA) in OTIS cohort 2004–2017 (n = 1391)

	COMPARISON GROUP N = 564		RA N = 657			JIA[c] N = 170		
	# events, n (%)	ADJUSTED RISK RATIO[a] (95% CI)	# events, n (%)	ADJUSTED RISK RATIO[a] (95% CI)	ADJUSTED RISK RATIO[b] (95% CI)	# events, n (%)	ADJUSTED RISK RATIO[a] (95% CI)	ADJUSTED RISK [b] (95% CI)
Pregnancy complications								
Preeclampsia	20 (3.6)	3.05 (1.21, 7.68)	37 (5.7)	**2.12 (1.28, 3.49)**	**2.05 (1.18, 3.55)**	15 (8.8)	1.87 (0.71, 4.96)	2.19 (0.82, 5.88)
PIH without preeclampsia	19 (3.4)	2.85 (0.96, 8.40)	35 (5.4)	**2.01 (1.14, 3.52)**	**1.88 (1.13, 3.13)**	10 (6.0)	0.60 (0.08, 4.78)	--
Placenta previa and/or abruption	9 (1.7)	**5.52 (2.06, 14.83)**	12 (1.9)	**4.01 (1.83, 8.77)**	**4.39 (2.26, 8.53)**	4 (2.4)	--	--
Gestational diabetes mellitus	26 (4.7)	0.80 (0.19, 3.34)	59 (9.1)	**1.95 (1.14, 3.32)**	**1.87 (1.10, 3.20)**	13 (7.8)	0.91 (0.25, 3.38)	0.86 (0.24, 2.97)
Fever during pregnancy	131 (23.2)	0.84 (0.42, 1.68)	141 (21.5)	0.86 (0.55, 1.33)	0.79 (0.50, 1.24)	47 (27.6)	**2.61 (1.21, 5.63)**	**3.06 (1.42, 6.56)**

[a]Multivariable adjusted risk ratio computed using Poisson regression with robust errors for: Maternal age, Race (white), SES (high), Pre-pregnancy BMI, Smoking, Parity, Preexisting medical disease (HTN, thyroid disease, diabetes), previous adverse pregnancy outcome (preeclampsia, preterm, IUGR) and each of the other listed factors listed in the table; of note, there were not enough smokers in the comparison group model for estimation, thus smoking was removed from multivariable adjustment

[b]Multivariable adjustment for the prior factors with the addition of corticosteroid use in first trimester and disease activity defined by Patient Activity Scale at intake for RA and JIA

[c]Placental previa was not able to be estimated in the JIA model and was removed from multivariable analyses, and PIH was removed from the (b) adjusted model and also excluded from analysis. Preeclampsia – data missing for 1 subject in controls, 3 for RA; PIH – data missing for 12 subjects in controls, 12 for RA, 4 for JIA; Placenta previa or abruption – data missing for 25 subjects in controls, 16 for RA, 6 for JIA; Gestational diabetes – data missing for 12 subjects in controls, 12 for RA, 4 for JIA; Delivery mode – data missing for 1 subject in controls, 1 for RA; PIH = pregnancy-induced hypertension