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Obstetric and neonatal complications among women with autoimmune disease

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ABSTRACT

Background: The impact of autoimmune diseases on pregnancy remains understudied on a population level. Examination of obstetric and neonatal outcomes among women with autoimmune disease and their infants can provide important insights for clinical management.

Methods: Autoimmune diseases and outcomes were identified using medical records. Cesarean delivery, preterm birth, preeclampsia, small for gestational age (SGA), neonatal intensive care (NICU) admission, neonatal respiratory distress syndrome (RDS), and perinatal mortality risk was assessed. Poisson regression with robust standard errors estimated relative risks (RR) and 95% confidence intervals (95% CI) with adjustment for maternal characteristics and other chronic conditions.

Results: Women with T1DM were at increased risk for nearly all outcomes including RDS (RR: 3.62; 95% CI: 2.84, 4.62), perinatal mortality (RR: 2.35; 95% CI: 1.12, 4.91), cesarean delivery (RR: 2.16; 95% CI: 2.02, 2.32) and preterm birth (RR: 3.52; 95% CI: 3.17, 3.91). Women with SLE also had higher risk for preterm delivery (RR: 2.90; 95% CI: 2.42, 3.48) and RDS (RR:2.99; 95% CI: 1.99, 4.51) as did women with Crohn's (cesarean delivery RR:1.31, 95% CI: 1.08, 1.60; preterm delivery RR: 1.84, 95% CI: 1.37, 2.49. RA increased risk for SGA (RR:1.66; 95% CI: 1.08, 2.55).

Conclusion(s): Despite the heterogeneity in autoimmune diseases, we observed elevated preterm birth risk for most women with autoimmune disease. SLE and T1DM appeared to confer increased risk for a wide range of adverse outcomes.

1. Introduction

The worldwide estimated cumulative prevalence of autoimmune disease is approximately 5% [1], and increasing [2]. Approximately 66% of autoimmune diseases have a mean age of onset less than 50 years [1], and 80% of autoimmune cases in the U.S. occur among women [3,4]. It is important to understand the effect autoimmune diseases have on pregnant women and their infants.

The physiologic regulation of inflammation during pregnancy plays an important function in obstetric and neonatal outcomes. Inflammation, an immune-mediated response, assists in implantation and placentation early in pregnancy. Inflammation also promotes parturition and placental expulsion [5]. Later in gestation, pro-inflammatory processes at the maternal/fetal interface due to infection or placental abruption may lead to preterm birth, preeclampsia, and other adverse outcomes [6]. Research into the etiology of these outcomes is warranted. Inflammation is a key feature of autoimmune disease [3,4,7]. However, the population-level impact of autoimmune diseases on pregnancy remains understudied. Our previous work found women with asthma or thyroid disease had an increased risk for poor obstetric and infant outcomes [8–10], yet not all cases of asthma or thyroid disease are autoimmune. The underlying biologic mechanisms linking autoimmune disease and increased risk of adverse obstetric and neonatal outcomes are not well understood yet may result from overlapping physiologic adaptations necessary for pregnancy [11,12], their disease states [13–20], the presence of autoantibodies or medications [21,22] required for management during pregnancy [17,21,23,24].

A challenge in studying the association of autoimmune diseases

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with obstetric and neonatal outcomes is the rarity of both. Research conducted to date is largely among homogenous populations outside the U.S. [14–17,22,25–41]. Studies conducted among U.S. populations are often limited by small sample sizes [21,30,40] or focused on a specific autoimmune disease and lacked detailed data on multiple obstetric and infant outcomes [34,42,43].

Cesarean delivery and preterm delivery are most frequently examined in the existing literature. Women with type 1 diabetes mellitus (T1DM) [12,32,41,44], systemic lupus erythematosus (SLE) [45–48], Crohn's disease [49–52] or rheumatoid arthritis (RA) [22,53,54] are reported to be at increased risk for cesarean delivery but evidence among women with multiple sclerosis (MS) is mixed. Two population-based studies found women with MS had approximately 40% higher risk for cesarean delivery [27,28], while two other population-based studies [26,55] and two small case-control studies [25,56] found no increased risk. In addition, prior studies did not explore the indications or timing of cesarean deliveries (prelabor or intrapartum).

Similarly, evidence among women with T1DM [14,44], SLE [18,57], Crohn's [52,58,59] or RA [18,31,34] suggests increased risk of preterm birth while reports of preterm birth risk among women with MS are inconsistent. Two population-based studies report an increased preterm birth risk among women with MS [27,28], and four other studies report no increased risk [25,26,29,30]. No data are available regarding precursors of preterm birth or spontaneous versus induced deliveries among women with autoimmune disease.

