ORIGINAL RESEARCH

Adverse Impact of Rheumatoid Arthritis on Pregnancy Outcomes: A Saudi Arabia Prospective Multicenter Study

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Background: Rheumatoid arthritis (RA) is associated with adverse pregnancy outcomes and postpartum complications, especially with severe disease activity.

Objective: The current study aimed to compare the pregnancy outcomes in patients with RA and healthy controls as well as to assess the impact of disease-related variables, medications and disease activity on pregnancy and neonatal-related outcomes in the Saudi population.

Methods: This prospective multicenter study included pregnant female patients with RA from three tertiary centers in Saudi Arabia. The demographics, disease activity scoring (DAS28-CRP), medication before and during pregnancy, pregnancy-related outcomes, and complications in comparison to age-matched healthy female controls were noted.

Results: A total of 77 pregnant patients with RA and 250 healthy age-matched pregnant controls were included in the study. A total of 67.53% were in remission before conception (DAS28CRP ≤ 2.6), and 81.8% of pregnancies were planned. Age of conception, preterm labor, neonatal intensive care unit (NICU) admission and low birth weight were statistically significant (p <0.05) and higher in RA patients than in healthy controls. Longer disease duration (p <0.001), and high C-reactive protein and erythrocyte sedimentation rate levels before conception (p ≤0.001) were statistically associated with preterm NICU admission. There was statistically significant association between mild (p = 0.015) or moderate to severe DAS28-CRP (p = 0.001) and RA patients regarding pregnancy outcomes. The classification table obtained from the logistic model showed patients with mild and moderate-severe DAS28-CRP have significantly high chances of having an adverse pregnancy outcome.

Conclusion: RA has a negative impact on pregnancy-related outcomes. Higher disease activity is considered a major risk; thus, tight disease control should be aimed. Planned pregnancy follow-up is associated with better pregnancy outcomes.

Keywords: rheumatoid arthritis, pregnancy, disease activity

Key Points

1. This study proposed, for the first time, to medical records review with follow-up to prospectively study pregnancy outcomes in Saudi patients with RA from three large tertiary hospitals.
2. RA patients should plan their pregnancies in terms of pregnancy timing, therapy modifications, and prenatal and postnatal follow-ups to reduce undesirable outcomes.
3. Despite the optimal management of disease activity during pregnancy, RA patients in remission harbor the risk of preterm labor with low birth weight and frequent neonatal newborn intensive care unit admission.

Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease that predominantly affects the skeletal system and connective tissues. RA usually targets women of childbearing age.[1] Women might avoid getting pregnant for fear of any adverse effect on their pregnancy such as the newborn might inherit the disease or medications for RA might negatively impact pregnancy outcome.[2]

It has long been known that RA symptoms might improve during pregnancy with variable percentages, but only a few studies used an objective disease activity score of 28-joint count C reactive protein (DAS28-CRP) to prove this assumption.[3] The relationship of disease control in Caucasian RA patients during pregnancy has a favorable outcome.[4] However, high disease severity is frequently associated with adverse pregnancy outcomes, such as size of the gestational newborns, preterm labor, increased number of cesarean sections, and pre-eclampsia with a controversial result.[1,2,5]

Recent data suggest that infants born small for gestational age and/or prematurely carry a higher risk for short- and long-term complications, ranging from higher rates of neonatal intensive care unit (NICU) admissions to adulthood morbidities.[6,7] The impact of RA on pregnancy and vice versa has not yet been extensively highlighted in different ethnicities such as the Saudi population. The current study aimed to assess the impact of RA on pregnancy and neonatal outcomes in the Saudi population in comparison to healthy controls and to study the effect of disease-related variables, medications and disease activity on pregnancy and neonatal-related outcomes.

Materials and Methods
Study Design

The present study was conducted at three tertiary centers in Saudi Arabia, Prince Sultan Military Medical City (PSMMC) in Riyadh, King Fahad Hospital in Jeddah, and Al-Hada Armed Forces Hospital in Taif. This was a multicenter case-control prospective study in the Saudi population. The primary outcome was to assess the effect of RA on pregnancy, primarily the obstetric complications and fetal outcomes, in comparison to healthy age-matched pregnant women. The secondary outcome was to assess the impact of disease-related clinical and laboratory variable, medications and disease activity (using DAS28-CRP) on pregnancy outcomes.

