

## ORIGINAL ARTICLE

## Impact of autoimmune rheumatic diseases on birth outcomes: a population-based study

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**ABSTRACT**

**Objectives** Autoimmune rheumatic diseases (ARDs) affect women of childbearing age and have been associated with adverse birth outcomes. The impact of diseases like ankylosing spondylitis and psoriatic arthritis (PsA) on birth outcomes remains less studied to date. Our objective was to evaluate the impact of ARDs on preterm birth (PTB), congenital anomalies, low birth weight (LBW) and small for gestational age (SGA), in a large cohort of women.

**Methods** We conducted a propensity score-matched analysis to predict ARD from a retrospective birth cohort of all live, singleton births in California occurring between 2007 and 2012. Data were derived from birth certificate records linked to hospital discharge International Classification of Diseases, ninth revision codes.

**Results** We matched 10 244 women with a recorded ARD diagnosis (rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), antiphospholipid syndrome, PsA); ankylosing spondylitis and juvenile idiopathic arthritis (JIA) to those without an ARD diagnosis. The adjusted OR (aOR) of PTB was increased for women with any ARD (aOR 1.93, 95% CI 1.78 to 2.10) and remained significant for those with RA, SLE, PsA and JIA. The odds of LBW and SGA were also significantly increased among women with an ARD diagnosis. ARDs were not associated with increased odds of congenital anomalies.

**Conclusion** Consistent with prior literature, we found that women with ARDs are more likely to have PTB or deliver an SGA infant. Some reassurance is provided that an increase in congenital anomalies was not found even in this large cohort.

**INTRODUCTION**

Autoimmune rheumatic diseases (ARDs) are painful, debilitating conditions characterised by abnormal immunological targeting of healthy muscle, joint, bone or organ tissue causing chronic inflammation and cell damage.<sup>1 2</sup> There usually is a delay in diagnosing these diseases, especially in women.<sup>3 4</sup> Women are disproportionately affected by ARDs, with disease onset often

**Key messages****What is already known about this subject?**

► It has been shown that, in general, autoimmune rheumatic diseases (ARDs) are associated with worse pregnancy outcomes.

**What does this study add?**

- Less common ARDs like psoriatic arthritis were also shown to have this association in our study.
- Given these results, women with ARDs should be counselled that there is an increased risk of adverse birth outcomes.
- Some reassurance is provided that an increase in congenital anomalies was not found even in this large cohort.

**How might this impact on clinical practice?**

- Future large studies using cohorts that could access linked mother–child records and assess the relative contributions of maternal disease severity and treatments used towards these adverse outcomes are needed.

occurring during childbearing years.<sup>5</sup> Female sex hormones, particularly oestrogens, have been shown to play an important role in disease development and progression.<sup>6</sup> Pregnancy is uniquely challenged in women with ARDs as disease-modifying drug regimens, disease flares and the presence of autoantibodies may adversely affect maternal and neonatal outcomes.<sup>2 6</sup>

Previous studies indicate that women with ARDs are more likely to experience fetal loss, intrauterine growth restriction (IUGR), low birth weight (LBW) and preterm birth (PTB).<sup>7 8</sup> As most of these studies were performed using small sample populations,<sup>9</sup> they were only powered to assess the impact of more common ARDs, such as rheumatoid arthritis (RA) and systemic lupus



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erythematosus (SLE), on birth outcomes. Fewer studies have assessed birth outcomes of women with less common ARDs such as ankylosing spondylitis (AS), which has been reported to be much less frequent in females than males, and psoriatic arthritis (PsA).<sup>10 11</sup>

The objective of this study was to evaluate the impact of ARDs on PTB, congenital anomalies, LBW and small for gestational age (SGA), in a large, racially diverse and ethnically diverse cohort of women. Identification of women at highest risk of adverse birth outcomes will help facilitate coordinated medical and obstetric care for improvement of pregnancy outcomes.

## MATERIALS AND METHODS

### Study population and data collection

In this retrospective cohort study, the sample was drawn from all California live (20–44 weeks gestation), singleton births between 1 January 2007 and 31 December 2012 (n=3 160 268). The sample population was restricted to only include those with linked mother and child birth records and hospital discharge summaries maintained by the California Office of Statewide Health Planning and Development (n=2 963 888). The database contains linked infant birth and death certificates and information about maternal and infant characteristics, diagnoses and procedures from up to 1 year prior to delivery and 1 year after delivery.

The data files contained International Classification of Diseases, ninth revision, Clinical Modification (ICD-9-CM) diagnoses codes.<sup>12</sup> We identified women with ARDs, diagnosed prior to pregnancy and up to 1 year after delivery, using the following ICD-9-CM codes: RA (714.0, 'rheumatoid arthritis'), SLE (710.0, 'systemic lupus erythematosus'), PsA (696.0, 'psoriatic arthropathy'), antiphospholipid syndrome (APS) (289.81, 646.80), juvenile idiopathic arthritis (JIA) (714.3, 'juvenile chronic polyarthritis') and AS (720.0, 'ankylosing spondylitis'). Information on a number of potential confounders was collected from birth certificate records. These included race and ethnicity, maternal age at delivery, pre-pregnancy body mass index (BMI) (calculated as pre-pregnancy weight (kg)/(height (m))<sup>2</sup>), expected payer for delivery, maternal education, smoking during pregnancy, previous PTB, maternal diabetes and year of birth. Additional variables identified from hospital discharge ICD-9-CM codes included: drug or alcohol dependence (648.3, 'drug dependence; 303, 'alcohol dependence syndrome; 304, 'drug dependence'; and 305, 'non-dependent abuse of drugs'), thyroid disorder (246.0, 'disorders of thyrocalcitonin secretion'; 246.9, 'unspecified disorder of thyroid' and 648.1, 'thyroid dysfunction complicating pregnancy childbirth or the puerperium'), asthma (493, 'asthma') and hypertensive disorder (642, 'hypertension complicating pregnancy, childbirth and the puerperium').