Evidence for other prevalent complications associated with autoimmune disease is also inconclusive. For example, among women with RA, four studies report an increased risk of small for gestational age (SGA) [21,31,32,60], while four studies report no increased risk of SGA [16,22,33,34]. Evidence regarding neonatal intensive care unit (NICU) admission is also sparse with mixed results [15–17,22,33,35–40]. For certain autoimmune diseases like T1DM, and Crohn's disease, studies are limited and none have been conducted among US populations [14,15,39,41].

Using a nationwide US cohort, we aimed to provide a more comprehensive description of the obstetric and neonatal risks among women with autoimmune disease and their infants. To better understand obstetric and neonatal risks associated with maternal autoimmune disease, we examined women in the Consortium on Safe Labor (CSL) diagnosed with T1DM, SLE, Crohn's, MS, or RA. These diseases are heterogeneous and their target tissues vary (pancreatic β-cells for T1DM [61]; various tissues including musculoskeletal, renal, and central nervous system for SLE [62]; bowel in Crohn's [63]; the nervous system in MS [64]; and musculoskeletal system in RA [65]).

2. Materials and methods

2.1. Consortium on Safe Labor

The CSL was a U.S. retrospective cohort study from 2002 to 2008 that abstracted labor and delivery information from electronic medical records from 19 U.S. hospitals. Data extracted for deliveries at 23 gestational weeks or later (n = 228,438) included: maternal sociodemographic characteristics, medical, reproductive and prenatal history, labor and delivery summaries, postpartum and newborn data [66]. For these analyses, we excluded multifetal pregnancies (n = 5,063, 2.2%), mothers with thyroid disease (n = 3,772, 1.6%), mothers with other autoimmune disease (n = 1,764, 0.7%) such as unspecified diseases of connective tissue, thrombophilia, hemorrhagic conditions, ulcerative colitis, coeliac disease, Grave's disease and Hashimoto's thyroiditis, and participants from one site for which ICD-9 codes were not reported and no cases of the autoimmune diseases of interest were identified (n = 12,318, 5.3%). Our final analytic sample included 205,521 deliveries. Institutional Review Boards approval was obtained at all participating sites and data are de-identified.

2.2. Autoimmune diseases of interest

Relatively common maternal autoimmune diseases were selected for analyses in part to ensure sufficient sample size. T1DM, SLE, Crohn's, MS, and RA were identified using delivery admission electronic medical records and discharge ICD-9 codes (Supplementary Table 1). The sensitivity of these codes for obstetric conditions is generally good [66–68]. For women with multiple pregnancies during the study period, a diagnosis of autoimmune disease was assumed for subsequent pregnancies (52 repeat pregnancies among women with autoimmune disease, 4.5% of pregnancies to women with autoimmune disease).

2.3. Obstetric and neonatal outcomes

Outcome variables were elected based on prevalence and prior studies: cesarean delivery (overall, pre-labor, after induced labor, and after spontaneous labor), preeclampsia, preterm birth (< 37 weeks of gestation; overall, spontaneous preterm delivery, indicated preterm delivery), small for gestational age, NICU admission, neonatal respiratory distress syndrome (RDS), and perinatal mortality (pregnancy loss ≥ 23 weeks of gestation through neonatal mortality ≤ 7 days) were identified from maternal and neonatal medical records supplemented with discharge ICD-9 codes (Supplementary Table 1).

2.4. Statistical analysis

Descriptive statistics were summarized by autoimmune disease status (Present/Absent). Binary Poisson regression models with the log link function and robust standard errors to account for repeat pregnancies estimated relative risks (RR) and 95% confidence intervals (95% CI) for the association between autoimmune disease and outcomes of interest. Women with autoimmune disease and their infants were compared to women without any autoimmune disease. Models were adjusted for maternal age (continuous), maternal race/ethnicity (White, Black, Hispanic, Asian/Pacific Islander, Other), health insurance (public, private, other), marital status (married, divorced/widowed, single, unknown), smoking during pregnancy (yes/no), alcohol use during pregnancy (yes/no), any other chronic diseases (yes/no: type 2 diabetes, asthma, depression, heart disease, hypertension, renal disease) and census region (Northeast, West, South, Midwest), based on previous literature [4,20,22,27,31,41,48,52].

We also compared indications for cesarean delivery and precursors for preterm delivery by autoimmune disease status. All statistical analyses were conducted using SAS 9.4 (SAS Institute Inc., Cary, NC, USA). We did not adjust for multiple comparisons [69].

3. Results

3.1. Prevalence of autoimmune diseases

The prevalence of autoimmune diseases (cases per 1000 pregnancies) for the CSL population by demographic variables are presented in Table 1.

