Disease Severity and Pregnancy Outcomes in Women with Rheumatoid Arthritis: Results from the Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project

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ABSTRACT. ***Objective.*** To determine the effect of rheumatoid arthritis (RA) disease severity on pregnancy outcomes in pregnant women with and without autoimmune diseases.

Methods. A prospective cohort study was conducted using the Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project. Pregnant women with RA enrolled between 2005 and 2013 were selected if they (1) delivered a live-born singleton infant; and (2) completed 3 telephone-based measures of RA disease severity prior to 20 weeks' gestation, including the Health Assessment Questionnaire Disability Index (HAQ-DI), pain score, and patient's global scale. Associations between RA disease severity and preterm delivery, small for gestational age (SGA), or cesarean delivery were tested in unadjusted and multivariate analyses using modified Poisson regression models.

Results. The sample consisted of 440 women with RA. Several unadjusted comparisons yielded significant associations. After adjustment for covariates, increasing disease severity was associated with risk for preterm delivery and SGA. For each unit increase in HAQ-DI (0–1), the adjusted relative risk (aRR) for preterm delivery increased by 58% (aRR 1.58, 95% CI 1.17–2.15). Among those with HAQ-DI > 0.5, the aRR for SGA was 1.81 (95% CI 1.01–3.33).

Conclusion. RA disease severity in early pregnancy, as measured in this study, was predictive of preterm delivery and SGA. These findings suggest that the risk of preterm delivery and SGA in women with RA might be lowered if RA is well controlled early in pregnancy. (First Release April 15 2015; J Rheumatol 2015;42:1376–82; doi:10.3899/jrheum.140583)

Key Indexing Terms:
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Rheumatoid arthritis (RA) is an autoimmune disease that has a variable course during pregnancy. While previous studies showed that pregnancy has a beneficial effect, with 50–75% reduction in disease activity, others have reported no improvement or even worsening of the disease during pregnancy[1,2,3,4].

Pregnant women with RA are at increased risk of delivering a preterm or small for gestational age (SGA) infant and have higher rates of cesarean delivery compared to women without RA[5,6,7,8,9,10]. However, little is known about the extent to which disease severity contributes to adverse pregnancy outcomes. To our knowledge, only 1 study has been published, by de Man, *et al*, assessing the effect of RA medications and disease activity on pregnancy outcome[11], as measured by the Disease Activity Score in 28 joints (DAS28). In that study, women with well-controlled RA during pregnancy had similar outcomes to that of the general population. However, the study participants were primigravid white women taking RA medications limited to prednisone, sulfasalazine, or hydroxychloroquine, and therefore the

results may not be generalizable to all women with RA. Except for the de Man, *et al* study, all previous cited studies have examined pregnancy outcomes comparing women with RA to women without RA without regard to disease severity. Thus, although it is important to assess pregnancy outcome by disease status, there is a need for further examination of disease severity and its effect on pregnancy outcomes within a population of women with RA.

The purpose of our study was to examine the association between RA disease severity as measured in early pregnancy and the risk for preterm delivery, SGA, and cesarean delivery among women with RA.

MATERIALS AND METHODS

Study design. Data were collected between 2005 and 2013 as part of the ongoing Organization of Teratology Information Specialists (OTIS) Autoimmune Diseases in Pregnancy Project. OTIS is a North American network of telephone-based teratogen counseling services located in universities and hospitals throughout the United States and Canada. The OTIS Autoimmune Diseases in Pregnancy Project is a prospective cohort study of pregnant women both with and without a diagnosis of 1 of several autoimmune diseases, including RA. This ongoing project, described in detail elsewhere, has maintained a loss to followup rate of < 5%[12,13,14].

Briefly, pregnant women were recruited throughout the United States and Canada, and followed from the study coordinating center located at the University of California San Diego. Participants were either self-referred or referred by their treating physician. Enrolled women were interviewed over the telephone at study entry (prior to 20 weeks' gestation), and 2 to 4 weeks after delivery. Maternal characteristics, disease-specific data, and birth outcomes were collected by telephone interviews conducted by trained personnel and through abstraction of medical records. For our study, pregnant women with a self-reported, verified diagnosis of RA and who delivered singleton live-born infants were included in the analysis.

