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RESEARCH ARTICLE

Maternal Cytokines and Disease Severity Influence Pregnancy Outcomes in Women with Rheumatoid Arthritis

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Abstract

Objectives: To assess the influence of maternal cytokine levels, disease activity and severity on preterm delivery, SGA and cesarean delivery in pregnant women with RA. **Methods:** A prospective study in 47 pregnant women with RA and 22 healthy pregnant controls. The main outcome measures were birth weight in relation to maternal serum levels of interleukin-6 (IL-6), interleukin-10 (IL-10) and RA activity and severity at three different time points: preconception and during the first and third trimesters. **Results**: During the third trimester, IL-10 was detectable in 23.4% of patients with RA, IL-6 in 76.6%. Mean birth weight born to mothers with RA was higher when IL-10 level was high compared with low (P=0.001), and lower when IL-6 was high compared with low (P=0.035). Also increase in DAS-28 (in 60.1%, P=0.001), HAQ – DI (in 87.5%, P=0.013), and PS (56.9 ± 11.4, P=0.003) associated with increased risk for SGA. High PGS was associated with unfavorable pregnancy outcome (preterm, SGA, and C.S).**Conclusion:** High maternal IL-10 levels are associated with higher birth weight and high IL-6 levels are associated with lower birth weight (SGA). Among women with RA, disease activity and severity are predictive of unfavorable pregnancy outcomes suggesting that better disease management early in the pregnancy could improve pregnancy outcomes.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, autoimmune disease characterized by destructive synovitis and may affect the internal organs. The estimated prevalence of RA is about 0.5 -1.0% in adults [(1)].

Studies of autoimmune rheumatologic disorders suggest that changes in cytokine levels are related to the pathogenesis of these disorders [(2)]. It may be that increased cytokine levels that are associated with the clinical manifestations of RA, maybe causally related to adverse pregnancy outcomes. Cytokines play an important role in inflammation and host defense; alterations of these levels could have potentially deleterious effects on the placenta, thereby affecting the fetus [(3)].

Rheumatoid arthritis (RA) is an autoimmune disease that has a variable course during pregnancy. While previous studies showed that pregnancy has beneficial effect, with 50-70% reduction in disease activity, others have reported no improvement or even worsening of the disease during pregnancy especially with repeated gestation [(4)].

Pregnant women with RA 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. However, little is known about the extent to which disease severity contribute to adverse pregnancy outcomes [(5)].

Aim

To assess the influence of maternal cytokine levels, disease activity and severity on preterm delivery, SGA and cesarean delivery in pregnant women with RA.

Materials and methods

A prospective study in pregnant women with RA was carried out at Rheumatology & Rehabilitation and Obstetrics & Gynecology Departments of Zagazig University Hospitals in Egypt, and Najid Consulting Hospital in KSA during a period from August 2012 to December 2014.

A total of 47 RA pregnant women (all teratogenic RA medications were stopped at least 3 months preconception) and 22 healthy pregnant women (without an adverse obstetric history) participants were enrolled in the study after a written consent.

Information was obtained at preconception (range of 3 months – 1 year before conception) and during the first trimester (range 8-12 weeks of gestation) and the third trimester (range 28-34 weeks of gestation).

All subjects were subjected to:

- Complete history taking included maternal age, estimated date of delivery, gravity, parity, gestational age at enrollment and at delivery, planned pregnancy, use of IVF in this pregnancy, use of folic acid supplements and pervious preterm delivery or IUGR.
- Prednisone use recorded and classified into ≥ 10 mg of prednisone and < 10 mg of prednisone during pregnancy.
- General and local musculoskeletal examination
- RA women met the 2010 ACR-EULAR CLASSIFICATION CRITERIA for Rheumatoid arthritis [(6)].

- Disease activity:

At every time point RA disease activity score (DAS 28) was calculated by examining 28 joints using three variables number of swollen joints, number of tender joints and serum C-reactive protein (CRP) [(7)].