Birth outcomes assessed included PTB, congenital anomalies, LBW and SGA. Gestational age was determined using best obstetric estimate and was obtained

from birth certificate records. Gestational age at delivery <37 weeks was considered preterm.<sup>13</sup> PTB was categorised as any, spontaneous, or medically indicated. Spontaneous PTB was further subdivided into either prelabour rupture of membranes (PROM) or labour with intact membranes (ie, no PROM). The preterm PROM group included all pregnancies with indication of preterm PROM on the infant's birth certificate or maternal hospital discharge record.<sup>14 15</sup> Women with birth certificate or hospital discharge indication of premature labour or tocolytic medication use, without recorded preterm PROM, were included in the spontaneous labour with intact membranes group. Medically indicated PTB was defined as induction or caesarean delivery <37 weeks gestation without PROM, premature labour or tocolytic administration.<sup>15</sup>

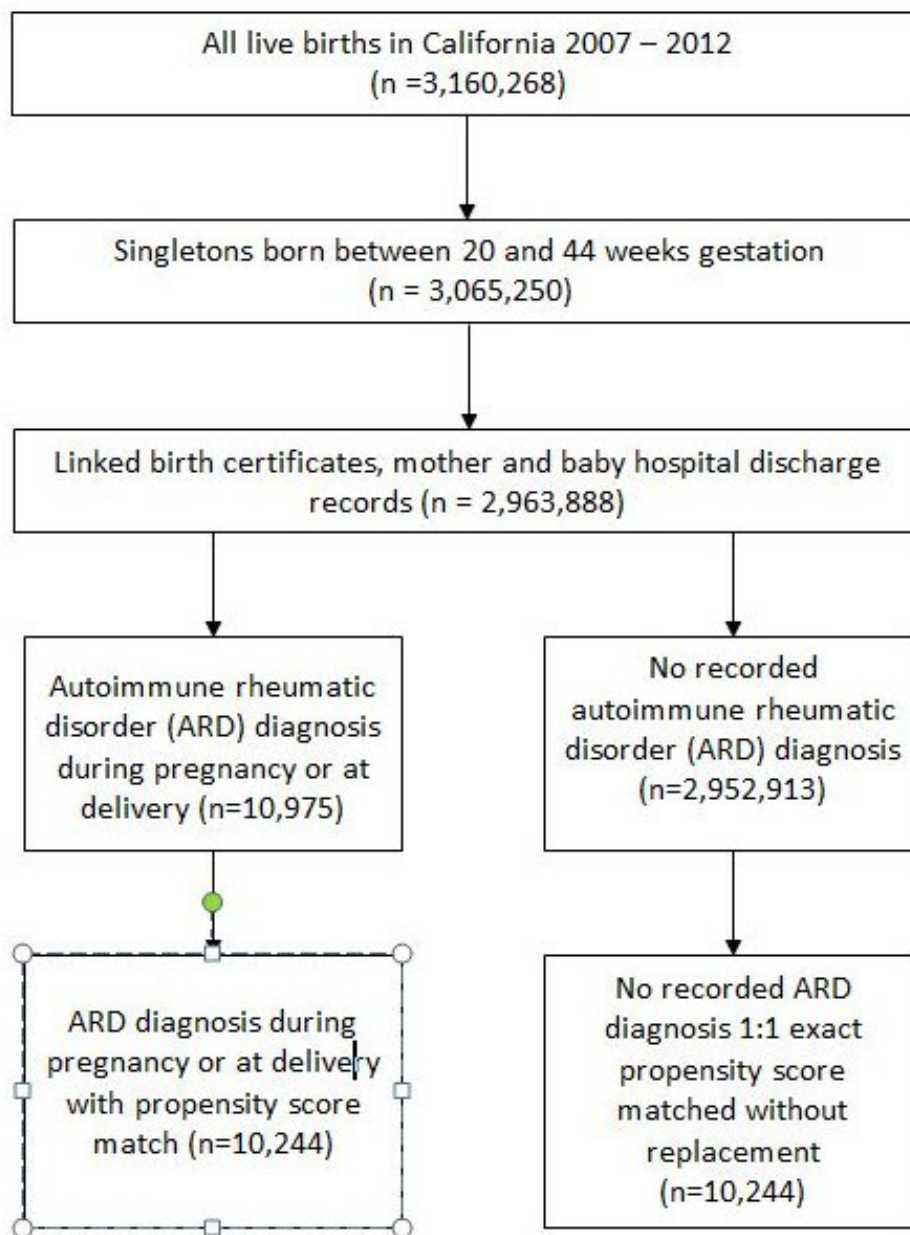
Both major structural birth defects and chromosomal abnormalities were included in the congenital anomalies outcome. Structural birth defects were considered to be 'major' if they were determined, on clinical review, to cause major morbidity or mortality and were likely to be identified in the hospital at birth or lead to hospitalisation during the first year of life.<sup>16</sup> Chromosomal abnormalities were identified by the ICD-9-CM code 758 for 'chromosomal anomalies' (online supplementary table 1).