Study Population

Patients with RA who were following up in the rheumatology clinics from January 2018 to January 2020 were recruited from three tertiary hospitals. Participants aged >18 years meeting the following inclusion criteria were enrolled: patients should be pregnant with RA before the gestational week of 12, fulfilling the ACR/EULAR 2010 criteria for RA,[8] on regular follow-up visits at least every 2 months in rheumatology clinic, with at least one measured DAS28-CRP done by Rheumatologist periconceptional, first, second and third trimester during follow-up, on medication with conventional synthetic disease modifying antirheumatic drugs (csDMARDs) and/or biological DMARDs (bDMARDs) or targeted synthetic DMARDs (tsDMARDs), and following up at Rheumatology clinic in the three tertiary hospitals. The inclusion criterion for the controls was age-matched healthy pregnant women without comorbidities.

The study exclusion criteria were any major comorbidity known to affect the pregnancy outcome in both groups, such as overlap with other rheumatic diseases, diabetes mellitus, hypertension, chronic renal disease, ovarian surgery, uterine anomalies, prior chemotherapeutic treatment of ectopic pregnancy, prior exposure to known or possible ovary-toxic medications, and twin pregnancy.

Methods

Participants in both groups underwent full history taking including clinical and laboratory assessment via direct interview during regular follow-up at rheumatology clinic for RA patients and prenatal care clinics for healthy controls. Data were collected in the research room or the clinic at the time of routine follow-up with the help of a research assistant, to report if the pregnancy was planned by both patient and rheumatologist with medication modification, or occurred without a planned protocol, patient physician protocol defined as prior disease activity control and medication adjustment before conception.

Laboratory variables included measurements of levels of Rheumatoid factor (RF), anti-cyclic citrullinated peptide antibodies (anti-CCP Abs) using the chemiluminescence microparticle immunoassay (CMIA), erythrocyte sedimentation rate ESR using the Westergren method, and CRP using the enzyme-linked immunosorbent assay (ELISA) technique.

Pregnancy outcomes in both groups were reported, including obstetric complications preeclampsia, gestational diabetes, preterm birth which defined as Preterm or premature birth refers to a delivery that occurs between 20 and 37

weeks of gestation,[9] elective termination of pregnancy. Fetal outcomes included Low birth weight (LBW) Less than 2500 grams,[10] congenital anomalies, NICU admission, stillbirth, live birth. For each live birth, the age of gestation was assessed, and any reported congenital anomalies were noted. Disease activity was assessed using the DAS28-CRP score[11] and recorded before and during pregnancy at the follow-up visits every trimester. Medications including anti-inflammatory or immunosuppressant drugs before and during pregnancy were also documented.

Ethical Approvals

This study complied with the Declaration of Helsinki and was approved by the local ethics research committees of Prince Sultan Military Medical City (PSMMC) in Riyadh (HP-01-R079), Al-Hada Armed Forces Hospital (H-02-T-078), and King Fahad Hospital in Jeddah (H-02-J-002). Written informed consent was obtained from all the patients and controls.

Statistical Analysis

Data were entered and analyzed using IBM SPSS statistics software for Windows, version 26.0 (Armonk, NY: IBM Corp). The data were represented as the mean and standard error of the mean (SEM) for quantitative variables. Frequencies and percentages were reported for the qualitative variables. The Welch t-test was used to observe the mean differences between the two groups. Welch one-way ANOVA was applied to compare the mean differences between more than two groups. Pearson chi-square and Fisher's exact tests were used to find associations between the qualitative variables (various parameters between pregnancy cases in RA and pregnancy healthy controls and RA pregnancy-related outcomes with smoking, medications used during pregnancy and disease activity scoring at conception). Statistical significance was set at $p < 0.05$. Binary logistic regression analysis. The categorical dependent variable was adverse pregnancy outcome (Yes, No). Value of model chi-square and Hosmer–Lemeshow was significant at 5% level of significance confirming that the fitted model was appropriate.