- 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). 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. HAQ-Dl 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 [(8)]. 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 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 [(9)].

- CRP and cytokines

CRP levels were directly measured using the Tina-Quant CRP Immunological Test System (Roche Diagnostics, Almere, and The Netherlands). After centrifugation, all samples were frozen at -80°C until assayed. Serum levels of IL-10, and IL-6 were determined using the immunoassay system, IMMULITE 1000 (Siemens Healthcare Diagnostics, Breda, The Netherlands). The intra-run/inter-run mean ± variation coefficient was: IL-10, 27.7 ± 4.6%/23.35 ± 5.4%; IL-6, 105.6 ± 4.9%/87.67 ± 6.1%. The lower limit of quantification was IL-10, 5.0; IL-6, 2.0. All cytokine levels are presented in pg./ml.

- Pregnancy outcome measures

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 (vaginal or cesarean) [(10)].

Eligibility criteria for enrolled patients were a singleton pregnancy without major fetal anomalies, known chromosomal abnormalities or other autoimmune diseases, and gestational age of 28-40 weeks, and reliable gestational dating consisting of a first trimester crown to rump length or a last menstrual period confirmed by an ultrasound performed prior to 20 weeks gestation.

Patients with preterm delivery before 28 weeks, pregnancy induced hypertension, chronic diabetes mellitus, and chronic renal disease were excluded from study.

Ultrasound biometry measurements including the biparietal diameter (PBD), head circumference (HC), abdominal circumference (AC), femur length (FL) were assessed for each fetus. The estimated fetal weight (EFW) was obtained by Hadlock's formula ($\log_{10}$ [EFW] =1.3596+ 0.0064 [HC] + 0.0424 [AC] + 0.174 [FL] + 0.00061 [BPD X AC] – 0.00386 [AC X FL]) [(11)]. The overall EFW percentile was computed according to William's tables, which are derived from a large population-based study referencing birth weight percentiles by gestational age and sex [(12)]. Also umbilical artery Doppler (S/D ratio) on ultrasound examination was done and any patient with abnormal umbilical artery Doppler was excluded (to exclude associated placental pathology).

The subjects were assigned to 1 of 2 groups: (1) EFW less than the 10^{th} percentile, and (2) EFW greater than the 10th percentile.

Participants in the study were followed up clinically with serial ultrasound assessments of fetal growth for the duration of pregnancy at intervals that varied between 2 and 4 weeks. These ultrasounds were conducted in accordance with the routine management of these high-risk pregnancies.

The assignment into 1 of the 2 groups was based on the last ultrasound examination prior to delivery, which in no case was more than 3 weeks prior to birth, and the mean time between last ultrasound and delivery was 7-21 days.

At delivery, the course, taken medication, and mode of delivery were recorded and all the newborns birth weight and Apgar scores (1 &5 min.) were estimated and score of < 7 at 5 min. was used as proxy for moderate or severe hypoxia and neonatology department admission.

The collected data were coded and analyzed using SPSS version 16.0 at 95% confidence interval, with level of significance <0.05, and 80% power of the study. For qualitative data, mean, median, standard deviation (SD), and range for its summarization. While F test (ANOVA test), post hoc (ducan test), student t test, Kruskal-Wallis test, Mann–Whitney test for their analysis.

Results:

In this study, 47 RA pregnant women (completely compensated at least 3 months preconception) and 22 healthy pregnant were enrolled. The participant's data displayed characteristics of women with RA and healthy controls. Mean maternal age was 31.1 years and mean RA disease duration was 6.4 years. Medication use was restricted to prednisone. 36.2% used < 10 mg and 63.8% used ≥ 10 mg prednisone. There was significant statistical difference ($P < 0.05$) between RA and reference groups regarding previous preterm delivery and previous IUGR (Table 1).

The IL-6 was detectable in 76.6% (n=36) and IL-10 was detectable in 23.4% (n=11). There was significant difference regarding levels of CRP, and IL-6 at study time points ($P < 0.05$) between RA women and healthy women. In addition, IL-10 showed significant increase ($P < 0.05$) between RA women and healthy women (Table 2).