Black women had the highest rates of T1DM (2.9/1000) and SLE (1.3/1000), while white women had the highest rates of Crohn's (1.4/1000), MS (1/1000), and RA (0.8/1000). Women with private insurance had the highest rates of SLE (1.1/1000), Crohn's (1.1/1000), and MS (0.9/1000). Women with public insurance had the highest rate of T1DM (2.9/1000). Rates of T1DM, SLE, and Crohn's varied by census region. Rates of T1DM were highest for women in the Midwest (3.1/1000) and the South (2.9/1000). Women in the South had the highest rate of SLE (1.4/1000), and women in the Northeast had the highest rate of Crohn's disease (1.4/1000).

Women with autoimmune disease and their infants generally experienced more adverse outcomes compared to women without autoimmune disease (Tables 2 and 3). Women with any of the examined

Table 1
Demographic characteristics of women without autoimmune disease and rate per 1000[a] (and frequency) of autoimmune disease by demographic variables from the Consortium of Safe Labor, 2002–2008 (n = 205521).

	Women without autoimmune disease (N = 204384)	Autoimmune Disease Rate of disease per 1000 (n)				
		Type I Diabetes 2.4 (507)	Systemic Lupus Erythematosus 0.9 (202)	Crohn's Disease 0.8 (169)	Multiple Sclerosis 0.7 (146)	Rheumatoid Arthritis 0.5 (123)
Race						
White	514.4 (105136)	2.6 (280)	0.9 (99)	1.4 (144)	1.0 (104)	0.8 (81)
Black	208.3 (42576)	2.9 (124)	1.3 (57)	0.5 (20)	0.7 (28)	0.5 (20)
Hispanic	168.5 (34439)	2.0 (70)	0.9 (30)	< 0.1 (1)	0.2 (8)	0.3 (10)
Other	108.7 (22233)	0.1 (33)	< .01 (16)	< 0.1 (4)	< 0.1 (6)	< 0.1 (12)
	p < 0.01	*p < 0.01*	*p = 0.16*	*p < 0.01*	*p < 0.01*	*p = 0.02*
Age						
< 20	92.7 (18953)	2.5 (47)	0.3 (6)	0.5 (9)	0.1 (2)	0.6 (12)
20-24	253.6 (51829)	2.4 (127)	0.9 (49)	0.5 (25)	0.3 (15)	0.3 (14)
25-29	280.4 (57304	2.4 (136)	0.9 (52)	1.0 (56)	0.6 (34)	0.4 (22)
30-34	224.2 (45826	2.6 (121)	1.4 (64)	1.1 (52)	1.2 (55)	0.8 (36)
> =35	149.1 (30472)	2.5 (76)	1.0 (31)	0.9 (27)	1.3 (40)	1.3 (39)
	p < 0.01	*p = 0.70*	*p < 0.01*	*p < 0.01*	*p < 0.01*	*p < 0.01*
Insurance						
Private	571.6 (116823)	2.5 (299)	1.1 (135)	1.1 (127)	0.9 (102)	0.7 (79)
Public	303.3 (61982)	2.9 (181)	1.0 (65)	0.5 (34)	0.5 (32)	0.6 (36)
Other	125.1 (25578)	0.9 (27)	0.1 (2)	0.3 (8)	0.5 (12)	0.3 (8)
	p < 0.01	*p < 0.01*	*p < 0.01*	*p < 0.01*	*p = 0.02*	*p = 0.19*
Region						
Northeast	190.6 (38958)	1.7 (67)	0.7 (26)	1.4 (54)	0.8 (32)	0.7 (29)
South	388.1 (79336)	2.9 (228)	1.4 (115)	0.8 (61)	0.7 (55)	0.7 (57)
Midwest	102.3 (20919)	3.1 (65)	0.9 (18)	0.9 (18)	0.7 (15)	0.4 (9)
West	318.8 (65171)	2.2 (147)	0.7 (43)	0.5 (36)	0.7 (44)	1.4 (28)
	p < 0.01	*p < 0.01*	*p < 0.01*	*p < 0.01*	*p = 0.84*	*p = 0.06*

p-values assessed using fisher's exact test.
[a] Rates per 1000 are specific for each demographic category (rate = (outcome n/autoimmune disease N)*1000).

autoimmune diseases, when compared to women without autoimmune disease, had significantly higher rates of cesarean delivery, pre-labor cesarean delivery, preterm birth, and spontaneous preterm birth. Women with T1DM, SLE, or Crohn's also had higher rates of pre-eclampsia and indicated preterm birth. Women with T1DM or SLE had similarly high rates of poor obstetric outcomes, except for cesarean delivery, where T1DM was associated with the highest rates (Table 2).

Only women with SLE or RA had significantly higher rates of SGA, while women with T1DM had lower rates of SGA as expected, compared to women without autoimmune disease.