This study was reviewed and approved by the University of California San Diego and the San Diego State University institutional review boards.

Variables. Disease severity was measured at enrollment using the 3 components of the Health Assessment Questionnaire (HAQ), including the HAQ Disability Index (HAQ-DI), pain score (PS), and patient's global scale (PGS)[15]. The HAQ-DI has been validated as a measure of functional status among patients with RA in the general population and studies have validated its use in pregnancy[16,17,18,19,20]. HAQ-DI assesses the ability to do 20 daily activities over the past week on a 4-point Likert scale (0–3). The activities are grouped into 8 domains. The highest score from each domain is selected and the final HAQ-DI score is the average score of these 8 domains; the score also ranges from 0–3, with a higher score implying more severe or a more disabling effect of the disease[21]. The PS is obtained from a single item asking the respondents to rate the severity of pain they have had in the past week on a scale of 0–100, where 0 represents no pain and 100 represents severe pain. The PGS is also obtained from a single item asking respondents to rate their overall health on a scale of 0–100, where 0 represents "very well" and 100 represents "very poor health." All 3 HAQ scores were used as continuous measures. In addition, the HAQ-DI score was dichotomized into 2 groups with a score of > 0.5 defined as functional disability[22].

The primary outcome measures were preterm delivery (defined as delivery before 37 completed weeks of gestation), SGA (defined as birth weight < 10th percentile adjusted for gestational age and sex), and mode of delivery (cesarean vs vaginal). Preterm delivery was categorized based on estimated gestational age at delivery calculated from the first day of last menstrual period and adjusted for ultrasounds that were discrepant according to prespecified criteria[23]. SGA was categorized based on percentiles calculated from the 2000 US National Center for Health Statistics growth curves for full-term and Lubchenco curves for preterm infants[23,24,25]. Cesarean was categorized as yes/no, regardless of the indication for the cesarean delivery.

Data were self-reported and verified with medical records to the extent possible. Because of the observational nature of the study, we verified the diagnosis of RA in most cases with records from rheumatologists and obstetricians. In the overall cohort study, the rate of medical records review is as high as 95%.

Maternal demographics included maternal age at estimated date of delivery, race/ethnicity, and family socioeconomic status (SES). SES was based on the 5-category Hollingshead method using parental education and occupation[26], and scores were categorized into low (scores 4–5) or higher (scores 1–3). Maternal education and annual household income were each categorized into 3 groups (< 12 yrs, 12–15 yrs, and > 15 yrs; and < $10,000, $10,000–$49,999, and ≥ $50,000, respectively).

Maternal lifestyle factors included tobacco use or alcohol consumption during the pregnancy (yes/no). Prepregnancy body mass index (BMI) was calculated for each woman using self-reported prepregnancy weight and height, and was categorized using the World Health Organization criteria into underweight, normal, overweight, and obese (< 18.5, 18.5–24.9, 25–29.9, and ≥ 30 kg/m^2, respectively).

Comorbidities previously associated with the study outcomes in the literature were evaluated as well. These included preexisting type 1 or type 2 diabetes, chronic hypertension, and current diagnosis of asthma or depression[27]. Comorbid autoimmune diseases included Crohn disease, ankylosing spondylitis, psoriasis, psoriatic arthritis, and other unspecified autoimmune diseases. Prednisone use was recorded as a dichotomous variable (yes/no) and also categorized into ≥ 10 mg of prednisone equivalent at any time during the pregnancy for any period of time, as well as ≥ 10 mg of prednisone equivalent during the first 20 weeks of gestation. Treatment with biologics at any time during pregnancy (yes/no) included the use of any of the following: etanercept, adalimumab, infliximab, certolizumab, tocilizumab, or abatacept.