Birth weight was obtained from birth certificate records. LBW was defined as weighing <2500 g at birth.<sup>17</sup> SGA was defined as having a birth weight in the lowest 10th percentile for gestational age.<sup>18</sup>

### Statistical analysis

To adjust for differences in baseline characteristics between women with an ARD diagnosis and those without, a propensity score matching analysis was performed. This analytical method is frequently used to approximate the experimental situation of randomisation in observational studies.<sup>19</sup> Logistic regression was used to create a propensity score for each individual to predict ARD diagnosis. All maternal characteristics identified as potential confounders, with the exception of pre-pregnancy BMI, were included in the propensity score model. Pre-pregnancy BMI was removed from the model due to the large number of women with missing data (6.7%). While many women were also missing information on level of education (3.7%), level of education among women with and without an ARD diagnosis differed significantly on removal of this variable from the model, necessitating its inclusion in the model. Propensity scores for women with an ARD were exact matched, without replacement, in a 1:1 ratio to the propensity scores for women without an ARD.

Maternal demographic and clinical characteristics were compared between women with a recorded ARD diagnosis and women without a recorded ARD diagnosis, both before and after propensity score matching, using  $\chi^2$  testing. Logistic regression was used to estimate the odds of PTB, congenital anomalies, LBW and SGA



**Figure 1** Sample selection.

among women with a recorded ARD compared with women without an ARD. P values were adjusted for using the Bonferroni correction. Statistical analyses were conducted using SAS V.9.4 software.

## RESULTS

In our study population, a total of 10 975 women had an ARD diagnosis during pregnancy or 1 year after delivery (figure 1). Of these women, 10 244 (93.3%) were exact propensity score matched to women without a recorded ARD diagnosis. The majority of recorded ARD diagnoses among women with a propensity score match included APS (35%, n=3908), SLE (33%, n=3595) and RA (26%, n=2921). A smaller proportion of women were diagnosed with JIA (3%, n=337), PsA (2%, n=161) and AS (1%, n=128).

Before propensity score matching, women with an ARD diagnosis were demographically and clinically different than women without an ARD diagnosis (table 1). Women with an ARD diagnosis were more likely to be white, not Hispanic, >34 years of age at delivery, have a pre-pregnancy BMI  $\geq 30.0$  kg/m<sup>2</sup>, delivery through caesarean section, be privately insured and have >12 years of education than women without an ARD diagnosis. Additionally, a greater proportion of women with an ARD diagnosis smoked or used drugs/alcohol during pregnancy, had a previous PTB and were diagnosed with a thyroid or hypertensive disorder, asthma or diabetes than women without an ARD diagnosis. After propensity score matching, all variables were balanced among the cases and controls ( $p > 0.05$ ), including BMI which was not included in the propensity score.

**Table 1** Maternal characteristics among women with and without an ARD diagnosis in the whole population and the propensity-matched sample.

Characteristic	Before propensity score matching			Propensity-matched sample		
	No ARD diagnosis n (%)	Any ARD diagnosis n (%)	P value	No ARD diagnosis n (%)	Any ARD diagnosis n (%)	P value
Sample size	2 952 913 (99.6)	10 975 (0.4)		10 244 (50.0)	10 244 (50.0)	
Race/ethnicity						
White, not Hispanic	768 872 (26.0)	4480 (40.8)	<0.001*	4309 (42.1)	4309 (42.1)	1.000
Hispanic	1 441 577 (48.8)	3779 (34.4)		3620 (35.3)	3620 (35.3)	
Black	158,030 (5.4)	772 (7.0)		714 (7.0)	714 (7.0)	
Asian	365 761 (12.4)	971 (8.9)		931 (9.1)	931 (9.1)	
Other	218 673 (7.4)	973 (8.9)		670 (6.5)	670 (6.5)	
Age at delivery						
<18 years	85 632 (2.9)	85 (0.8)	<0.001*	78 (0.8)	78 (0.8)	1.000
18–34 years	2 343 913 (79.4)	7732 (70.5)		7286 (71.1)	7286 (71.1)	
>34 years	523 257 (17.7)	3158 (28.8)		2880 (28.1)	2880 (28.1)	
Missing	111	0		0	0	
Pre-pregnancy body mass index						
<18.5 kg/m <sup>2</sup>	143 904 (5.2)	482 (4.7)	<0.001*	397 (4.1)	454 (4.7)	0.166
18.5–24.9 kg/m <sup>2</sup>	1 347 265 (48.9)	4963 (48.0)		4644 (48.1)	4660 (48.1)	
25.0–29.9 kg/m <sup>2</sup>	701 724 (25.5)	2591 (25.0)		2399 (24.9)	2431 (25.1)	
≥30.0 kg/m <sup>2</sup>	560 763 (20.4)	2314 (22.4)		2211 (22.9)	2142 (22.1)	
Missing	199 257	625		593	557	
Mode of delivery						
Vaginal	2 001 137 (68.2)	6038 (55.5)	<0.001*	5713 (55.8)	5713 (55.8)	1.000
Caesarean	933 625 (31.8)	4840 (44.5)		4531 (44.2)	4531 (44.2)	
Missing	18 151	97		0	0	
Primary insurance enrolment						
Private	1 366 774 (46.4)	6765 (61.7)	<0.001*	6362 (62.1)	6362 (62.1)	1.000
Medicaid/Medical	1 426 764 (48.4)	3675 (33.5)		3414 (33.3)	3414 (33.3)	
Self-pay	59 765 (2.0)	90 (0.8)		71 (0.7)	71 (0.7)	
Other	94 846 (3.2)	432 (3.4)		397 (3.9)	397 (3.9)	
Missing	4764	13		0	0	
Maternal education						
<12 years	707 492 (24.9)	1315 (12.5)	<0.001*	1257 (12.3)	1257 (12.3)	1.000
12 years	755 504 (26.6)	2342 (22.3)		2255 (22.0)	2255 (22.0)	
>12 years	1 380 922 (48.6)	6856 (65.2)		6732 (65.7)	6732 (65.7)	
Missing	108 995	462		0	0	
Smoked during pregnancy	134 019 (4.5)	663 (6.0)	<0.001*	559 (5.5)	559 (5.5)	1.000
Drug/alcohol use during pregnancy	56 888 (1.9)	506 (4.6)	<0.001*	405 (4.0)	405 (4.0)	1.000
Previous preterm birth	19 798 (0.7)	234 (2.1)	<0.001*	188 (1.8)	188 (1.8)	1.000
Thyroid disorder	58 690 (2.0)	897 (8.2)	<0.001*	772 (7.5)	772 (7.5)	1.000
Asthma	118 695 (4.0)	1100 (10.0)	<0.001*	969 (9.5)	969 (9.5)	1.000
Diabetes	277 977 (9.4)	1351 (12.3)	<0.001*	1194 (11.7)	1194 (11.7)	1.000
Hypertensive disorder	210 825 (7.1)	1765 (16.1)	<0.001*	1578 (15.4)	1578 (15.4)	1.000