There was significant increase ($P < 0.05$) in both DAS – 28 and HAQ- DI in study time points reflecting unfavorable effect of pregnancy on activity and severity parameters of RA. More likely marked in 3rd trimester (Table 3).

The women who delivered preterm babies or an infant with SGA compared to women who delivered full term or non-SGA infants were more likely to have used ≥ 10 mg prednisone. High IL-10 was associated with higher birth weight (Non-SGA). High IL-6 was associated with lower birth weight (SGA). This indicated that increase in Das-

28, HAQ – DI, PS and PGS was associated with increased risk for unfavorable pregnancy outcome (preterm, SGA, and C.S) (Table 4). In Figs 1, 2, 3 and 4 there was increased preterm delivery and delivery by C.S. especially with increased RA activity.

Table (1): Patient and pregnancy characteristics:

	Rheumatoid group No = 47	**Reference group healthy pregnant No = 22**	**P**
Maternal age (y)	31.1 ± 1.4 (30 - 35)	32.7 ± 0.9 (31 - 35)	0.741
Gestational age (w)	37.6 ± 2.4 (33 -40)	38.7 ± 3.4 (35 - 40)	0.853
Age at delivery (y)	32.1 ± 1.1 (32.1 ± 35)	33.1 ± 1 (31 - 36)	0.872
RA duration at delivery (y)	6.4 ± 1.4	-	
Parity: 0 1 2+	10 (21.3) 23 (48.9) 14 (29.8)	4 (18.2) 10 (45.5) 8 (36.4)	0.641
Use of IVF	5 (10.6)	1 (4.5)	0.982
Use of folic acid	39 (82.9)	14 (63.6)	0.491
Use of prednisone < 10 mg ≥ 10 mg	 17 (36.2) 30 (63.8)	 -	 -
Previous preterm delivery.	10 (21.3)	0(0.0)	0.022
Previous IUGR	8 (17.0)	0(0.0)	0.041
IVF= in vitro fertilization **IUGR= intrauterine growth retardation**			

Table (2) CRP, cytokines levels at time points in study and reference groups:

	Preconception	**1st trimester**	**3rd trimester**	**P**
CRP in RA (**mg/L)**	6.9 ± 8.1 (1-24)	12.8 ± 14.3 (1 - 40)	15.7 ± 12.2 (6 – 48)	0.001
CRP in control (**mg/L)**	1 ± 0.5 (0.5 – 4)	1 ± 1.4 (0.5 - 5)	2.6 ± 1.5 (2 – 7)	0.433
P	0.052	0.001	0.001	
IL-6 in RA (**pg./mL)**	4.6 ± 2.9 (1 - 10)	4.7 ± 3.2 (1.5 – 11.5)	3.6 ± 3.3 (1 – 12.8)	0.001
IL-6 in control (**pg./mL)**	2.3 ± 0.6 (2 - 6)	1.4 ± 1.3 (0.5 – 4)	2.2 ± 3.2 (2 - 6)	0.532
P	0.001	0.042	0.051	
IL-10 in RA (**pg./mL)**	8.1 ± 2.1 (5.5 – 11.5)	8.5 ± 2.1 (5.1 – 9.5)	7.1 ± 1.7 (5.1 – 9.5)	0.114
IL-10 in control (**pg./mL)**	2.2 ± 3.2 (1 - 8)	0.7 ± 1.3 (0.5 - 4)	6.8 ± 4.0 (1 – 11)	0.092
P	0.001	0.001	0.793	
CRP= C reactive protein **IL-6=Interleukin-6** **IL-10= Interleukin-10**				

Table (3): RA disease activity and severity at time points in study group:

	Preconception	**1st trimester**	**3rd trimester**	**P**
DAS – 28	2.9 ± 0.6	3.2 ± 0.6	3.6 ± 0.7	0.074
Low < 3.2	38 (80.8)	26 (55.3)	19 (40.4)	0.001
Intermediate 3.2-5.1	9 (19.1)	13 (27.7)	16 (34.5)	0.002
High > 5.1	0 (0.0)	8 (17.0)	12 (25.6)	0.001
HAQ- DI	0.5 (0.1 – 1)	0.7 (0.1 - 1.5)	0.8 (0.3 - 2)	0.434
< 0.5	29 (61.7)	19 (40.4)	18 (38.3)	0.023
> 0.5	18 (38.3)	28 (59.6)	29 (61.7)	0.031
PS	24.8 ± 1.6	37.3 ± 1.7	47.6 ± 20.4	0.002
PGS	20.6 ± 12.2	30.4 ± 11.7	44.2 ± 15.8	0.001

DAS= disease activity score
HAQ- DI= Health Assessment Questionnaire-Disability Index
PS= pain score
PGS= patient's global scale

Table (4): Effect of prednisone use, duration of RA, cytokines disease activity and severity on pregnancy outcomes:

	Full term No = 30	Preterm No = 17	P	Non SGA No = 31	SGA No = 16	P	Vaginal No = 35	C.S No = 12	P
-duration of RA	6.2 ± 1.6 (4-7)	6.8 ± 0.28 (6.5 - 8)	0.69	5.3 ± 1.1 (4 - 7)	7.6 ± 0.2 (8 – 7.5)	0.001	5.9 ± 1.5 (4 – 7.5)	6.7 ± 1.3 (4.5 - 8)	0.012
-prednisone < 10mg ≥ 10 mg	16 (53.3) 14 (46.7)	5 (29.9) 12 (70.6)	0.001	16 (51.6) 15 (48.4)	1 (6.3) 15 (93.8)	0.001	15 (42.9) 20 (57.1)	2 (16.7) 10 (83.3)	0.172
-CRP mg/L	8.9±1.9 (6-24)	19.9 ±2.9 (12-48)	0.131	9.7±1.2 (6-11)	23.4 ±10.3 (12-48)	0.001	8.7±1.5 (6-11)	21.2 ±5.4 (12-48)	0.001
-IL 6 pg./mL	2.3± 1.2 (1-6.8)	5.7 ±2.2 (3.8-12.8)	0.180	1.9 ±1.2 (0.5-5.7)	7.6 ±2.1 (5-12.8)	0.035	8.9±1.7 (6.10.6)	8±204 (5.88-12.8)	0.271
-IL 10 pg./mL	8.01±0.6 (6.1-11.5)	5.9±0.03 (5.5-8.45)	0.011	7.9±1.4 (6-9.5)	6.2±2.8 (5.4-8)	0.001	7.9±1.5 (5.5-9.6)	7±1.9 (5.4-9.5)	0.183
-DAS -28 < 3.2 3.2 – 5.1 > 5.1	 18 (60) 11 (36.7) 1 (3.3)	 2 (5.9) 5 (29.4) 11 (64.7)	 0.001	 19 (61.3) 6 (19.4) 6 (19.4)	 0 (0.0) 10 (62.5) 6 (37.5)	 0.001 0.012 0.043	 16 (45.7) 11 (31.4) 8 (22.8)	 3 (15.0) 5 (41.6) 4 (33.3)	 0.001 0.001 0.752
-HAQ – DI < 0.5 > 0.5	 13 (43.3) 17 (56.7)	 5 (29.9) 12 (70.6)	 0.221	 16 (51.6) 15 (48.9)	 2 (125) 14 (87.5)	 0.013	 14 (40) 21 (60)	 4 (33.3) 8 (66.7)	 0.741
-PS	40.3±12.3 (20-60)	65.2 ±13.8 (50-80)	0.033	31.3 ±16.5 (10-60)	56.9 ±11.4 (40-80)	0.003	36.6±14.1 (20-50)	55.8 ±9.9 (50-80)	0.105
-PGS	31.4 ± 10.3 (20-50)	47.3 ± 12.3 (35-70)	0.001	37.9±8.8 (20-64)	48.7±15.8 (30-70)	0.004	29.7±9.4 (20-34)	47.9±13.7 (30-70)	0.001