Pregnancy-related characteristics included gravidity, parity, gestational age at enrollment, gestational age at delivery, pregnancy planning (planned or unplanned), use of birth control[28] for any period of time from the first day of the last menstrual period until enrollment in the study, use of *in vitro* fertilization (IVF)[29] in the current pregnancy, use of folic acid supplements[30] at the time of conception, and previous pregnancies ending in either preterm delivery or a baby with intrauterine growth restriction (IUGR).

Statistical analyses. Descriptive statistics (Student t test for continuous variables and chi-square test for categorical variables) were used to compare the characteristics of women who did or did not have each of the 3 birth outcomes. Unadjusted comparisons of disease severity measures by birth outcome were performed using non-parametric Wilcoxon tests as the disease severity scores were not normally distributed.

The correlation between the 3 severity scores (HAQ-DI, PS, and PGS) was assessed. These highly correlated variables were further examined using tolerance levels to assess collinearity. Modified Poisson regression models were used to estimate adjusted relative risks (aRR) for each outcome. The modified Poisson model has the advantage of providing a robust variance. The structure for the Poisson regression model was chosen based on the quasi-likelihood under the independence model criterion[31,32]. Covariates were selected to be included in multivariate models if they were associated with the outcome on bivariate analyses at $p \leq 0.20$. Those predictors that were independently associated with the outcome at $p < 0.05$ and those covariates that altered the risk estimate of the disease severity measure in relation to the specific outcomes by > 15% were adjusted for in the final models. Gestational age at enrollment was forced in the final models to account for the possibility of varying severity during the course of pregnancy.

Analyses were performed using SAS version 9.2 (SAS Institute Inc.).

RESULTS

After the exclusion of 7 women (3 with systemic lupus erythematosus and 4 where RA diagnosis could not be

verified), data were available for 440 women with RA who delivered a live-born singleton infant. Table 1 displays selected characteristics of women with RA in the OTIS cohort. Overall, women enrolled at a mean (± SD) gestational age of 11.5 weeks (± 4.4). The overall prevalence of women with preterm birth, SGA, and cesarean delivery were as follows: 15%, 9%, and 42%, respectively. The overall proportion of women taking prednisone and biologics were 54% and 67%, respectively. While 54% of women were taking prednisone at some point during pregnancy, a smaller proportion (19%) of women were taking ≥ 10 mg prednisone for any period of time in the first 20 weeks of gestation (Table 1).

Table 1. Selected characteristics of women with RA in the OTIS cohort (n = 440), 2005–2013. Percentages may not add to 100 because of rounding or missing numbers.

Characteristics	Categories	Values
Maternal age, yrs, mean (SD)		32.7 (4.6)
Race/ethnicity, n (%)		
	White	348 (79)
	Hispanic	47 (11)
	Asian/Pacific Islander	23 (5)
	Black	12 (3)
	Indian/Native American	8 (2)
SES*, n (%)		
	Higher SES, scores 1–3	342 (78)
	Low SES, scores 4–5	96 (22)
Maternal education, yrs, n (%)		
	< 12	41 (9)
	12–15	282 (64)
	> 15	117 (27)
Annual household income, $, n (%)		
	10,000	20 (5)
	10,000–49,000	72 (16)
	≥ 50,000	339 (77)
Prepregnancy BMI, kg/m^2, n (%)		
	Underweight, < 18.5	20 (5)
	Normal weight, 18.5–24.9	251 (57)
	Overweight, 25–29.9	93 (21)
	Obese, ≥ 30	76 (17)
Alcohol use, any during this pregnancy, n (%)		224 (51)
Other autoimmune diseases, n (%)		
	Crohn disease	8 (2)
	Ankylosing spondylitis	2 (0.3)
	Psoriasis	24 (5)
	Psoriatic arthritis	9 (2)
	Nonspecified autoimmune disorders	44 (10)
Prednisone, any during pregnancy, n (%)		237 (54)
Prednisone, ≥ 10 mg anytime during pregnancy, n (%)		91 (21)
Prednisone, ≥ 10 mg prior to 20 wks' gestation, n (%)		83 (19)
Biologics, any during pregnancy, n (%)		295 (67)
Parity, n (%)		
	0	200 (46)
	1	169 (38)
	2 or more	71 (16)
Gestational age at enrollment, wks, mean (SD)		11.5 (4.4)
Planned pregnancy, n (%)		305 (69)
Use of IVF in this pregnancy, n (%)		18 (4)
Periconceptional use of vitamins containing folic acid, n (%)		268 (61)
Previous preterm delivery, n (%)		41 (9)
Previous baby with IUGR, n (%)		10 (2)