3.2. Risk of adverse obstetric and neonatal outcomes

Results were similar in adjusted analyses (Table 3), with all autoimmune diseases associated with increased risk for cesarean delivery, including for pre-labor cesarean and cesarean after induced or spontaneous labor, and preterm birth, including both indicated and spontaneous preterm birth.

Models adjusted for maternal age, maternal race/ethnicity, pre-conception body mass index, health insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region.; *p < 0.05 indicates rates among women with autoimmune disease different than rates among women without

Table 2
Rate per 1000[a] (and frequency) of obstetric and neonatal outcomes for singleton pregnancies from the Consortium of Safe Labor 2002–2008 (n = 205521).

	Women without autoimmune disease (n = 204384)	Autoimmune Disease				
		Type I Diabetes (n = 507)	Systemic Lupus Erythematosus (n = 202)	Crohn's Disease (n = 169)	Multiple Sclerosis (n = 146)	Rheumatoid Arthritis (n = 123)
Cesarean Delivery	278.5 (56926)	670.6 (340)[b]	391.1 (79)[b]	360.9 (61)[b]	424.7 (62)[b]	390.2 (48)[b]
Prelabor cesarean	113.6 (23218)	270.2 (137)[b]	183.2 (37)[b]	183.4 (31)[b]	232.9 (34)[b]	211.4 (26)[b]
After spontaneous labor	93.0 (19016)	195.3 (99)[b]	123.8 (25)	118.3 (20)	123.3 (18)	130.1 (16)
After induced labor	71.9 (14692)	205.1 (104)[b]	84.2 (17)	59.2 (10)	68.5 (10)	48.8 (6)
Preterm Birth	111.0 (22701)	426.0 (216)[b]	376.2 (76)[b]	195.3 (33)[b]	191.7 (28)[b]	178.8 (22)[b]
Spontaneous	78.4 (16038)	248.5 (126)[b]	232.7 (47)[b]	130.1 (22)[b]	143.8 (21)[b]	154.4 (19)[b]
Indicated	17.8 (3650)	145.9 (74)[b]	103.9 (21)[b]	29.5 (5)[b]	27.3 (4)	16.2 (2)
Preeclampsia	46.4 (9498)	159.7 (81)[b]	138.6 (28)[b]	82.8 (14)[b]	61.6 (9)	81.3 (10)
NICU Admission	115.4 (23593)	408.2 (207)[b]	282.1 (57)[b]	195.3 (33)[b]	164.3 (24)	195.1 (24)[b]
Neonatal Respiratory Distress Syndrome	31.1 (6357)	130.1 (66)[b]	113.8 (23)[b]	47.3 (8)	34.0 (5)	48.7 (6)
Small for Gestational Age	109.3 (22350)	65.0 (33)[b]	178.2 (36)[b]	124.2 (21)	75.3 (11)	170.7 (21)[b]
Perinatal Mortality	5.9 (1214)	13.8 (7)[b]	19.8 (4)[b]	5.9 (1)	0 (0)	0 (0)

[a] Rates per 1000 are specific for each autoimmune disease category (rate = (outcome n/autoimmune disease N)*1000).
[b] p < 0.05 indicates rates among women with autoimmune disease different than rates among women without autoimmune disease. P-values obtain using generalized estimating equations to account for women who had more than one pregnancy in the study.

Table 3
The association between autoimmune disease and adverse obstetric and neonatal outcomes among women with autoimmune disease and their infants in the Consortium of Safe Labor Singleton Pregnancies (n = 205521), 2002–2008.