Results

A total of 77 pregnant women with RA and 250 healthy pregnant controls were recruited for the study. The mean age of the participants at conception was 32.78 ± 0.69 years for RA patients and 30.32 ± 0.84 for controls, for RA patient's disease duration was 9.16 ± 0.55 years. The majority (67.53%) of the patients were in remission before conception (DAS28-CRP ≤ 2.6), and 81.8% of pregnancies were planned by both patients and the consulting rheumatologists with medication modification. The demographic data of the study group are illustrated in Table 1.

Table 1 Demographics and Clinical Data of Rheumatoid Arthritis Patients

RA Group (n = 77)	Data
Age at pregnancy[¥], mean ± SEM, years	32.78 ± 0.69[¥]
Age of disease onset[¥], mean ± SEM, years	26.49 ± 0.82[¥]
Duration of disease[¥], mean ± SEM, years	9.16 ± 0.55[¥]
RF-CCP Status, n (%)[¥] Seropositive	47 (61.04%)
Smoking (yes), n (%)	5 (6.49%)
Planned pregnancies of RA patients, n (%)	63 (81.8%)

DMARDs used during pregnancy
    Patients without medication n (%)
    Patients with steroid monotherapy or csDMARDs and steroids n (%)
    Patients were on bDMARDs n (%)
	23 (29.87%)
	33 (42.86%)
	21 (27.27%)

ESR before conception[¥], mean ± SEM	18.12 ± 2.33[¥]
CRP before conception[¥], mean ± SEM	11.28 ± 1.90[¥]

Note: [¥]Valid n is given.
Abbreviations: SEM, standard error of the mean; RA, rheumatoid arthritis; RF-CCP, rheumatoid factor-cyclic citrullinated peptide; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein; DMARDs, disease modifying antirheumatic drugs.

DMARDs used before conception were as follows: 48 (62.34%) patients were on biologic bDMARDs with or without csDMARDs, 1 patient (1.3%) was on tsDMARDs, tofacitinib and 28 (36.36%) patients were using only csDMARDs. Of the patients using biologics, 19 were on etanercept, 11 on certolizumab, 8 on tocilizumab, 8 on adalimumab, and 1 patient each on infliximab and rituximab. Patients using only the csDMARDs, 5 were prescribed hydroxychloroquine (HCQ), 18 patients were given methotrexate, 9 patients were on sulfasalazine (SSZ), and 7 on concomitant use of ≤5 mg steroids.

During pregnancy, 23 (29.87%) patients were not on medication, 33 (42.86%) patients were on steroid monotherapy or csDMARDs and steroids. Of the 16 patients who were on ≤10 mg prednisolone, 5 were on prednisolone monotherapy and 11 on steroid in combination with either HCQ or SSZ. Twenty patients were on HCQ alone, 8 on SSZ alone, 21 (27.27%) patients were on bDMARDs, of which 16 were on certolizumab, 4 on etanercept, and 1 patient was on tocilizumab.

Table 2 presents the comparison between the pregnant RA group and healthy pregnant controls. Our results showed that the age of conception, preterm labor, NICU admission, and low birth weight were statistically significant (p <0.05), and higher in pregnant RA patients than in healthy controls. No significant difference was observed in the events of the rate of abortion, stillbirths, congenital anomalies, cesarean section, ectopic pregnancy, and preeclampsia between pregnant RA patients and healthy controls (p >0.05).

The DAS28-CRP score of pregnant RA patients indicated that the disease remission occurred during preconception, within 3–6 months, 9 months of pregnancy and within 3 months after delivery in 67.53%, 71.42%, 73.33% and, 67.34% pregnant RA cases, respectively (Figure 1).

The relationship between the different clinical variables and RA pregnancy-related outcomes is illustrated in (Table 3), we observed that cases with longer disease duration (p <0.001), high ESR (p <0.001), and high CRP levels (p = 0.001) were statistically associated with cases of NICU admission; however, patients with higher age at conception (p = 0.003) were statistically related to stillbirth. Table 4 showed a significant relation between higher disease activity levels with abortion, preterm, and NICU admission pregnancy outcome (p <0.05), however no statistically significant difference between the adverse pregnancy outcomes and csDMARDs, bDMARDs or prednisolone use (p 0>0.05).

