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Pregnancy outcomes and contraceptive use in women with rheumatoid arthritis: A comparative study

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Abstract---Rheumatoid arthritis (RA) is a common chronic autoimmune disorder that has a female predominance and commonly affects women of childbearing age, it is shown to remit during pregnancy in most studies and improve in about half of the patients when assessed with objective disease activity measurements. To assess the pregnancy outcomes in women with rheumatoid arthritis prior and after diagnosis and compare it with women with no chronic illness. To evaluate contraceptive practices and correlated contraceptive method efficacy with use of concomitant rheumatic medications. (Methotrexate, leflunomide). A total of 100 female patients diagnosed with rheumatoid arthritis according to ACR/EULAR 2010 classification criteria were compared with apparently healthy female controls matching in age in this case-control study. Data was collected by questionnaires and interview. The questionnaires included demographic data and pregnancy outcomes, mode of delivery, contraceptive methods used by patients with the current use of methotrexate and leflunomide. The mean age for the patients and controls were 38.4±5.1 and 36.7±4.5 years respectively. The live births significantly decreased in female patients with rheumatoid arthritis in compare with controls and before diagnosis (p 0.010, p 0.002 respectively). There is increase in the frequency of caesarean section in controls group in compare with patients with rheumatoid arthritis (p 0.001). But increase in the frequency of caesarean section in patients with rheumatoid arthritis in compare before diagnosis (p 0.021). There is significant decrease in the frequency of unplanned pregnancy after diagnosis of rheumatoid arthritis in compare before the diagnosis (p 0.000). About 75.4% of

patients have completed their family before the diagnosis and 24.6% have fear from the effect of rheumatoid arthritis on themselves and their children. The patients use methotrexate 27.16% use long acting reversible contraceptive methods, (30.86%, and 24.69%) using not effective or no contraception at all respectively and 43.2% of them receive rheumatological consultation about the contraceptive methods. About 31.58% patients on leflunomide using long acting reversible methods, 36.84% using effective methods, and 15.79% using not effective methods or nocontraception. There is an adverse effect of rheumatoid arthritis on pregnancy outcomes.

Keywords---rheumatoid arthritis, leflunomide, methotrexate, tumor necrosis factor-alpha.

Introduction

Rheumatoid arthritis is a chronic inflammatory joint disease that has a characteristic pattern of bone and joint involvement that result in destructive deformities and multiple extra-articular manifestations that lead to severe disability and increase mortality [1]. Definite Rheumatoid arthritis was observed in 1% of population samples in Iraq. Its predominantly affects female (female: male, 3:1) [2]. The peak onset of RA is in the fourth or fifth decade for women and the sixth to eighth decades for men [3].

Conceiving a child is a major life event, RA is one of the most chronic inflammatory joint diseases that affect women of childbearing age, about one-third of women with RA experience fertility problems, and they have a prolonged time to pregnancy (TTP) [4]. In a study done in 2018 reports that 60% of pregnant women with RA improved during pregnancy and 46.7% flared up post-partum [5]. Family planning is particularly important for women with rheumatic diseases. Well-controlled disease at the time of conception has been associated with better outcomes (e.g., normal birth weight and term deliveries) conversely, whereas poorly controlled disease at conception increases the risk of intrauterine growth restriction, caesarean section, preeclampsia, and/or fetal loss among pregnant women [6].

Given these considerations, in 2014, the American College of Rheumatology published information for female patients that included the following recommendations: women should receive risk counseling from their physician if contemplating pregnancy, rheumatic disease should be controlled for at least 3–6 months before conception, and any medication changes should be discussed in advance with a rheumatologist [7].

Patients and Methods

Study design, setting and time of study

This case controls study was carried out on a sample of 100 female patients diagnosed with RA according to the 2010 American college of Rheumatology

(ACR)/European League Against Rheumatism (EULAR) RA classification criteria, or has been diagnosed previously according to the ACR revised criteria of RA 1987 with history of at least one pregnancy were selected to study the pregnancy outcomes. An age-matched sample of healthy controls with at least one pregnancy from those attending outpatients, inpatients, ward of Rheumatology Unit /Baghdad Teaching Hospital. Patients were selected to contraceptive study group and their data on contraceptive practices currently being used in relation to medications (methotrexate, leflunomide). This study carried out from December 2019 to July 2020.

Ethical issue, approval and official permission

Prior to collection of data, an informed consent from each of the participants was obtained after explaining the aim of study and ensuring privacy of data. This study was approved by Iraqi BOARD for medical specialties with ethical approval NO.100 dated 02 January 2020.

Inclusion criteria

Female patients diagnosed with rheumatoid arthritis aged between 16-49 years with history of at least one pregnancy.

Exclusion criteria for contraceptive study group

1. Pregnancy
2. Trying to conceive
3. Menopause
4. Hysterectomy
5. Systemic illness (diabetes, hypertension, hypothyroidism, others)

Data collection

Data were collected using an interviewer –administered questionnaire for patients group and control group regarding pregnancy outcomes while data were collected using an interviewer –administered questionnaire for patients group regarding contraceptive practices in relation to the concomitant use of methotrexate and leflunomide.

Definitions used [8]

Fetal loss: total number of still births, spontaneous abortions, ectopic pregnancy

Still birth: was defined as birth of infant that has died in utero after 28 weeks of gestation.

Miss carriage: when pregnancy loss occurred before 28 weeks of gestation.

Full term delivery: labor after completing 42 weeks of gestation.

Pre term delivery: labor occurring after completing 37 weeks of gestation.