* Using Hollingshead scoring criteria. RA: rheumatoid arthritis; OTIS: Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project; SES: socioeconomic status; BMI: body mass index; IVF: *in vitro* fertilization; IUGR: intrauterine growth restriction.

On bivariate analyses, when compared to women who delivered at full term, those who delivered preterm babies were older, were more likely to have had < 12 or > 15 years of education, had another unspecified autoimmune disease, had used ≥ 10 mg prednisone, had a previous preterm delivery, had a previous baby with IUGR, and were less likely to be white non-Hispanic ($p < 0.05$). Women who delivered an infant who was SGA compared to women who delivered larger infants were more likely to have comorbid Crohn disease, to have used ≥ 10 mg prednisone, and to be primiparous ($p < 0.05$). Women who had cesarean delivery compared to women who delivered vaginally were older and more likely to be overweight or obese ($p < 0.05$; Table 2). BMI was examined as a potential confounder for the pregnancy outcomes, but was not statistically significant.

Correlation analyses showed that all 3 severity scores (HAQ-DI, PS, and PGS) were significantly correlated with one another at $p < 0.01$ ($r = 0.745$, $r = 0.765$, and $r = 0.821$ for HAQ-DI: PS, HAQ-DI: PGS, and PS: PGS, respectively). In addition, when all 3 scores were included in a single multivariate model, they significantly inflated the standard errors, suggesting collinearity. Therefore, each severity measure was analyzed separately to decrease the risk of overcontrolling in the final model.

Disease severity by pregnancy outcome. The median HAQ-DI in the overall sample was 0.25 [interquartile range (IQR) 0–0.88] and the prevalence of more severe disease (HAQ-DI > 0.5) was 36%. The median PS was 20 (IQR 5–50) and the median PGS was 15 (IQR 5–45; Table 3).

In bivariate analysis, the HAQ-DI (both continuous and categorical) was significantly associated with preterm delivery ($p = 0.008$ and $p = 0.024$, respectively; Table 3 and Table 4). The PGS was also significantly associated with preterm delivery ($p = 0.012$; Table 3). Only the HAQ-DI > 0.5 was associated with SGA outcome ($p = 0.046$, Table 4), whereas for cesarean delivery, only the HAQ-DI continuous measure was significantly associated with this outcome ($p = 0.030$; Table 3).

Multivariable analyses of disease severity by pregnancy outcome. In a modified Poisson regression model, adjusting for previous preterm delivery, maternal age at delivery, ≥ 10 mg of prednisone equivalent any time during pregnancy for any period of time, maternal education, and gestational age at enrollment, the aRR for preterm delivery using the continuous HAQ-DI score at enrollment was 1.58 (95% CI 1.17–2.15), indicating that for every 1 unit (0 to 1) increase in HAQ-DI score, there was a 58% increase in risk for delivery at < 37 weeks' gestation. The strength of the associ-

Table 2. Selected characteristics of women with RA by pregnancy outcomes in the OTIS cohort (n = 440), 2005–2013. Percentages may not add to 100 because of rounding or missing numbers.