The classification table obtained from the logistic model showed an overall accuracy of 76.1%. Patients with mild and moderate-severe DAS28-CRP have significantly high chances of having an adverse pregnancy outcome (AOR=11.44; 95% CI=1.598–81.90, p=0.015) and (AOR=100.30; 95% CI=3.072–3275.90, p=0.010) respectively with higher significance in moderate-severe disease activity (Table 5).

Discussion

RA influences pregnancy in different ways. It can affect patients' fertility as well as maternal and fetal outcomes. Before conception, it can affect patients' fertility, and after

Table 2 Comparison Between RA Group and Healthy Controls Groups

Parameters	Pregnancy Cases with RA (n = 77)	Pregnancy Cases as Healthy Controls (n = 250)	p-value
Age at pregnancy, mean ± SEM, years	32.78 ± 0.69[¥]	30.32 ± 0.84	0.034*
Neonatal outcomes			
Newborn weight, mean ± SEM, gm	2701.50 ± 87.39[¥]	3044.09 ± 47.14	0.001*
Congenital anomalies, n (%)[¥]	1 (1.3)	4 (1.6)	0.849
Stillbirth, n (%)[¥]	1 (1.3)	3 (1.2)	0.944
Preterm birth, n (%)[¥]	17 (22.1)	21 (8.4)	0.001*
NICU admission, n (%)[¥]	3 (3.9)	0 (0.0)	0.001*
Pregnancy related			
Preeclampsia, n (%)[¥]	0 (0.0)	1 (0.4)	0.651
C-section, n (%)[¥]	8 (10.39)	17 (6.8)	0.298
Abortions, n (%)[¥]	8 (10.4)	15 (6.0)	0.18
Ectopic pregnancy, n (%)[¥]	0 (0.0)	2 (0.8)	0.429

Notes: *Statistically significant at the 5% level of significance; [¥]valid n is given.
Abbreviations: SEM, standard error of the mean; RA, rheumatoid arthritis; NICU, neonatal intensive care unit; C-section, cesarean-section.

170

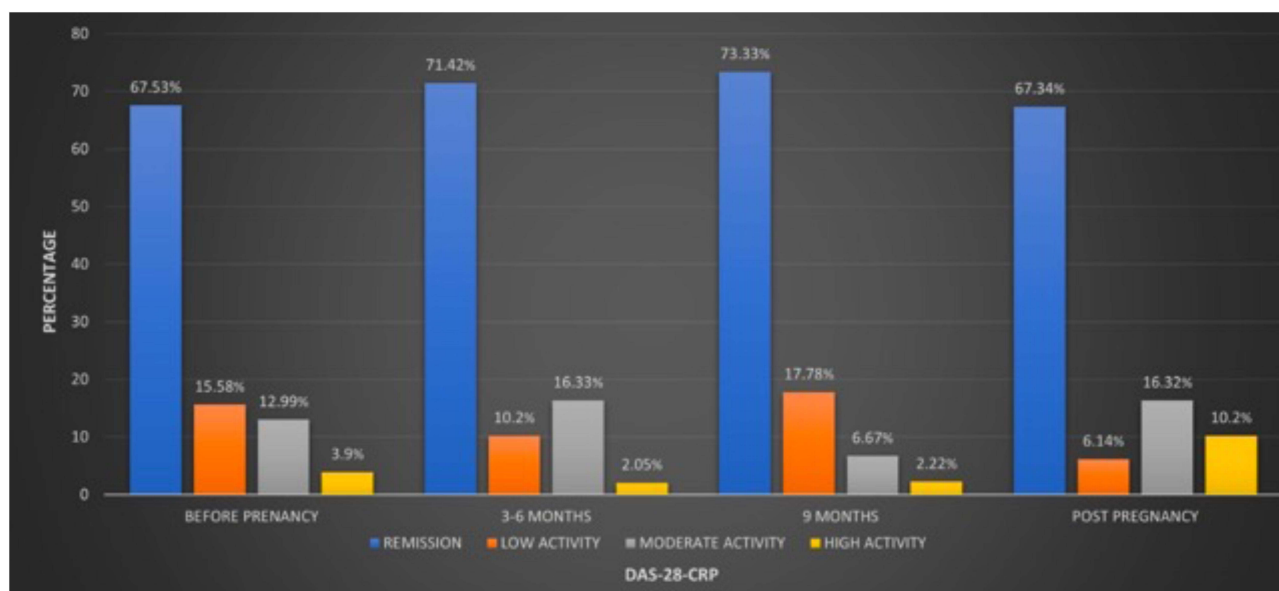Open Access Rheumatology: Research and Reviews 2021:13