Continued

Table 1 Continued

Characteristic	Before propensity score matching			Propensity-matched sample		
	No ARD diagnosis n (%)	Any ARD diagnosis n (%)	P value	No ARD diagnosis n (%)	Any ARD diagnosis n (%)	P value
Year of birth						
2007	529 945 (18.0)	1494 (13.6)	<0.001*	1392 (13.6)	1392 (13.6)	1.000
2008	516 603 (17.5)	1697 (15.5)		1571 (15.3)	1571 (15.3)	
2009	492 401 (16.7)	1841 (16.8)		1713 (16.7)	1713 (16.7)	
2010	476 945 (16.2)	1861 (17.0)		1755 (17.1)	1755 (17.1)	
2011	469 026 (15.9)	1964 (17.9)		1843 (18.0)	1843 (18.0)	
2012	467 993 (15.9)	2118 (19.3)		1970 (19.2)	1970 (19.2)	

P values were calculated using Pearson's  $\chi^2$  test.

\*P<0.05.

ARD, autoimmune rheumatic disease.

### Majority of ARDs associated with an increased risk of adverse pregnancy outcomes

Women with an ARD diagnosis had nearly a twofold increase in odds of having a PTB compared with women without an ARD diagnosis (OR 1.93, 95% CI 1.78 to 2.10) (table 2). This finding was consistent across all subtypes of PTB: spontaneous labour, PROM (OR 1.94, 95% CI 1.62 to 2.31); spontaneous labour, no PROM (OR 1.83, 95% CI 1.63 to 2.04) and medically indicated (OR 1.85, 95% CI 1.56 to 2.21). The odds of LBW and SGA were also significantly increased among women with an ARD diagnosis compared with women without an ARD diagnosis (OR 1.70, 95% CI 1.43 to 2.02; OR 1.49, 95% CI 1.36 to 1.63, respectively). Women with an ARD diagnosis were not found to be at increased odds of congenital anomalies compared with women without an ARD diagnosis.

When assessing each ARD individually, the odds of PTB were the highest among women with SLE (OR 2.84, 95% CI 2.57 to 3.15) (figure 2 and table 2). While the odds were significantly increased for all PTB subtypes among women with SLE, after Bonferroni correction, the odds of medically indicated PTB were the highest, with women with SLE experiencing a nearly threefold increase in odds compared with women without an ARD diagnosis (OR 2.82, 95% CI 2.30 to 3.45). Women with RA, APS and more than one ARD diagnosis were also at increased odds of delivering preterm compared with women without an ARD diagnosis (OR 1.55, 95% CI 1.37 to 1.75; OR 1.65, 95% CI 1.48 to 1.85; OR 1.82, 95% CI 1.52 to 2.17). The odds of LBW and SGA also varied by the type of ARD diagnosis. Similar to what was observed for PTB, women with SLE were at the highest odds of LBW and SGA (OR 2.35, 95% CI 1.91 to 2.89; OR 2.08, 95% CI 1.86 to 2.32, respectively) (table 2). The odds of LBW and SGA were also significantly increased, after Bonferroni correction, for women with RA (OR 1.57, 95% CI 1.22 to 2.01; OR 1.42, 95% CI 1.25 to 1.62). Women with more than one ARD were at increased odds of SGA, but not LBW.