	Women without autoimmune disease (n = 204384)	Type I Diabetes (n = 507) RR (95% CI)	Systemic Lupus Erythematosus (n = 202) RR (95% CI)	Crohn's Disease (n = 169) RR (95% CI)	Multiple Sclerosis (n = 146) RR (95% CI)	Rheumatoid Arthritis (n = 123) RR (95% CI)
Cesarean	Reference	2.16 (2.02, 2.32)*	1.21 (1.02, 1.44)*	1.31 (1.08, 1.60)*	1.33 (1.11, 1.61) *	1.18 (0.94, 1.49)
Prelabor	Reference	1.13 (1.09, 1.16)*	1.03 (0.99, 1.08)	1.05 (1.00, 1.11)*	1.07 (1.02, 1.13) *	1.05 (0.99, 1.11)
After Induction	Reference	2.58 (2.17, 3.06)*	1.05 (0.66, 1.66)	0.91 (0.50, 1.64)	0.96 (0.53, 1.74)	0.64 (0.29, 1.43)
After Spontaneous	Reference	1.90 (1.61, 2.26)*	1.23 (0.86, 1.77)	1.36 (0.90, 2.05)	1.23 (0.80, 1.87)	1.33 (0.85, 2.09)
Preterm	Reference	3.52 (3.17, 3.91)*	2.90 (2.42, 3.48)*	1.84 (1.37, 2.49)*	1.67 (1.20, 2.30) *	1.42 (0.97, 2.07)
Indicated	Reference	7.12 (5.73, 8.84)*	4.59 (3.05, 6.91)*	1.79 (0.76, 4.20)	1.48 (0.57, 3.81)	0.80 (0.20, 3.10)
Spontaneous	Reference	3.06 (2.61, 3.58)*	2.62 (2.01, 3.40)*	1.68 (1.12, 2.53)*	1.73 (1.14, 2.64) *	1.87 (1.23, 2.86) *
Preeclampsia	Reference	1.11 (1.02, 1.20)*	1.09 (0.96, 1.24)	1.03 (0.89, 1.20)	1.02 (0.87, 1.19)	1.03 (0.87, 1.23)
Small for Gestational Age	Reference	0.61 (0.43, 0.86)*	1.68 (1.21, 2.32)*	1.26 (0.82, 1.93)	0.76 (0.42, 1.38)	1.66 (1.08, 2.55) *
Respiratory Distress Syndrome	Reference	3.62 (2.84, 4.62)*	2.99 (1.99, 4.51)*	1.62 (0.81, 3.23)	1.08 (0.45, 2.58)	1.44 (0.65, 3.21)
NICU	Reference	1.25 (1.16, 1.35)*	1.13 (1.00, 1.28)*	1.07 (0.93, 1.23)	1.04 (0.89, 1.21)	1.06 (0.90, 1.25)
Admission						
Perinatal Mortalityrowhead	Reference	2.35 (1.12, 4.91)*	–	–	–	–

Models adjusted for maternal age, maternal race/ethnicity, preconception body mass index, health insurance, marital status, smoking in pregnancy, alcohol use in pregnancy, other chronic diseases, and census region.; * $p < .05$ indicates rates among women with autoimmune disease different than rates among women without autoimmune disease.

autoimmune disease.

Women with T1DM were at increased risk for most poor obstetric outcomes, except for SGA (RR:0.61, 95% CI: 0.43, 0.86). Similarly, women with SLE were at increased risk for most obstetric outcomes.

Infants born to women with autoimmune disease, compared to those born to women without autoimmune disease, appear to have elevated risk for most adverse neonatal outcomes, but many associations did not reach statistical significance (Tables 2 and 3). However, compared to infants born to women without autoimmune disease, infants born to women with T1DM were three times more likely to experience RDS (RR: 3.62; 95% CI: 2.84, 4.62), and twice as likely to experience perinatal mortality (RR: 2.35; 95% CI: 1.12, 4.91), and had a 25% risk of NICU admission (RR: 1.25; 95% CI: 1.16, 1.35). Infants born to women with SLE had similar increases in risk for RDS and NICU admission.

3.3. Intrapartum cesarean delivery and indicated preterm delivery

As risk of cesarean or preterm delivery were increased for women with autoimmune diseases, we examined indications for intrapartum cesarean deliveries (Table 4) and for indicated preterm deliveries (Table 5).

For intrapartum cesarean deliveries (Table 4), failure to progress was the most common indication for women with T1DM, Crohn's, MS or RA. Among women with T1DM, Crohn's or MS, rate of failure to progress was significantly higher than among women without autoimmune disease. Among women with SLE, non-reassuring fetal heart rate tracing was the most common indication and was nearly three-fold higher than among women without autoimmune disease. Compared to women without autoimmune disease, women with T1DM, SLE, Crohn's or RA had three-to five-fold higher rates of hypertensive disorders as indication for intrapartum cesarean delivery. Women with T1DM had the greatest number of significantly higher rates of indications, including prior uterine scar (90.7/1000), fetal distress (78.9/1000) and elective (47.3/1000).

For indicated preterm deliveries (Table 5), rates of preeclampsia, superimposed preeclampsia, and maternal conditions were higher among women with T1DM, SLE, Crohn's or MS compared to women without autoimmune disease. Women with T1DM had significantly higher rates for nine indications, including chronic hypertension (15.77/1000), fetal anomaly (27.6/1000), fetal macrosomia (1.97/1000), and history of previous pregnancy condition (27.61/1000). Women with SLE had statistically significant higher rates for six indications, including chorioamnionitis (4.95/1000), fetal anomaly (24.75/1000), and other fetal conditions (14.8/1000).

4. Discussion

Despite advances in management of autoimmune disease that aid women in fulfilling family plans, pregnant women with autoimmune diseases continue to experience increased risk of poor obstetric and neonatal outcomes. We found the risk for cesarean delivery after spontaneous or induced labor was similar among women with T1DM. However, the increased risk of overall cesarean delivery for women with SLE, Crohn's, MS or RA may have been due to increased risk of cesarean delivery after spontaneous labor. The increased risk of preterm delivery may be driven by indicated preterm deliveries among women with T1DM or SLE, but both indicated and spontaneous preterm delivery risk were elevated for women with Crohn's, MS or RA.