Figure 1 Comparison of DAS28-CRP before conception, during pregnancy (between 3–6 months and at 9 months), and post pregnancy.

conception, both maternal and fetal outcomes are at stake.[1] We have studied a total of 77 pregnant patients with RA and 250 healthy age-matched pregnant controls. A total of 67.53% of RA patients were in remission before conception and 15.58% were having low disease activity score, and 81.8% of pregnancies were planned. Age of conception, preterm labor, neonatal intensive care unit (NICU) admission and low birth weight were higher in RA patients than healthy controls. Clinical and laboratory variables as longer disease duration and high C-reactive protein and erythrocyte sedimentation rate levels before conception were associated with preterm NICU admission. The higher the disease activity the more frequent the adverse pregnancy outcome.

Most of the current studies either prospective[3,4] or retrospective[12,13] designed with limited data about the effect of planned follow-up protocol prospectively. To the best of our knowledge, the current study is considered the first prospectively designed pregnancy with a planned follow-up protocol in the Saudi population.

The mean age of patients with RA at conception was significantly higher than that of healthy controls, which is in agreement with a previous retrospective study by Nørgaard et al.[5] This could be related to the high incidence of RA-related infertility or the need for disease control before conception.[8]

The majority (80%) of our patients were in remission and had low disease activity, and 81.8% had a planned

Table 3 The Relation Between Clinical Variables and RA Pregnancy-Related Outcomes

Parameters	Total Adverse Pregnancy Outcomes (n = 27)	Abortion (n = 8)	Preterm (n = 17)	Stillbirth (n = 1)	NICU Admission (from Preterm) (n = 3)	p-value
Disease duration, mean ± SEM, years	6.07 ± 0.68	5.75 ± 1.7	6.41 ± 0.76	5.0 ± 0.0	9.67 ± 0.88[†]	<0.001*
Age at pregnancy, mean ± SEM, years	32.85 ± 1.01	34.25 ± 2.3	32.53 ± 1.10	25.0 ± 0.0[†]	31.67 ± 5.23	0.003*
ESR, mean ± SEM	27.74 ± 3.62	25.6 ± 6.9	30.12 ± 4.70	21.0 ± 0.0	53.67 ± 2.33[†]	<0.001*
CRP, mean ± SEM	13.0 ± 2.61	18.25 ± 5.6	11.41 ± 3.15	6.0 ± 0.0	24.78 ± 14.32[†]	0.001*

Notes: *Statistically significant at the 5% level of significance; [†]significant difference with others.
Abbreviations: SEM, standard error of the mean; RA, rheumatoid arthritis; NICU, neonatal intensive care unit; ESR, erythrocyte sedimentation rate, CRP, C-reactive protein.