### Less common ARDs are also associated with adverse pregnancy outcomes

Less common ARDs (ie, PsA, JIA and AS) were also associated with an increased odds of PTB (figure 2 and table 2). Among women with PsA and JIA, the odds of PTB was higher compared with women without any ARD (OR 1.77, 95% CI 1.15 to 2.73; OR 1.60, 95% CI 1.17 to 2.19). The odds of PTB did not differ between women with AS and women without an ARD (OR 1.09, 95% CI 0.61 to 1.94). The odds of SGA were increased among women with AS (OR 2.06, 95% CI 1.28 to 3.30); however, this association did not meet statistical significance after adjusting for multiple comparisons. Diagnosis of PsA, JIA or AS was not associated with an increase in odds of congenital anomalies or LBW.

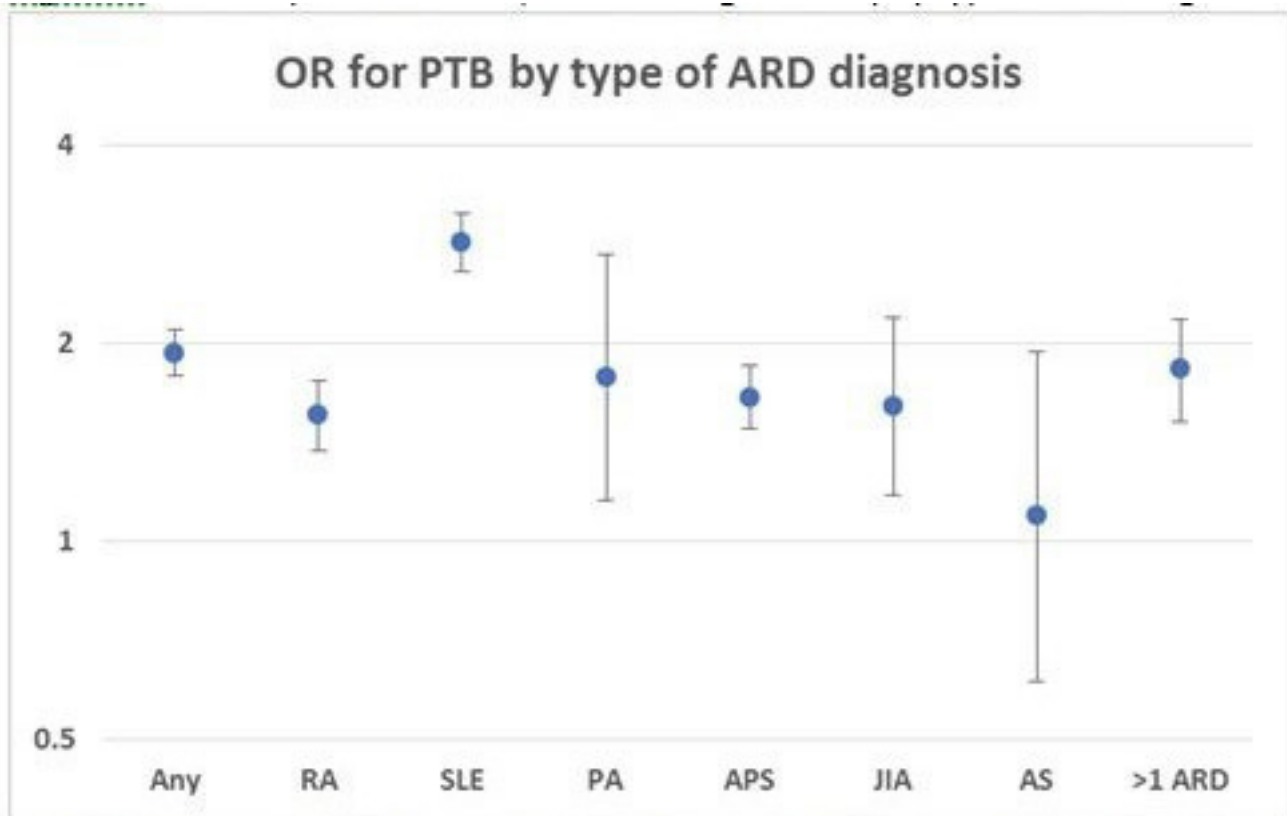
### DISCUSSION

Using a large, racially and ethnically diverse sample of pregnant women with linked birth records, our study showed that women with documented diagnoses of ARDs, including RA, SLE, PsA, APS, JIA and AS, have significantly higher odds of adverse birth outcomes such as PTB, LBW and SGA compared with women without one of these ARDs. However, ARDs were not associated with an increase in odds of congenital anomalies.

Previous work has shown that 0.09% of obstetric hospitalisations have a discharge diagnosis of SLE, which is comparable to the 0.12% of women that had a diagnosis of SLE in our study population.<sup>8 20</sup> Most research to date on PTB in women with ARDs has focused on SLE. This is likely due to the larger number of women in the childbearing age group with this disease. We found that SLE was significantly associated with adverse pregnancy outcomes. Previously, a large meta-analysis showed worse pregnancy outcomes among women with SLE compared with those without SLE.<sup>21</sup> Multiple studies have shown an increased prevalence of PTB of about 21%,<sup>7 22</sup> which is similar to our finding of 22.8%. To our knowledge, this is