Characteristics	Preterm Delivery, n = 66	Full-term Delivery, n = 373	p	SGA, n = 39	Non-SGA, n = 393	p	Cesarean Delivery, n = 182	Vaginal Delivery, n = 255	p
Maternal age, yrs, mean (SD)	34.6 (4.5)	32.2 (4.5)	< 0.001	32.1 (4.5)	32.7 (4.6)	0.463	33.7 (4.6)	31.9 (4.3)	< 0.001
Race/ethnicity, n (%)			0.014			0.061			0.093
White	45 (66)	309 (82)		26 (63)	324 (81)		138 (74)	216 (83)	
Hispanic	12 (18)	36 (10)		7 (17)	39 (10)		24 (13)	24 (9)	
Asian/Pacific Islander	3 (4)	19 (5)		4 (10)	17 (4)		12 (6)	11 (4)	
Black	5 (7)	7 (2)		3 (7)	9 (2)		9 (5)	3 (1)	
Indian/Native American	2 (3)	6 (2)		1 (2)	7 (2)		3 (2)	5 (2)	
SES*, n (%)			0.629			0.355			0.681
Higher SES, scores 1–3	53 (80)	288 (78)		28 (72)	306 (78)		144 (79)	196 (77)	
Low SES, scores 4–5	13 (20)	83 (22)		11 (28)	85 (22)		38 (21)	57 (23)	
Maternal education, yrs, n (%)			0.028			0.575			0.209
< 12	10 (15)	31 (8)		5 (13)	36 (9)		18 (10)	22 (9)	
12–15	33 (50)	248 (66)		26 (67)	251 (64)		108 (59)	172 (67)	
> 15	23 (35)	94 (25)		8 (21)	106 (27)		56 (31)	61 (24)	
Annual household income, US$, n (%)			0.122			0.240		0.526	
10,000	4 (6)	16 (4)		2 (5)	18 (5)		8 (4)	12 (5)	
10,000–49,000	5 (8)	67 (18)		10 (26)	61 (16)		26 (14)	45 (18)	
≥ 50,000	53 (85)	285 (77)		26 (68)	307 (80)		148 (81)	190 (77)	
Prepregnancy BMI, kg/m^2, n (%)			0.509			1.000			0.040
< 18.5, underweight	5 (8)	15 (4)		2 (5)	17 (4)		9 (5)	11 (4)	
18.5–24.9, normal weight	35 (53)	215 (58)		26 (67)	222 (56)		90 (49)	160 (63)	
25.0–29.9, overweight	16 (24)	77 (21)		6 (15)	86 (22)		43 (24)	48 (19)	
≥ 30, obese	10 (15)	66 (18)		5 (13)	68 (17)		40 (22)	36 (14)	
Crohn disease, n (%)	1 (2)	7 (2)	1.000	3 (8)	5 (1)	0.028	4 (2)	4 (2)	0.724
Ankylosing spondylitis, n (%)	0 (0)	2 (1)	NA	1 (3)	1 (0)	0.173	1 (1)	1 (0)	1.000
Psoriasis, n (%)	3 (5)	20 (5)	1.000	3 (8)	20 (5)	0.451	11 (6)	12 (5)	0.537
Psoriatic arthritis, n (%)	2 (3)	7 (2)	0.630	1 (3)	8 (2)	0.577	6 (3)	3 (1)	0.173
Nonspecified autoimmune disorders, n (%)	12 (18)	32 (9)	0.017	7 (18)	37 (9)	0.099	19 (10)	25 (10)	0.828
Prednisone, any during pregnancy, n (%)	45 (68)	192 (51)	0.012	21 (54)	211 (80)	0.985	91 (50)	144 (56)	0.181
Prednisone, ≥ 10 mg anytime during pregnancy, n (%)	22 (33)	69 (19)	0.006	14 (36)	76 (19)	0.015	42 (23)	48 (19)	0.278
Prednisone, ≥ 10 mg prior to 20 weeks' gestation, n (%)	20 (30)	63 (17)	0.010	14 (36)	69 (18)	0.006	37 (20)	45 (18)	0.479
Parity, n (%)			0.307			0.040			0.298
0	26 (39)	173 (46)		25 (64)	171 (44)		83 (46)	115 (45)	
1	31 (47)	138 (37)		11 (28)	154 (39)		75 (41)	93 (36)	
2 or more	9 (14)	62 (17)		3 (8)	68 (17)		24 (13)	47 (18)	
Planned pregnancy, n (%)	41 (63)	264 (75)	0.056	27 (71)	273 (73)	0.798	125 (71)	178 (74)	0.422
Periconceptional use of vitamins containing folic acid, n (%)	36 (55)	232 (62)	0.240	25 (64)	240 (61)	0.711	120 (66)	147 (58)	0.080
Previous preterm delivery, n (%)	15 (23)	26 (7)	< 0.001	3 (8)	36 (9)	1.000	17 (9)	24 (9)	0.980
Previous baby with IUGR, n (%)	4 (6)	6 (2)	0.048	3 (8)	7 (2)	0.052	4 (2)	6 (2)	1.000