The richness of the CSL data allowed us to examine indications for cesarean delivery and preterm delivery. Despite heterogeneity of symptoms across types of autoimmune disease, failure to progress, non-reassuring fetal heart rate tracing, and maternal hypertensive disorders were common indications for intrapartum cesarean section across types of autoimmune disease, with evidence particularly strong among women with T1DM (Table 4). Preeclampsia and maternal comorbidities

Table 4
Rate per 1,000[a] (and frequency) of intrapartum cesarean delivery: overall and by indication.

	Women without autoimmune disease (n = 204,384)	Type I Diabetes (n = 507)	Systemic Lupus Erythematosus (n = 202)	Crohn's Disease (n = 169)	Multiple Sclerosis (n = 146)	Rheumatoid Arthritis (n = 123)
Intrapartum Cesarean Delivery	164.9 (33708)	400.3 (203)[c]	207.9 (42)	177.5 (30)	191.7 (28)	178.8 (22)
Failure to progress	65.5 (13394)	149.9 (76)[c]	44.5 (9)[c]	88.7 (15)[c]	95.8 (14)[c]	48.7 (6)[c]
NRFHRT[b]	37.7 (7714)	78.9 (40)[c]	113.8 (23)[c]	29.5 (5)	6.8 (1)[c]	40.6 (5)
Prior uterine scar	33.5 (6856)	90.7 (46)[c]	34.6 (7)	11.8 (2)[c]	41.0 (6)	48.7 (6)
Breech	14.9 (3057)	19.7 (10)	4.9 (1)	17.7 (3)	27.3 (4)[c]	8.1 (1)
Elective	11.1 (2273)	47.3 (24)[c]	19.8 (4)	5.9 (1)	0 (0)	8.1 (1)
Other	10.1 (2082)	19.7 (10)	0 (0)	11.8 (2)	20.5 (3)	0 (0)
Hypertensive disorder	3.3 (685)	19.7 (10)[c]	14.8 (3)[c]	11.8 (2)[c]	0 (0)	16.2 (2)[c]
Failed induction	2.6 (551)	9.8 (5)[c]	9.9 (2)[c]	0 (0)	0 (0)	0 (0)
Chorioamnionitis	1.5 (326)	0 (0)	0 (0)	5.9 (1)	0 (0)	0 (0)
Fetal indication	1.9 (404)	3.8 (2)	0 (0)	5.9 (1)	6.8 (1)	0 (0)
Placenta abruption	0.9 (188)	1.9 (1)	4.9 (1)	5.9 (1)	0 (0)	0 (0)
Placenta previa	0.7 (160)	1.9 (1)	0 (0)	0 (0)	6.8 (1)	0 (0)
Emergency	0.7 (149)	1.9 (1)	4.9 (1)	0 (0)	0 (0)	8.1 (1)
HIV/Herpes	0.6 (137)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Failed forceps/vacuum	0.5 (110)	1.9 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Failed VBAC	0.2 (46)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Shoulder dystocia	0.07 (15)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
History of shoulder dystocia	0.06 (14)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

[a] . Categories for the indicated precursors are not mutually exclusive as multiple obstetric or fetal conditions were included in the same pregnancy.
[b] . NRFHRT, non-reassuring fetal heart rate tracing.
[c] $p < 0.05$ Indicates rate among women with autoimmune disease different than rate among women without autoimmune disease.

Table 5
Rate per 1,000[a] (and frequency) of indicated PTB: overall and by indication.