**Table 2** Odds of adverse birth outcomes among women with an ARD compared with women without a recorded ARD

		ARD diagnosis															
Variable	Sample size	None		Rheumatoid arthritis		Systemic lupus erythematosus		Psoriatic arthropathy		Antiphospholipid syndrome		Juvenile idiopathic arthritis		Ankylosing spondylitis		More than one	
		n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)	n, %	OR (95% CI)
	10 244	10 244		2921	3595	161	3908	337	128	779							
	REF																
Any	962 (9.4)	1709 (16.7)	404 (13.8)	818 (22.8)	25 (15.5)	572 (14.6)	48 (14.2)	13 (10.2)	163 (20.9)								
	1.93 (1.78 to 2.10)*	1.55 (1.37 to 1.75)*	2.84 (2.57 to 3.15)*	1.77 (1.15 to 2.73)**	1.65 (1.48 to 1.85)*	1.60 (1.17 to 2.19)**	1.09 (0.61 to 1.94)	1.82 (1.52 to 2.17)*									
Spontaneous labour																	
PROM	194 (1.9)	369 (3.6)	117 (4.0)	162 (4.5)	–	110 (2.8)	16 (4.8)	–	41 (5.3)								
	1.94 (1.62 to 2.31)*	2.16 (1.71 to 2.73)*	2.45 (1.98 to 3.02)*	1.89 (1.10 to 3.23)***	–	1.50 (1.18 to 1.90)*	2.58 (1.53 to 4.35)*	–	2.04 (1.47 to 2.83)*								
No PROM	529 (5.2)	926 (9.0)	198 (6.8)	435 (12.1)	15 (9.3)	333 (8.5)	24 (7.1)	6 (4.7)	84 (10.8)								
	1.83 (1.63 to 2.04)*	1.83 (1.13 to 2.94)*	1.34 (1.13 to 1.58)*	2.53 (2.21 to 2.89)*	1.89 (1.10 to 3.23)***	1.71 (1.48 to 1.97)*	1.41 (0.92 to 2.15)	0.90 (0.40 to 2.06)	1.62 (1.28 to 2.04)*								
Medically indicated	198 (1.9)	361 (3.5)	75 (2.6)	189 (5.3)	6 (3.7)	116 (3.0)	8 (2.4)	–	32 (4.1)								
	1.85 (1.56 to 2.21)*	1.34 (1.02 to 1.75)***	2.82 (2.30 to 3.45)*	1.96 (0.86 to 4.49)	1.96 (0.86 to 4.49)	1.55 (1.23 to 1.96)*	1.23 (0.60 to 2.52)	–	1.56 (1.08 to 2.24)***								
Congenital anomalies†	311 (3.0)	357 (3.5)	97 (3.3)	125 (3.5)	5 (3.1)	140 (3.6)	6 (1.8)	5 (3.9)	21 (2.7)								
	1.15 (0.99 to 1.35)	1.10 (0.87 to 1.38)	1.10 (0.87 to 1.38)	1.15 (0.93 to 1.42)	1.02 (0.42 to 2.51)	1.19 (0.97 to 1.45)	0.58 (0.26 to 1.31)	1.30 (0.53 to 3.20)	0.82 (0.53 to 1.27)								
LBW\$	208 (2.0)	348 (3.4)	92 (3.2)	167 (4.7)	–	110 (2.8)	6 (1.8)	5 (3.9)	33 (4.2)								
	1.70 (1.43 to 2.02)*	1.57 (1.22 to 2.01)*	2.35 (1.91 to 2.89)*	2.89 (1.91 to 4.35)*	–	1.40 (1.11 to 1.77)**	0.88 (0.39 to 1.98)	1.96 (0.79 to 4.85)	1.62 (1.13 to 2.32)**								
SGA¶	892 (8.7)	1277 (12.5)	349 (12.0)	594 (16.5)	17 (10.6)	396 (10.1)	37 (11.0)	21 (16.4)	131 (16.8)								
	1.49 (1.36 to 1.63)*	1.42 (1.25 to 1.62)*	2.08 (1.86 to 2.32)*	2.08 (1.86 to 2.32)*	1.24 (0.75 to 2.06)	1.18 (1.04 to 1.34)**	1.29 (0.91 to 1.83)	2.06 (1.28 to 3.30)**	1.75 (1.45 to 2.13)*								



**Figure 2** Odds of PTB (<37 weeks' gestation) by type of ARD diagnosis. ARD, autoimmune rheumatic disease; APS, antiphospholipid syndrome; AS, ankylosing spondylitis; JIA, juvenile idiopathic arthritis; PA, psoriatic arthritis; PTB, preterm birth; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus.

the largest study to assess the risk of congenital anomalies among women with SLE.

Our study of women with RA is one of the largest in the literature. We found similar odds of PTB to other studies that had noted a 15%–17% prevalence of PTB in women with RA,<sup>23 24</sup> which is comparable to our finding of 13.8%. LBW and SGA were also increased in women with RA in our study. In the National Inpatient Sample among women with JIA, there was an aOR of 2.1 for PTB and no difference in SGA.<sup>25</sup> In our study, JIA was associated with PTB but not SGA or LBW.

There have been no large studies performed in the USA on birth outcomes of mothers with PsA. In a racially homogenous Scandinavian population, Broms *et al* studied 964 births among women with PsA and showed an increase in adverse pregnancy outcomes.<sup>10</sup> Another study followed 29 women with 42 pregnancies and was only able to comment that 95% of births were live births.<sup>26</sup>

There are very few studies focusing on large groups of women with AS and their pregnancy outcomes, which may be due in part to its under-recognition and delayed diagnosis among women. Jakobsson *et al* had analysed 388 pregnancies in 301 Swedish women with AS and found an increased frequency of caesarean delivery; PTB was increased in women with AS relative to the general population (9% vs 4.9%).<sup>11</sup> The OR for SGA in their study was 2.12 (95% CI 1.00 to 4.50), similar to an aOR

of 2.06 (95% CI 1.28 to 3.30) in our cohort, emphasising that these pregnancies also need increased surveillance.