* Using Hollingshead scoring criteria. RA: rheumatoid arthritis; OTIS: Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project; SGA: small for gestational age; SES: socioeconomic status; BMI: body mass index; IUGR: intrauterine growth restriction; NA: not applicable.

ation with the HAQ-DI categorical measure (HAQ-DI > 0.5) was similar (aRR 1.48); however, the 95% CI included the null value of 1 (0.95–2.23). In both models, prednisone use (≥ 10 mg prednisone anytime during pregnancy) was an independent significant predictor of preterm delivery (p = 0.001); however, prednisone use did not modify the association between HAQ-DI and preterm delivery in either model (Table 5).

The aRR for each 20-point increment in the PS or PGS were also significantly elevated at 1.18 (95% CI 1.20–1.38) and 1.23 (95% CI 1.05–1.45), respectively (Table 5). For SGA, after adjusting for concomitant Crohn disease, use of

Table 3. Unadjusted association of disease severity measures early in pregnancy in women with RA by pregnancy outcomes in the OTIS cohort (n = 440), 2005–2013. Values are median (IQR) unless otherwise specified.

Enrollment Scores	Overall, n = 440	Preterm Delivery, n = 66	Full-term Delivery, n = 373	p*	SGA n = 39	Non-SGA, n = 393	p*	Cesarean Delivery, n = 182	Vaginal Delivery, n = 255	p*
HAQ-DI, 0–3	0.25 (0–0.88)	0.50 (0.09–1.38)	0.25 (0–0.75)	0.008	0.63 (0–0.88)	0.25 (0–0.88)	0.472	0.38 (0.0–1.00)	0.25 (0–0.70)	0.030
Pain score, 0–100	20 (5–50)	30 (5–66)	20 (5–50)	0.162	30 (8–60)	20 (5–52)	0.147	20 (5–58)	20 (5–50)	0.173
Patient global scale, 0–100	15 (5–45)	30 (5–56)	15 (5–40)	0.012	25 (5–50)	15 (5–40)	0.104	15 (3–50)	15 (5–40)	0.894

* p using Wilcoxon signed-rank test. RA: rheumatoid arthritis; OTIS: Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project; IQR: interquartile range; SGA: small for gestational age; HAQ-DI: Health Assessment Questionnaire–Disability Index measured in early pregnancy for every unit (0–1) increase in HAQ score.

Table 4. Unadjusted association of functional disability in pregnant women with RA by pregnancy outcomes in the OTIS cohort (n = 440), 2005–2013. Functional disability was configured using HAQ-DI > 0.5. Values are n (%) unless otherwise specified.

Outcomes	Severe Disease, HAQ-DI > 0.5	None or Mild Disease, HAQ-DI ≤ 0.5	p*
Preterm delivery	32/159 (20)	34/280 (12)	0.024
SGA	20/158 (13)	19/274 (7)	0.046
Cesarean delivery	73/158 (46)	109/279 (39)	0.146

* p value using chi-square test. RA: rheumatoid arthritis; OTIS: Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project; HAQ-DI: Health Assessment Questionnaire Disability Index measured in early pregnancy; SGA: small for gestational age.

IVF, and gestational age at enrollment, the point estimates for all measures were elevated, but all CI included 1 except for HAQ-DI > 0.5 (aRR 1.81, 95% CI 1.01–3.33). For cesarean delivery, adjusting for maternal age, periconceptional use of vitamins containing folic acid, and gestational age at enrollment, the relative risks were modestly elevated for the HAQ-DI measures, but not for the other severity measures (all 95% CI included 1; Table 5).

