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Original Research Article

A Case Control Study Assessing Pregnancy Outcomes in Patients with RA and Impact of Disease-Related Variables

Ankita Kumari[1], Masuraj Atal Bihari Mandal[2]

[1]Senior resident, Department of Obstetrics and Gynaecology, PMCH, Patna, Bihar, India

[2]Senior Resident, Department of Orthopaedics, PMCH, Patna, Bihar, India

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Corresponding Author: Dr. Masuraj Atal Bihari Mandal
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Abstract

Aim: The aim of the present study was comparing 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.

Methods: The present study was conducted in the Department of Obstetrics and Gynaecology, PMCH, Patna, Bihar, India. A total of 50 pregnant women with RA and 200 healthy pregnant controls were recruited for the study.

Results: The mean age of the participants at conception was 32.77 ± 0.66 years for RA patients and for RA patient's disease duration was 9.16 ± 0.55 years. 80% of pregnancies were planned by both patients and the consulting rheumatologists with medication modification. 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 ($p > 0.05$). 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. Patients with mild and moderate-severe DAS28-CRP have significantly high chances of having an adverse pregnancy outcome and respectively with higher significance in moderate-severe disease activity.

Conclusion: We concluded 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.

Keywords: rheumatoid arthritis, pregnancy, disease activity

Introduction

Rheumatoid arthritis (RA) is the most common chronic inflammatory rheumatic disease. It is characterised by painful and swollen joints and is a major public health problem. Data on the prevalence of RA in adults vary considerably between studies and countries, ranging from 0.00% to 2.70%. [1] There is a clear female predominance, with women being 2.6 times more affected than men. Although the peak age of onset is around 50 years, RA can also affect women of childbearing age. [2]

Pregnancy is a particular period, which may be associated with a spontaneous but transient improvement in rheumatic activity despite reduced rates of medication use compared with before conception. A recent meta-analysis showed that disease activity improved in 60% of patients with RA in pregnancy and flared in 47% post partum. [3] On the other hand, RA can have a negative influence on pregnancy and may lead to adverse birth outcomes, such as prematurity, caesarean sections and low birth weight. [4] This would appear to be particularly significant in active RA. [5]

The management of these patients has evolved over the last decade, especially with the development of new therapeutic molecules. Recent European Alliance of Associations for Rheumatology recommendations on the use of antirheumatic drugs during pregnancy emphasise the need to adjust treatment in patients planning a pregnancy to promote disease control in the mother while limiting

risks to the fetus. Indeed, only a limited number of drugs available in the RA therapeutic arsenal meet these conditions. Compatibility with pregnancy has been found for sulfasalazine and glucocorticoids, but not for methotrexate, which should be discontinued before conception because of its proven teratogenicity. Among biologics, tumour necrosis factor inhibitors (TNFi) are best studied and appear reasonably safe during pregnancy. [6] Insufficient documentation regarding fetal safety implies the discontinuation of other therapeutic classes (interleukin-6 inhibitors (IL-6i), cytotoxic T lymphocyte-associated protein 4 immunoglobulin (CTLA4-Ig), anti-cluster of differentiation 20 (CD20) antibody, Janus kinase inhibitors (JAKi)) before a planned pregnancy. [7]

A meta-analysis has reported that maternal RA increased the risk of autism spectrum disorders in offspring. [8] However, this meta-analysis has not reported the maternal outcomes and other fetal outcomes. [8] A meta-analysis performed by Huang et al. showed that maternal RA was significantly correlated with an increased risk of adverse maternal and fetal outcomes [9]; however, the association between disease activity and pregnancy outcomes was not explored in their meta-analysis. Existing studies have shown that higher disease activity of RA was correlated with the higher risk of adverse pregnancy outcomes. [10,11] A study by de Man et al. has reported that pregnancy outcomes of women with well-controlled RA was comparable with those of the general population. [12]

The aim of the present study was 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.

Materials and Methods

The present study was conducted in the Department of Obstetrics and Gynaecology, PMCH, Patna, Bihar, India for one year. A total of 50 pregnant women with RA and 200 healthy pregnant controls were recruited for the study.

Study Population

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 anti- bodies (anti-CCP Abs) using the chemiluminescence micro- particle 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[13], elective termination of pregnancy. Fetal outcomes included Low birth weight (LBW) Less than 2500 grams[14], 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[15] 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.

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 con- firming that the fitted model was appropriate.

Results

Table 1: Demographics and Clinical Data of Rheumatoid Arthritis Patients

RA Group (n = 50)	Data
Age at pregnancy, mean ± SEM, years	32.77 ± 0.66
Age of disease onset, mean ± SEM, years	26.46 ± 0.84
Duration of disease, mean ± SEM, years	9.16 ± 0.55
RF-CCP Status, (%) n Seropositive	31 (62%)
Smoking (yes), n (%)	3 (6%)
Planned pregnancies of RA patients, n (%)	40 (80%)
DMARDs used during pregnancy	
Patients without medication n (%)	15 (30%)
Patients with steroid monotherapy or csDMARDs and steroids n (%)	21 (42%)
Patients were on bDMARDs n (%)	14 (28%)
ESR before conception, mean ± SEM	18.14 ± 2.34
CRP before conception, mean ± SEM	11.27 ± 1.92

The mean age of the participants at conception was 32.77 ± 0.66 years for RA patients and for RA patient's disease duration was 9.16 ± 0.55 years. 80% of pregnancies were planned by both patients and the consulting rheumatologists with medication modification.