Table 4 Association Between Smoking, Medications Used During Pregnancy and Disease Activity Scoring at Conception and RA Pregnancy-Related Outcomes

Clinical Parameters	Adverse Pregnancy Outcome							
	Preterm N=17 n (%)		NICU Admission (from Preterm) N=3 n (%)		Abortion N=8 n (%)		Stillbirth N=1 n (%)	
	No	Yes	No	Yes	No	Yes	No	Yes
Smoker								
No	47 (75.8)	15 (24.2)	60 (96.8)	2 (3.20)	55 (88.7)	7 (11.3)	61 (98.4)	1 (1.60)
Yes	3 (60.0)	2 (40.0)	4 (80.0)	1 (20.0)	4 (80.0)	1 (20.0)	5 (100.0)	0 (0.00)
p-value	0.595		0.211		0.482		0.775	
bDMARDs								
No	30 (69.8)	13 (30.2)	41 (95.3)	2 (4.70)	38 (88.4)	5 (11.6)	42 (97.7)	1 (2.3)
Yes	20 (83.3)	4 (16.70)	23 (95.8)	1 (4.20)	21 (87.5)	3 (12.5)	24 (100)	0 (0.00)
p-value	0.221		0.927		0.916		0.452	
Prednisolone								
No	43 (78.2)	12 (21.8)	54 (98.2)	1 (1.80)	48 (87.3)	7 (12.7)	54 (98.2)	1 (1.8)
Yes	7 (58.3)	5 (41.7)	10 (83.3)	2 (16.7)	11 (91.7)	1 (8.3)	12 (100)	0 (0.00)
p-value	0.164		0.080		0.671		0.638	
csDMARDs								
No	29 (69.0)	13 (31.0)	41 (97.6)	1 (2.40)	39 (92.9)	3 (7.1)	41 (97.6)	1 (2.4)
Yes	21 (84.0)	4 (16.0)	23 (92.0)	2 (8.00)	20 (80.0)	5 (20.0)	25 (100)	0 (0.00)
p-value	0.174		0.551		0.138		0.437	
DAS28-CRP								
Remission	35 (83.3)	7 (16.7)	42 (100)	0 (0.0)	40 (95.2)	2 (4.80)	42 (100)	0 (0.0)
Mild	10 (83.3)	2 (16.7)	12 (100)	0 (0.0)	9 (75.0)	3 (25.0)	11 (91.7)	1 (8.3)
Moderate-Severe	5 (38.5)	8 (61.5)	10 (76.9)	3 (23.1)	10 (76.9)	3 (23.1)	13 (100)	0 (0.0)
p-value	0.006*		0.011*		0.030*		0.179	

Note: *Statistically significant.

pregnancy. This figure was higher than those of another study[12] in which 75% were planned pregnancy and 54% had mild disease activity scores before conception. Nevertheless, our study was prospective and 62.34% of our patients were on biologics of variable classes. Approximately 30% were off-medication during pregnancy, the number being lower than that reported by Eudy et al,[12] in which half of the patients were off-medications during pregnancy.

We have reported a comparable abortion rate between planned pregnancy RA patients vs healthy controls. Brouwer et al[14] reported that the risk of abortion in women with RA is comparable to that in the general population. Most of our cohort consisted of RA patients with a planned pregnancy, implicating that disease remission can be associated with better outcomes. Surprisingly, we found it even better than the general population with the usual unplanned pregnancy. The retrospective study by Eudy et al[12] revealed a better outcome in the planned RA pregnancy; all the patients had early deliveries and episodes of preeclampsia; only 50% were taking RA-related medications, although the study design of being prospective in our cohort and different ethnicity could be the reason behind the difference.[12]

Norgaard et al[5] have reported a slight increase in the risk of preeclampsia from 3.4% in control to 5.0% in RA patients, while other studies did not confirm these findings, probably due to lack of power.[4] Two prior retrospective

Table 5 Binary Logistic Regression Using Backward Selection for Assessing the Relation Between Clinical Variables and RA Pregnancy-Related Outcomes

Parameters	β	S.E.	Wald	p-value	Adjusted Odds Ratio	95% C.I.	
Age at pregnancy	0.538	0.604	0.795	0.373	1.713	0.525	5.59
Age of diagnosis	−0.447	0.606	0.543	0.461	0.64	0.195	2.098
Disease Duration	−0.529	0.635	0.695	0.404	0.589	0.17	2.045
Seropositive	−0.393	0.814	0.234	0.629	0.675	0.137	3.324
Smoker	−0.129	1.794	0.005	0.943	0.879	0.026	29.586
ESR	−0.017	0.04	0.183	0.669	0.983	0.909	1.063
CRP	0.023	0.043	0.289	0.591	1.023	0.941	1.114
bDMARDs	−1.705	0.916	3.463	0.063	0.182	0.03	1.095
Prednisolone	−1.41	1.183	1.422	0.233	0.244	0.024	2.478
csDMARDs	−1.176	0.9	1.706	0.191	0.309	0.053	1.801
DAS28-CRP (Mild)	2.437	1.004	5.888	0.015*	11.44	1.598	81.903
DAS28-CRP (Moderate-Severe)	4.608	1.779	6.713	0.001*	100.308	3.072	3275.802