SGA=small for gestational age
CRP= C reactive protein
IL-6=Interleukin-6
IL-10= Interleukin-10
DAS= disease activity score
HAQ- DI= Health Assessment Questionnaire-Disability Index
PS= pain score
PGS= patient's global scale

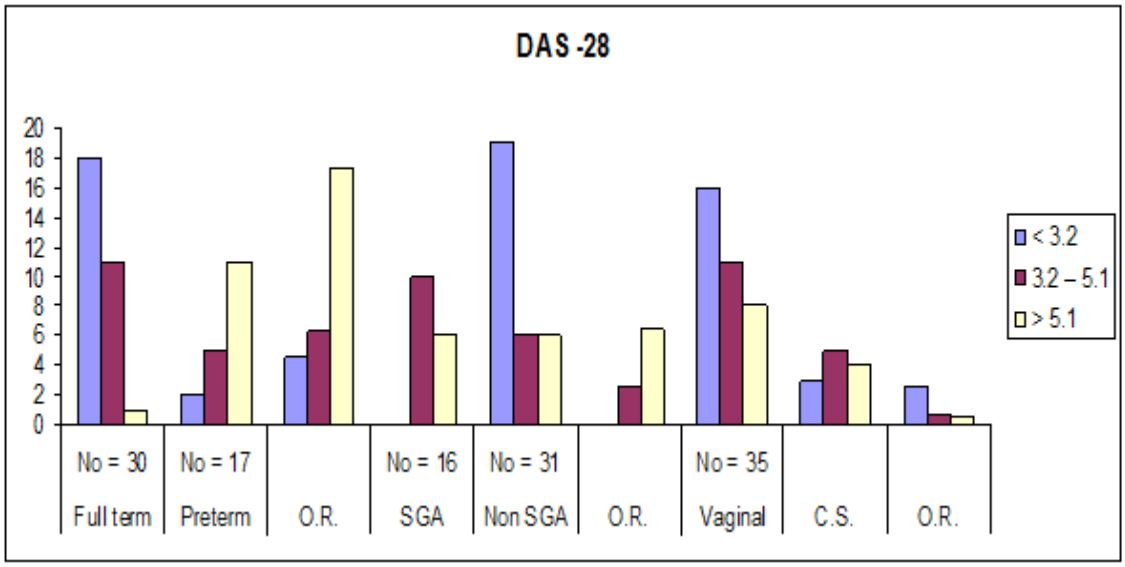

Fig1: Showing effects of rheumatoid activity on fetal outcome

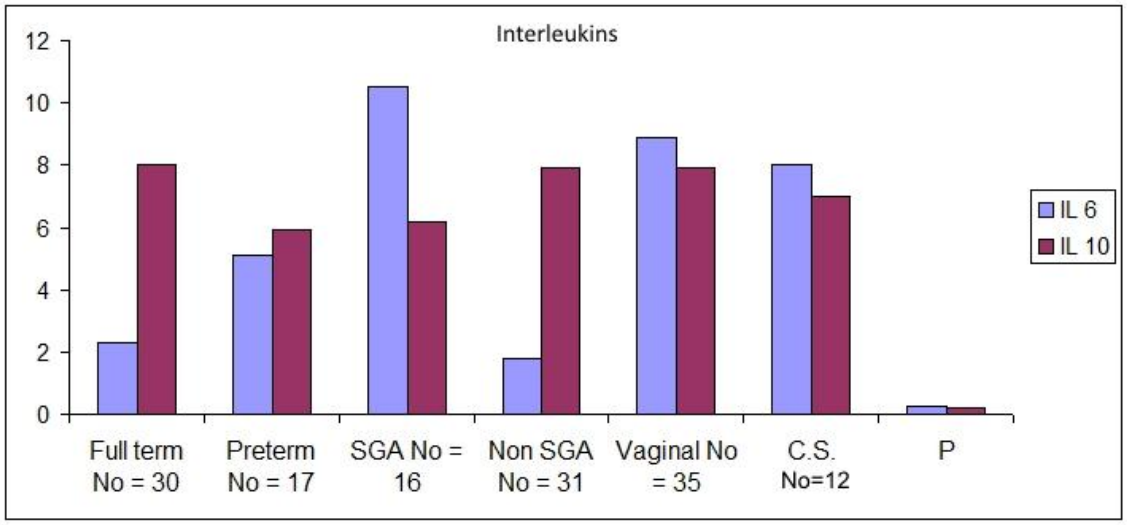

Fig2: Showing effects of cytokines on fetal outcome

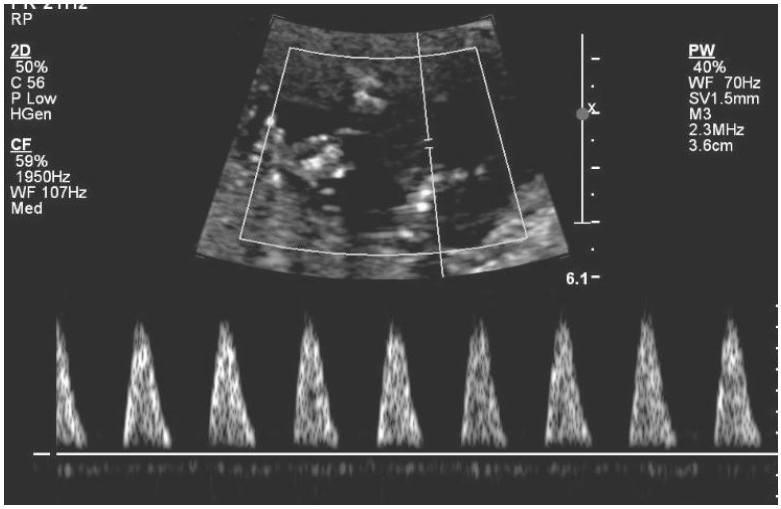

Fig3: patient aged 36 year developed severe fetal distress with loss of end diastolic volume at pulsed Doppler of umbilical cord at 34 weeks and delivered by C.S