Table 2: Comparison Between RA Group and Healthy Controls Groups

Parameters	Pregnancy Cases with RA (n = 50)	Cases as Healthy Controls(n = 200)	p-value
Age at pregnancy, mean ± SEM, years	31.77 ± 0.66	30.32 ± 0.88	0.036
Neonatal outcomes			
Newborn weight, mean ± SEM, gm	2710.50 ± 88.42	3048.08 ±	0.001
Congenital anomalies, n (%)	1 (2)	48.11	0.832
Stillbirth, n (%)	1 (2)	3 (1.5)	0.955
Preterm birth, n (%)	11 (22)	2 (1)	0.001
NICU admission, n (%)	2 (4)	16 (8)	0.001
		0 (0.0)	
Pregnancy related Preeclampsia, n (%)	0 (0.0)	1 (0.5)	0.634
C-section, n (%)	5 (10)	12 (6)	0.289
Abortions, n (%)	5 (10)	12 (6)	0.16
Ectopic pregnancy, n (%)	0 (0.0)	2 (1)	0.422

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 ($p > 0.05$).

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

Parameters	Total Adverse Pregnancy Outcomes (n = 24)	Abortion (n = 5)	Preterm (n = 15)	Stillbirth (n = 1)	NICU Admission (fromPreterm) (n = 3)	p-value
Disease duration, mean ± SEM, years	6.04 ± 0.66	5.78 ± 1.8	6.44 ± 0.74	5.0 ± 0.0	9.67 ± 0.88	<0.001
Age at pregnancy, mean ± SEM, years	32.88 ± 1.01	34.25 ± 2.3	33.55 ± 1.10	25.0 ± 0.0	32.68 ± 5.25	0.003
ESR, mean ± SEM	27.73 ± 3.62	25.6 ± 6.9	30.12 ± 4.70	22.0 ± 0.0	54.66 ± 2.35	<0.001
CRP, mean ± SEM	12.0 ± 2.61	18.22 ± 5.6	11.41 ± 3.15	6.0 ± 0.0	25.75 ± 15.35	0.001

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: 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	0.375	1.713	0.525	5.59
Age of diagnosis	−0.447	0.606	0.543	0.462	0.64	0.195	2.098
Disease Duration	−0.529	0.635	0.695	0.408	0.589	0.17	2.045
Seropositive	−0.393	0.814	0.234	0.630	0.675	0.137	3.324
Smoker	−0.129	1.794	0.005	0.944	0.879	0.026	29.586
ESR	−0.017	0.04	0.183	0.675	0.983	0.909	1.063
CRP	0.023	0.043	0.289	0.590	1.023	0.941	1.114
bDMARDs	−1.705	0.916	3.463	0.066	0.182	0.03	1.095
Prednisolone	−1.41	1.184	1.422	0.235	0.244	0.024	2.478
csDMARDs	−1.176	0.9	1.706	0.195	0.309	0.053	1.801
DAS28-CRP (Mild)	2.437	1.005	5.888	0.016	11.44	1.598	81.903
DAS28-CRP (Moderate-Severe)	4.608	1.778	6.714	0.001	100.308	3.072	3275.802

Patients with mild and moderate-severe DAS28-CRP have significantly high chances of having an adverse pregnancy outcome and respectively with higher significance in moderate-severe disease activity.

Discussion

Rheumatoid arthritis (RA) is a common autoimmune dis- ease that predominantly affects the skeletal system and connective tissues. RA usually targets women of child- bearing age.[16] 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. [17] 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. [18] The relationship of disease control in Caucasian RA patients during pregnancy has a favorable outcome. [19]

The mean age of the participants at conception was 32.77 ± 0.66 years for RA patients and for RA patient's disease duration was 9.16 ± 0.55 years. 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. [20] This could be related to the high incidence of RA-related infertility or the need for disease control before conception. [21] 80% of pregnancies were planned by both patients and the consulting rheumatologists with medication modification. This figure was higher than those of another study [22] 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 [22] in which half of the patients were off- medications during pregnancy.

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 ($p > 0.05$). We have reported a comparable abortion rate between planned pregnancy RA patients vs healthy controls. Brouwer et al [23] 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.

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. Patients with mild and moderate-severe DAS28-CRP have significantly high chances of having an adverse pregnancy outcome and respectively with higher significance in moderate-severe disease activity. 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 auto- immune diseases. [24]

Conclusion

We concluded 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.

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