There have been a number of studies on APS in pregnancy likely due to its association with miscarriage. Other studies have shown a prevalence of PTB ranging from 19% to 48% and an increased frequency of SGA/IUGR at 5%–31%.<sup>27 28</sup> These findings are similar to our study with 14.6% of women with APS having PTB and an increased frequency of LBW at 2.8%. There was no increased risk of congenital anomalies evaluated in these prior studies.

Worse outcomes among women with ARDs likely have a multifactorial aetiology. Many explanations have been postulated in the past. Poorly controlled ARDs and increased prednisone use have been shown to increase the risk of delivering a low birthweight infant.<sup>29</sup> It has also been suggested that tumour necrosis factor alpha, interleukin-1 beta and interleukin-6 can decrease the level of the enzyme that deactivates maternal cortisol and may lead to lower birth weights in a similar mechanism. All of these cytokines have also been associated with poorly controlled RA in the past.<sup>30</sup> Adams and Nelson proposed that microchimerism may be an underlying cause of differences in outcomes even within women with a specific ARD and between pregnancies for one woman given the way specific maternal immune systems interact with fetal cells in circulation.<sup>31</sup>

Our study has several major strengths, most notably a large racially and ethnically diverse cohort which allowed us to analyse less common ARDs. Given that it is a population-based study, it is more likely to include the entire population of women with ARDs. Some prior work has excluded women with severe disease and other work may not include women with mild disease as they are not followed as frequently in clinical practice. Other studies, especially internationally, may have larger populations of white women, whereas our study included a larger number of women of other races and ethnicities that may have a predisposition to worse birth outcomes and more severe ARD manifestations. Our study was also strengthened by our use of propensity score matching, which aided in reducing bias and confounding introduced by non-randomisation of the cohort and allowed for a more accurate comparison of outcomes between the exposure groups.<sup>32</sup> Due to our large sample size, we were able to match almost all women with an ARD to those without an ARD.

Our study has a few limitations. Given the use of a database, there are some inherent limitations such as the lack of information about activity and severity of rheumatic disease and medication use. Medications usage was not available for this cohort, and so we were unable to assess the effect of disease-modifying antirheumatic agents on adverse pregnancy outcomes. Future studies are needed to examine the risk of PTB among women being treated with disease-modifying antirheumatic drugs like methotrexate or tumour necrosis factor inhibitors compared with women who are not treated to better understand what is driving the increased risk of PTB observed in this study. Discharge records are limited in capture of behavioural and illicit exposures; smoking and alcohol use are usually under-reported and some comorbidities, if not severe, do not get coded. We used ICD codes for identification of ARDs, and hence, disease misclassification is possible. Prior work has shown that SLE diagnoses by ICD-9 codes from health plans in pregnancy have good validity, including a positive predictive value of 93% for SLE from birth records to correlating chart review.<sup>11</sup> The timing of diagnosis of ARDs in this study included prior to pregnancy and up to 12 months after delivery. Although it is possible that the ARD was diagnosed a year after birth, based on the progression of this disease, it is likely the ARD was present during pregnancy. We conducted a sensitivity analysis of women with ARD diagnosis limited to only prior to delivery and found women with ARDs had 2.18 times the odds of giving birth preterm than women who did not have ARD prior to delivery, giving robustness to our results. Since there is usually a delay in diagnosis of these diseases, we feel it was imperative to include women diagnosed a year after delivery in our study cohort.

## CONCLUSIONS

Our study confirmed the previously reported association between ARDs and adverse pregnancy outcomes. Women

with SLE were found to have the highest risk of adverse outcomes. We were also able to show an association with less common ARDs and worse pregnancy outcomes in a large racially and ethnically diverse population. While outcomes such as PTB were increased among women with ARDs, congenital anomalies were not statistically increased. Given these results, women with ARDs should be counselled that there is an increased risk of adverse birth outcomes but not of congenital anomalies. Further studies using cohorts that could access linked mother-child records and assess the relative contributions of maternal disease severity and treatments used towards these adverse outcomes are needed.