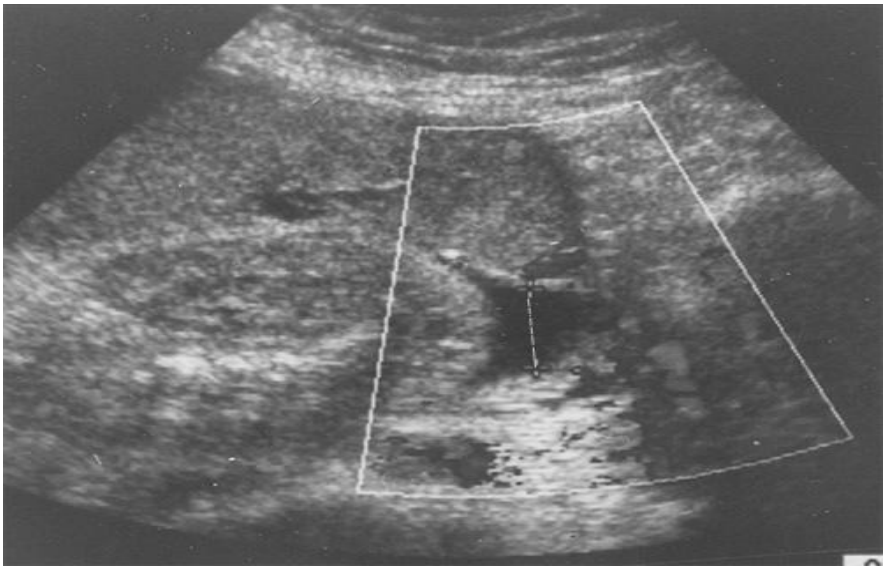

Fig4: Patient with oligohydramnios (1.7 cm pocket) at 28 weeks, which showed persistent fetal bradycardia and delivered by C.S at 34 weeks

Discussion

Prior studies hypothesized that high maternal serum cytokine levels influence fetal growth in pregnant women with RA. In our prospective study, we observed that both IL-10 and IL-6 levels influence fetal growth in pregnant women with RA. During pregnancy, high IL-10 levels are associated with higher birth weight and high IL-6 levels are associated with lower birth weight [(12)].