In additional Poisson models in which the HAQ-DI and all covariates listed above were included plus either the PS or the PGS score, the predictive value of the models was not improved over and above the adjusted HAQ-DI score alone (data not shown).

To address the contribution of comorbidity with multiple autoimmune diseases, a subgroup analysis was conducted, restricting the analysis only to women with a diagnosis of RA (i.e., without any other coexisting autoimmune diseases, n = 355). The association between disease severity and preterm delivery remained statistically significant (aRR 1.74, 95% CI 1.26–2.40; data not shown).

DISCUSSION

Previous studies have assessed risk for adverse pregnancy outcomes and higher rates of cesarean delivery in women with RA, but were limited in their ability to address the contribution of disease severity with standard measures[5,6,7,8,9]. We found that irrespective of treatment, disease severity scores as measured by the HAQ-DI, PS, and PGS in early pregnancy were each significantly predictive of preterm delivery. However, the 3 severity measures were highly correlated, and a model with the addition of PS or PGS score did not improve the predictive value of the HAQ-DI score alone.

To our knowledge, this is the first study correlating

Table 5. Adjusted associations between disease severity measures in pregnant women with RA with pregnancy outcomes in the OTIS cohort (n = 440), 2005–2013.

Disease Severity Measures	Preterm Delivery*, n = 66/439		SGA**, n = 39/432		Cesarean Delivery†, n = 182/437	
	Crude RR‡ (95% CI)	aRR‡ (95% CI)	Crude RR‡ (95% CI)	aRR‡ (95% CI)	Crude RR‡ (95% CI)	aRR‡ (95% CI)
HAQ-DI, 0–3	1.75 (1.37–2.34)	1.58 (1.17–2.15)	1.23 (1.08–1.89)	1.31 (0.85–2.03)	1.17 (0.99–1.38)	1.15 (0.97–1.36)
HAQ-DI > 0.5	1.66 (1.06–2.58)	1.48 (0.95–2.23)	1.82 (1.01–3.29)	1.81 (1.01–3.33)	1.18 (0.94–1.48)	1.04 (0.91–1.42)
PS, /20 units	1.19 (1.03–1.39)	1.18 (1.20–1.38)	1.19 (0.98–1.44)	1.21 (1.00–1.47)	1.05 (0.98–1.14)	1.05 (0.98–1.13)
PGS, /20 units	1.27 (1.09–1.48)	1.23 (1.05–1.45)	1.22 (0.99–1.51)	1.22 (0.99–1.51)	1.03 (0.95–1.12)	1.03 (0.95–1.12)

* Adjusted for previous preterm delivery, maternal age at delivery, prednisone (≥ 10 mg anytime during pregnancy), maternal education, and gestational age at enrollment. ** Adjusted for Crohn disease, *in vitro* fertilization, and gestational age at enrollment. † Adjusted for maternal age, periconceptional use of vitamins containing folic acid, and gestational age at enrollment. ‡ Using modified Poisson regression models. RA: rheumatoid arthritis; OTIS: Organization of Teratology Information Specialists Autoimmune Diseases in Pregnancy Project; SGA: small for gestational age; crude RR: crude relative risk; aRR: adjusted relative risk; HAQ-DI: Health Assessment Questionnaire–Disability Index measured in early pregnancy — for the continuous HAQ-DI, for every unit (0–1) increase, functional disability was configured using HAQ-DI > 0.5; PS: pain score; PGS: patient global score. Prednisone (≥ 10 mg anytime during pregnancy) was an independent predictor of preterm delivery (p = 0.009), but not for SGA.

HAQ-DI (collected from maternal interview early in pregnancy) with pregnancy outcomes in women with RA. The only other published study[3] examining disease severity with pregnancy outcomes in women with RA used the DAS28. In large observational studies, it is not always feasible to collect clinical measures. Thus, the HAQ-DI is an alternate useful measure of disease severity.