Note: *Statistically significant.

studies[5,15] have claimed that there is a modestly increased risk for preterm birth and preeclampsia in pregnant women with RA, although absolute numbers reported were relatively low. Some reports have shown an increased risk for cesarean delivery (26–34%) compared with (16.5–19.5%) in the general population.[5,15] Active disease was associated with an increased risk for cesarean section in 22%;[15] however, most of our patients were in remission with low disease activity; further, cesarean deliveries vary with different countries.

There was no increased risk of fetal-related congenital malformations or perinatal death for any pregnant women with RA; these findings were similar to those reported in previous studies.[15,16]

The current study revealed that preterm labor, NICU admission, and low fetal birth weight were higher in pregnant patients with RA than in healthy controls, which is in agreement with previous studies.[5,12,15–17] Moreover, our analyses showed that longer disease duration, and higher CRP and ESR levels before conception were associated with preterm NICU admission, however, higher age at disease onset was associated with abortion, and stillbirth was associated with higher age at conception. Higher disease activity was associated with abortion, preterm, and NICU admission pregnancy outcome. Binary logistic analysis showed that the higher the disease activity the higher the risk of the adverse pregnancy outcomes. Alike our results de Man et al[4] reported that an increase in the lower birth weight of infants for patients with RA was

related to the disease activity during pregnancy. Cytokine concentrations like high IL-6 and low IL-10 levels were found to be associated with low fetal birth weight and poorer pregnancy outcomes in pregnant women with RA, apart from teratogenic medications and high disease activity.[18]

A strong risk of preterm delivery associated with high disease activity was also reported.[19] The same study also indicated an association of preterm delivery with comorbid autoimmune disease, use of >10 mg prednisone, previous history of preterm labor, and previous intrauterine growth restriction. In our study, there was no association between prednisolone use and adverse outcome, as most of the RA patients were in remission and using <10 mg prednisolone. Besides, we had excluded patients having comorbid autoimmune diseases.

This study had some limitations. The small sample size of pregnant cases, to assess the exact percentage of planned pregnancy in healthy controls; however, planned pregnancy protocols are usually applied and recommended in women with chronic diseases, rather than in the general population. Another limitation where RA participants were older, which could interact with all adverse outcomes, a small population of pregnant women with active RA; however, most of our patients had planned pregnancy protocol, in which the recommendation advice is to conceive in low disease activity or remission stage for better fertility and outcome.[20,21]

Conclusion

We conclude that RA is associated with numerous adverse pregnancy-related outcomes. Patients with active disease were at a higher risk for adverse pregnancy outcomes, including a high risk of preterm labor with or without NICU admission and abortion; nevertheless, tight disease control should be aimed. Disease remission before conception is advised. Pregnant women with RA should be educated and encouraged to plan their pregnancies with their physician as other patients with chronic diseases.

Abbreviations

RA, rheumatoid arthritis; DAS 28, disease activity scoring; NICU, neonatal intensive care unit; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; ACR, American College of Rheumatology; EULAR, European League Against Rheumatism; RF, rheumatoid factor; Anti-CCP Abs, anti-cyclic citrullinated peptide antibodies; CMIA, chemiluminescence microparticle immunoassay; ESR, erythrocyte sedimentation rate; CRP, C reactive protein; ELISA, enzyme-linked immunosorbent assay; csDMARDs, conventional synthetic disease modifying antirheumatic drugs; bDMARDs, biological disease modifying antirheumatic drugs; tsDMARDs, targeted synthetic disease modifying antirheumatic drugs.

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