Unlike most studies, our study focused on not only the last trimester of the pregnancy, but also preconception and the first trimester, emphasizing the importance of cytokine levels at the beginning of pregnancy.

To evaluate the effects of high cytokine levels, we studied an RA population that is often characterized by high serum cytokine levels. Even though the previous studies indicates that different diseases may be associated with specific cytokine profiles during pregnancy [(13)].

A comparison group of 22 healthy pregnant women were included in the study. The main purpose of this reference group was to observe maternal serum cytokine levels in normal pregnancies. The number is too small to draw conclusions.

Prior studies revealed high RA disease activity is associated with lower birth weight and postnatal catch-up growth in the offspring [(14)]. There is a theory that high IL-10 levels are responsible for the improvement in RA during pregnancy [(15)]. One could speculate that the effect of IL-10 levels in birth weight is not related to their effect on placentation, but acts indirectly by reducing maternal disease activity during pregnancy. However in our study, high IL-10 levels were not associated with an improvement in RA during pregnancy (P=0.11) but associated with increased number of patients with delivery of normal birth weight outcomes (P=0.001).

Significant association was reported between RA disease activity measured by DAS-28 with preterm delivery (in 64.7%, P=0.001), and SGA (in 37.5%, P=0.043), and. This is consistent with the findings of de Man et al. [(16)].

Additionally, de Man et al reported significant association between prednisone use and preterm delivery, independent of disease severity [(16)]. In our study there was association between prednisone ≥ 10 mg use and preterm delivery (70.6%, P=0.001), and SGA (93.8%, P=0.001). We considered the possibility that prednisone may be simply a marker of more severe disease.

In this study there was significant higher rates of cesarean delivery with RA disease duration (P=0.01), and increased RA severity (high PGS 47.9 ± 13.7, P=0.001). Previous studies showed increased of risk for unfavorable 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 [17].

Women in our study had severe disease as shown by levels of HAQ DI, PS, PGS in contrast with previous studies reported median HAQ-DI values of 0.69 and 0.90 [18]. Women in our study have slightly less severe form disease of lower median HAQ-DI 0.5, 0.7, 0.8 respectively at study time points but the number of women in the third trimester had showed significant increase (in 61.7%, P=0.03) when compared with the number of first trimester . This difference could be explained by our study consisted of younger women of reproductive age who may have had a less severe form of disease, or a shorter duration, or may have been actively treated for RA achieving good disease control.

In our study, we found nearly similar rates of unfavorable pregnancy outcomes, preterm delivery, SGA and Cesarean delivery (36%, 34%, and 25% respectively) as reported by Langen, et al, where preterm delivery, SGA and Cesarean delivery rates were 28%, 18% and 33% respectively [19]. In contrast to other previous studies with lower rates of preterm delivery and SGA. [20, 21, 22, 23]. This difference could have occurred because of the demographics of the study participants.

An association was found between disease severity when measured by HAQ-DI (in 48.9%, P=0.01) and increased risk of SGA, PS (56.9±11.4, p=0.003) and increased risk of preterm delivery and SGA, PGS (47.3±12.3, p=0.001) and increased risk of preterm delivery, SGA and CS.

Association of disease severity and preterm delivery may be to 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 [24, 25, 26].

Conclusion

High maternal IL-10 levels are associated with higher birth weight and high IL-6 levels are associated with lower birth weight (SGA). Among women with RA, disease activity and severity are predictive of unfavorable pregnancy outcomes suggesting that better disease management early in the pregnancy could improve pregnancy outcomes.

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