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## REFERENCES

1. Rheumatic diseases in America. The problem, the impact, and the answers 2012.



2. Chen JS, Roberts CL, Simpson JM, *et al.* Pregnancy outcomes in women with rare autoimmune diseases. *Arthritis Rheumatol* 2015;67:3314–23.
3. Jovani V, Blasco-Blasco M, Ruiz-Cantero MT, *et al.* Understanding how the diagnostic delay of spondyloarthritis differs between women and men: a systematic review and Metaanalysis. *J Rheumatol* 2017;44:174–83.
4. Barhamain AS, Magliah RF, Shaheen MH, *et al.* The journey of rheumatoid arthritis patients: a review of reported lag times from the onset of symptoms. *Open Access Rheumatol* 2017;9:139–50.
5. Diseases AR. *The Lancet* 2013;382.
6. Ostensen M, Brucato A, Carp H, *et al.* Pregnancy and reproduction in autoimmune rheumatic diseases. *Rheumatology* 2011;50:657–64.
7. Clowse MEB, Jamison M, Myers E, *et al.* A national study of the complications of lupus in pregnancy. *Am J Obstet Gynecol* 2008;199:127.e1–127.e6.
8. Chakravarty EF, Nelson L, Krishnan E. Obstetric hospitalizations in the United states for women with systemic lupus erythematosus and rheumatoid arthritis. *Arthritis Rheum* 2006;54:899–907.
9. Smyth A, Oliveira GHM, Lahr BD, *et al.* A systematic review and meta-analysis of pregnancy outcomes in patients with systemic lupus erythematosus and lupus nephritis. *Clin J Am Soc Nephrol* 2010;5:2060–8.
10. Bröms G, Haerskjold A, Granath F, *et al.* Effect of maternal psoriasis on pregnancy and birth outcomes: a population-based cohort study from Denmark and Sweden. *Acta Derm Venereol* 2018;98:728–34.
11. Jakobsson GL, Stephansson O, Askling J, *et al.* Pregnancy outcomes in patients with ankylosing spondylitis: a nationwide register study. *Ann Rheum Dis* 2016;75:1838–42.
12. American Medical Association. *International classification of diseases, 9th revision, clinical modification*. Chicago, IL: American Medical Association, 2008.
13. WHO. WHO: recommended definitions, terminology and format for statistical tables related to the perinatal period and use of a new certificate for cause of perinatal deaths. Modifications recommended by FIGO as amended October 14, 1976. *Acta Obstet Gynecol Scand* 1977;56:247–53.
14. Baer RJ, Chambers CD, Bandoli G, Jelliffe-Pawlowski LL: Risk of preterm birth by subtype among Medi-Cal participants with mental illness. *Am J Obstet Gynecol* 2016;215:519.e511–519.
15. Felder JN, Baer RJ, Rand L, *et al.* Sleep disorder diagnosis during pregnancy and risk of preterm birth. *Obstet Gynecol* 2017;130:573–81.
16. Baer RJ, Norton ME, Shaw GM, *et al.* Risk of selected structural abnormalities in infants after increased nuchal translucency measurement. *Am J Obstet Gynecol* 2014;211:675.e1–675.e19.
17. WHO. *International statistical classification of diseases and related health problems, tenth revision*. 2nd ed. World Health Organization, 2004.
18. Talge NM, Mudd LM, Sikorskii A, *et al.* United States birth weight reference corrected for implausible gestational age estimates. *Pediatrics* 2014;133:844–53.
19. Mauriello C, Chouillard E, d'alessandro A, *et al.* Retrospective comparison of single-port sleeve gastrectomy versus Three-Port laparoscopic sleeve gastrectomy: a propensity score adjustment analysis. *Obes Surg* 2018;28:2105–12.
20. Clowse MEB, Grotegut C. Racial and ethnic disparities in the pregnancies of women with systemic lupus erythematosus. *Arthritis Care Res* 2016;68:1567–72.
21. Wei S, Lai K, Yang Z, *et al.* Systemic lupus erythematosus and risk of preterm birth: a systematic review and meta-analysis of observational studies. *Lupus* 2017;26:563–71.
22. Yasmeen S, Wilkins EE, Field NT, *et al.* Pregnancy outcomes in women with systemic lupus erythematosus. *J Matern Fetal Neonatal Med* 2001;10:91–6.
23. Bharti B, Lee SJ, Lindsay SP, *et al.* Disease severity and pregnancy outcomes in women with rheumatoid arthritis: results from the organization of teratology information specialists autoimmune diseases in pregnancy project. *J Rheumatol* 2015;42:1376–82.
24. Ma KK, Nelson JL, Guthrie KA, *et al.* Adverse pregnancy outcomes and risk of subsequent rheumatoid arthritis. *Arthritis Rheumatol* 2014;66:508–12.
25. Mohamed MA, Goldman C, El-Dib M, *et al.* Maternal juvenile rheumatoid arthritis may be associated with preterm birth but not poor fetal growth. *J Perinatol* 2016;36:268–71.
26. Cervera R, Serrano R, Pons-Estel GJ, *et al.* Morbidity and mortality in the antiphospholipid syndrome during a 10-year period: a multicentre prospective study of 1000 patients. *Ann Rheum Dis* 2015;74:1011–8.
27. Tincani A, Lojaco A, Taglietti M, *et al.* Pregnancy and neonatal outcome in primary antiphospholipid syndrome. *Lupus* 2002;11.
28. de Man YA, Hazes JMW, van der Heide H, *et al.* Association of higher rheumatoid arthritis disease activity during pregnancy with lower birth weight: results of a national prospective study. *Arthritis Rheum* 2009;60:3196–206.
29. Kossintseva I, Wong S, Johnstone E, *et al.* Proinflammatory cytokines inhibit human placental 11beta-hydroxysteroid dehydrogenase type 2 activity through  $Ca^{2+}$  and cAMP pathways. *Am J Physiol Endocrinol Metab* 2006;290:E282–E288.
30. Adams Waldorf KM, Nelson JL. Autoimmune disease during pregnancy and the microchimerism legacy of pregnancy. *Immunol Invest* 2008;37:631–44.
31. Mullins CD, Ernst FR, Krukas MR, *et al.* Value of propensity score matching for equalizing comparator groups in observational database studies: a case study in Anti-infectives. *Clinical Therapeutics* 2016;38:2676–81.
32. Polachek A, Li S, Polachek IS, *et al.* Psoriatic arthritis disease activity during pregnancy and the first-year postpartum. *Semin Arthritis Rheum* 2017;46:740–5.