	Women without autoimmune disease (n = 204,384)	Type I Diabetes (n = 507)	Systemic Lupus Erythematosus (n = 202)	Crohn's Disease (n = 169)	Multiple Sclerosis (n = 146)	Rheumatoid Arthritis (n = 123)
Indicated Preterm Delivery	17.8 (3650)	145.9 (74)*	103.9 (21)*	29.5 (5)*	27.3 (4)	16.2 (2)
Preeclampsia (all)	6.59 (1348)	47.33 (24)*	29.70 (6)*	17.75 (3)	6.84 (1)	0 (0)
Maternal Condition[b]	4.95 (1012)	43.39 (22)*	49.50 (10)[b]	17.75 (3)*	6.84 (1)	0 (0)
Admission for maternal reason	2.98 (611)	27.61 (14)*	14.85 (3)	11.83 (2)	0 (0)	0 (0)
History of pregnancy condition[c]	2.89 (592)	27.61 (14)*	24.75 (5)	5.91 (1)	6.84 (1)	8.13 (1)
Fetal anomaly	2.64 (540)	27.61 (14)*	24.75 (5)*	0 (0)	0 (0)	8.13 (1)
Fetal condition[d]	2.16 (443)	7.88 (4)	14.85 (3)*	0 (0)	0 (0)	0 (0)
Gestational diabetes	1.89 (388)	0 (0)	4.95 (1)	11.83 (2)	13.69 (2)	8.13 (1)
Superimposed Preeclampsia	1.68 (345)	23.66 (12)*	4.95 (1)*	5.91 (1)	6.84 (1)	0 (0)
Stillbirth	1.51 (310)	3.94 (2)	4.95 (1)	0 (0)	0 (0)	0 (0)
Pregestational diabetes	1.25 (256)	145.9 (74)	9.90 (2)	5.91 (1)	0 (0)	0 (0)
Gestational Hypertension	1.23 (252)	11.83 (6)	9.90 (2)	0 (0)	0 (0)	0 (0)
Maternal Fever	1.15 (237)	7.88 (4)	4.95 (1)	0 (0)	0 (0)	0 (0)
Admission for fetal reason[e]	1.12 (229)	3.94 (2)	4.95 (1)	0 (0)	0 (0)	0 (0)
Chronic hypertension	0.94 (194)	15.77 (8)*	9.90 (2)	0 (0)	0 (0)	8.13 (1)
Abruption	0.81 (167)	1.97 (1)	9.90 (2)	0 (0)	0 (0)	0 (0)
Prior uterine scar	0.67 (138)	1.97 (1)	0 (0)	0 (0)	0 (0)	0 (0)
Unspecified HTN	0.27 (57)	1.97 (1)*	0 (0)	0 (0)	6.84 (1)	0 (0)
Chorioamnionitis	0.25 (53)	1.97 (1)	4.95 (1)*	0 (0)	0 (0)	0 (0)
Fetal macrosomia	0.20 (42)	1.97 (1)*	0 (0)	0 (0)	0 (0)	0 (0)
Vaginal bleeding	0.20 (41)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Previa	0.13 (28)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Eclampsia	0.12 (26)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

*$p < 0.05$ Indicates rate among women with autoimmune disease different than rate among women without autoimmune disease.
[a] Categories for the indicated precursors are not mutually exclusive as multiple obstetric or fetal conditions were included in the same pregnancy.
[b] Maternal conditions included maternal medical problems such as cardiac or renal disease.
[c] History of maternal or fetal condition included pregnancy complications in a previous pregnancy only.
[d] Fetal conditions included intrauterine growth restriction and abnormal antenatal testing.
[e] Admission for fetal or maternal reason was included only if there was no other pregnancy condition.

were more likely to be indicators for preterm delivery among women with autoimmune diseases compared to women without autoimmune disease (Table 5). Examining these indications can provide clinicians with new information on risk factors for poor obstetric outcomes among women with autoimmune disease.

These observations among women with a heterogenous set of autoimmune diseases underscores the importance of immunologic health during pregnancy, and the importance of a mother's immunologic health for her neonate. For instance, women with T1DM or SLE had similarly increased risk for a range of adverse obstetric and neonatal outcomes, despite heterogenous symptoms and different target tissues. The observations among women with T1DM or SLE align

with previous evidence regarding cesarean delivery, preterm delivery, and small for gestational age births [12,14,17,18,32,41,44–48,57]. We provide the first evidence among a U.S. cohort that infants born to women with T1DM or SLE were at increased risk for RDS and NICU admission.

Obstetric risks for women with MS or RA have been underexamined in extant literature. Our observation of increased preterm delivery risk among women with MS suggests this association merits further attention. We also add evidence suggesting an increased risk of SGA births among women with RA.

The results which were not statistically significant still provide interesting details regarding obstetric and neonatal risks among women with autoimmune disease. For example, the risk estimates for cesarean delivery after spontaneous labor suggest increased risk among women with SLE, Crohn's, MS or RA, but with a lack of statistical power. Similarly, results suggest infants of women with Crohn's may be at increased risk for SGA and RDS, and women with RA may be at increased risk for cesarean delivery overall and after spontaneous labor, at increased risk for overall and indicated preterm delivery, and RDS, although estimates were imprecise. Additionally, the differences in magnitude of effects observed across autoimmune diseases and obstetric outcomes are notable. For example, the risk for cesarean delivery after induced labor among women with SLE, Crohn's, MS or RA is close to null. These results differ from the 250% increased risk for cesarean delivery after induced labor among women with T1DM, suggesting the risk of poor outcomes is not uniform across autoimmune diseases.