Women in our study cohort had milder disease, as shown by the low median HAQ-DI of 0.25 in contrast to other studies that have reported median HAQ-DI values of 0.69 and 0.90[2,17]. This difference could be a result of a number of factors. Our cohort consisted primarily of younger women of reproductive age who may have had a less severe form of the disease, or a shorter duration of disease, or may have been actively treated for RA achieving good disease control. The version of the HAQ that we used did not include the use of aids and devices, the addition of which could have raised the median HAQ-DI. However, use of aids is usually associated with more debilitating disease than was typical of our study participants.

In our cohort of women with RA, we found similar rates of adverse pregnancy outcomes and cesarean delivery, as previously reported[6,7,8,33,34]. However, the rates of preterm delivery and SGA were lower than those reported recently by Langen, *et al,* where preterm delivery, SGA, and cesarean delivery rates were 28%, 18%, and 33%, respectively[35]. The higher rates of SGA and cesarean delivery could have occurred because of the demographics of the study participants.

An association was found between disease severity (continuous HAQ-DI), as measured in early pregnancy, and an increased risk for preterm delivery among women with RA. We found less evidence for SGA where only the HAQ-DI categorical measure was associated with smaller birth size and found no association with disease severity (continuous or categorical) for cesarean delivery. In contrast, de Man, *et al*, who examined disease severity and pregnancy outcomes in women with RA (using DAS28), found that disease activity measured in the third trimester was associated with a significant reduction in birth weight, whereas the same measures collected earlier in pregnancy were not associated after adjustment for confounding[11]. Our findings may differ from de Man, *et al* because of the use of a different measure of disease severity (HAQ-DI vs DAS28), and/or a different measure of outcome (adjusted mean birth weight vs SGA).

Additionally, de Man, *et al* reported a significant association between prednisone use and preterm delivery, independent of disease severity[11]. Similarly, prednisone use (≥ 10 mg prednisone equivalent in current pregnancy) in our study was also independently associated with preterm birth. We considered the possibility that prednisone may be simply a marker of more severe disease[36]. However, it did not confound the association between disease severity and preterm delivery, consistent with the findings by de Man, *et al*.

The association of disease severity and preterm delivery is biologically plausible. The multiple possible pathophysiologic mechanisms that may be involved in the increased risk of pregnancy outcomes have been extensively reviewed in the literature. Increased estrogen during pregnancy, HLA-DQ–induced immune suppression, and glycosylation could be potential mechanisms by which the severity of the disease increases the risk for adverse pregnancy outcomes[37,38,39,40,41]. It is difficult to determine the contribution of other coexisting autoimmune diseases to the risk of preterm delivery. For this reason, we carried out additional analyses, restricting the sample to women with only a diagnosis of RA. We found that the adjusted association between disease severity and preterm delivery was similarly significantly elevated.

Our study was limited by some methodological issues. First, our study population was a volunteer sample. Thus, our findings might not be generalizable to all women with RA. Second, the HAQ-DI has only recently been used and was not validated until 2007[18]. However, there have been subsequent studies that have used the HAQ in pregnancy, either alone or in combination with other clinical or laboratory variables[16,20]. Third, we included women with previous pregnancies. This could be a potential selection bias because the choice to initiate the current pregnancy could be a result of prior good pregnancy course or good pregnancy outcome. Medication-specific analyses were not conducted as this was outside the scope of this paper and this analysis did not evaluate the contribution of any specific medications, other than prednisone, that were used. Fourth, we had women with coexisting autoimmune diseases. It was therefore difficult to know the contribution of pain and global scale from RA alone. Finally, although the HAQ-DI measure in early pregnancy was predictive of preterm delivery, it may well be that the HAQ-DI in our population did not represent current disease activity, but rather disease-related disability that may have occurred prior to pregnancy. Parity could have an effect on pregnancy outcomes; however, when we examined its effect, we found on bivariate analysis that except for SGA, parity was not significantly associated with either preterm delivery or cesarean delivery. Additionally, this association lost significance when the model was adjusted for other variables.

The finding of our study that among women with RA, disease severity is predictive of preterm delivery, suggests that better disease management early in the pregnancy could improve pregnancy outcomes. Further analysis is being undertaken to address how change in disease severity/activity over the course of pregnancy affects pregnancy outcomes.

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