This study has several notable strengths. This is the first study of a large, U.S.-based cohort of pregnant women with a heterogeneous group of autoimmune diseases that assessed multiple obstetric and neonatal outcomes. While the CSL is not a nationally representative sample, the CSL is geographically varied, racially/ethnically diverse and includes women across the reproductive age range, it is a good representation of the pregnancy outcomes among women with autoimmune diseases in the U.S. To the best of our knowledge, this is the first study to examine a large, U.S.-based cohort in which women with T1DM are compared to general population controls. Additionally, we provide the first evidence of NICU admission risk among the infants of women with a variety of autoimmune diseases. We also provide novel evidence that infants born to women with SLE and T1DM are at increased risk for RDS. The neonatal risks observed are not only important in the short-term, but also can impact the health of these children as they age [70,71]. Cohort studies enriched with children born to mothers with autoimmune disease may be required to fully explore these risks due to the rarity of autoimmunity in pregnancy.

Our novel observations fill existing knowledge gaps that can inform clinicians counseling women with autoimmune disease regarding their family plans. There are few resources for clinicians that evaluate common autoimmune disorders and identify the obstetric and neonatal risks for women who are affected. This information allows women with autoimmune disease to make better informed decisions regarding their reproductive health in consultation with their physicians.

The retrospective cross-sectional design of the CSL limited our ability to consider two important aspects of autoimmune disease. First, we do not have data on diagnosis date to determine the length of time with disease prior to pregnancy. Evidence suggests women who have had an autoimmune disease for a longer period of time have worse health outcomes compared to women who have had the same autoimmune disease for a shorter period of time [72]. Secondly, we do not have data regarding disease management and symptomology during pregnancy. As autoimmune diseases are often managed on a daily basis, the disease activity during pregnancy is known to be an important determinant of pregnancy outcomes. Additionally, CSL data lacks medication use and biologic measures that would be helpful to assess mechanisms linking autoimmune disease and pregnancy outcomes.

Potential mechanisms linking maternal autoimmune disease with obstetric and neonatal outcomes are not well understood. Longitudinal investigations of immunologic health of pregnant women with autoimmune diseases are needed to better understand the general physiology of autoimmune disease during pregnancy, and to understand how daily management of these diseases, including disease flare ups, impacts pregnancy. While advances in the treatment and management of autoimmune disease have aided women in fulfilling their family plans, our data indicate that women with autoimmune disease may still have high risk for adverse outcomes.

Relying on the ICD-9 codes for autoimmune diagnoses may have missed several cases, but we expect that these conditions would be recorded in the medical records since they are likely to cause complications of pregnancy and are relevant for labor and delivery. Since the delivery admission hospitalization record has limited data on maternal chronic disease, we assume the reported risks of poor obstetric and neonatal outcomes among women with autoimmune disease are average risks. We recognize that unmeasured factors such as disease severity, length of time with disease, and management of disease may result in a risk profile differing from our observations. Clinical researchers can build upon this foundation to better understand how risk profiles may differ in order to provide better treatment options and allow for more informed decision making among their patients.

While we did not have treatment or disease severity data, recent recommendations suggest women with autoimmune disease wishing to become pregnant should discuss treatment options with their clinicians [73–79]. Preconception management may include altering medication, as certain treatments for RA, Crohn's and SLE are contraindicated with pregnancy [74,75,77,78]. Management of preconception blood glucose levels may limit risk of nephropathy among women with T1DM, and nephropathy has been suggested as a potential mechanism for increased risk of preeclampsia among women with T1DM [73], and poor glucose control during pregnancy and labor may increase risk for perinatal mortality [80]. During pregnancy, standard course of care is typically recognized as safe for mother and fetus, unless medications have been contraindicated for pregnancy [73–79]. Infants born to women with autoimmune disease may require initial NICU admission or additional examinations per hospital policy, thus clinicians and pregnant women with autoimmune disease should discuss potential care plans covering the immediate postpartum period. For example, women with T1DM should be aware that NICU admission, blood glucose testing, blood lipids testing, and echocardiograms may be included as standard course of care for their infants [79]. Furthermore, clinicians should closely monitor blood glucose levels of women with T1DM during labor and delivery, and insulin drip during labor has been recommended to maintain blood glucose levels [80]. These findings of increased risk of NICU admission and RDS among neonates suggest more attention to neonates of mothers with autoimmune disease is warranted.

In conclusion, in this comprehensive examination of multiple autoimmune diseases and various obstetric and neonatal outcomes in a national sample of U.S. women and their infants, maternal autoimmune disease was associated with poor obstetric and infant outcomes, especially preterm birth. These increased risks were observed despite the heterogeneity of symptomology across various autoimmune diseases, highlighting the importance of research to better understand immunologic function during pregnancy and to better guide prenatal care and inform patient-provider decision making regarding pregnancy for women with autoimmune disease.

Conflicts of interest

Authors report no conflict of interest.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.jaut.2019.05.015.

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