Contraceptive methods evaluation [9]

The patients were asked if using methotrexate or leflunomide or both of them, also asked if any rheumatologist had discussed contraceptive methods, current contraceptive methods. Contraceptive methods were grouped into the following effectiveness categories as defined by the centers for disease control and prevention:

1. Highly effective methods including surgical methods (tubal ligation, vasectomy).
2. Long acting reversible contraceptive methods (intra-uterine devices and implants).
3. Effective methods (oral contraceptive pills and other hormonal methods (patches, rings, depot medroxy progesterone).
4. Ineffective methods (barrier methods, rhythm methods, withdrawal).

Patients were considered not to be using any contraception if they did not report using any of the above methods. Our primary outcomes of interest were contraceptive method using by patient in relation to current medications (methotrexate, leflunomide), effect of educational level to contraceptive methods (primary school, high school, university degree) and if received rheumatological consultation.

Statistical Analysis

Statistical package for the social sciences (SPSS) version 23 was used for data entry and analysis, mean and standard deviation were used to express the numerical data while frequency and percentages were used to express the categorical data. Appropriate tests, independent students, t-test, chi square (Fischer exact test if not applicable). P value less than 0.05 was considered significant.

Results

In this study, 100 Iraqi female patients with RA were selected. The mean age at the time of the study is 39.5 years old, SD± 6.7, the mean of BMI is 26.4 Kg/m², SD± 3.2, 59% have primary school degree, 29% have high school degree, and 12% have a university degree. Out of the 100 patients with RA, 39 of them continue to get pregnant after diagnosis, in compare with 39 healthy controls. The mean age of RA patients at the time of the study is 38.4 years old, SD± 5.1, of controls group is 36.7 years old, SD± 4.5 ($p=0.123$) which is statistically not significant. There is no statistically significant difference regarding BMI between two groups ($P = 0.9$). For the educational level of the two groups, there is a statistically significant difference ($p=0.002$) as shown in table 1.

Table 1. Baseline characteristics of the studied groups

Variables	Groups		p-value
	Patients N(39)	Controls N(39)	
Age (Mean ±SD) years	38.4 ±5.1	36.7±4.5	0.123

BMI (Mean $\pm$ SD) (Kg/m ²)		28.9 $\pm$ 5.9	28.8 $\pm$ 5.5	0.939
Educational level (%)	Primary school	69.2	51.3	0.002
	High school	28.2	15.4	
	University degree	2.6	33.3	

BMI: Body mass index, SD: Standard deviation

Pregnancy outcome

I- pregnancy outcome in women with rheumatoid arthritis in compare to healthy control

There were 95 pregnancies in 39 women with RA and 148 pregnancies in 39 healthy controls. The frequency of live birth in RA group is 67.4% and in healthy control is 81.7%, ($p = 0.01$) which is statistically significant. The frequency of preterm delivery in RA group is 5.3% and in healthy control is 4 % ($p=0.435$) which is statistically not significant. The rate of cesarean section in RA group is less than healthy control 48.6% VS. 23.2% ($p=0.001$) which is statistically significant. There is no significant differences statistically in pregnancy loss (spontaneous abortion, still birth, ectopic pregnancy) between RA and healthy control groups ($p=0.4$) as shown in table 2.

Table 2. Pregnancy outcome in women with rheumatoid arthritis in compared with healthy controls.

Variables	Groups		p-value
	Patients N(39)	Controls N(39)	
	No.of pregnancies N(95) %	No.of pregnancies N(148) %	
Live birth	67.4	81.7	0.01
-Full term	62.1	77.7	0.435
-Pre-term delivery	5.3	4	0.435
Pregnancy loss	32.6	18.2	0.421
-Spontaneous abortion	29.5	14.2	
-Still birth	3.1	4	
-Ectopic pregnancy	0	0	
C-section	23.2	48.6	0.001

C-section: caesarean section

II- Pregnancy outcome in women with rheumatoid arthritis before and after diagnosis.

Number of pregnancies before diagnosis of RA is higher than after diagnosis 154 VS. 95. The percentage of live birth after diagnosis is 67.4% and before diagnosis is 84.4% ($p=0.002$) which is statistically significant. The percentage of preterm delivery after diagnosis is higher than before diagnosis 5.3%, 2.6% respectively ($p=0.142$), which is statistically not significant. The percentage of caesarean

section after diagnosis of RA is 23.2% and before diagnosis of RA is 16.2% ($p=0.02$) which is significant statistically. There is no significant difference statistically in pregnancy loss before and after diagnosis of RA ($p=0.985$) as shown in table 3.

Table 3. Pregnancy outcome in women with RA before and after diagnosis.

Variables	Groups		p- value
	Patients N(39) before diagnosis	Patients N(39) after diagnosis	
	No. of pregnancies N(154) %	No. of pregnancies N(95) %	
Live birth	84.4	67.4	0.002
-Full term	81.8	62.1	0.142
-Pre-term delivery	2.6	5.3	0.142
Pregnancy loss	15.6	32.6	0.985
-Spontaneous abortion	14.3	29.5	
-Still birth	1.3	3.1	
-Ectopic pregnancy	0	0	
C-section	16.2	23.2	0.021

C-section: caesarean section

III -The pregnancy planning before and after diagnosis with rheumatoid arthritis.

After diagnosis of RA 74.7% of women had planned pregnancy and 25.3% had unplanned pregnancy which is lower than before diagnosis which is 77.2% ($p=0.000$) which is statistically significant as in table 4.

Table 4. The effect of rheumatoid arthritis on the pregnancy planning.

Variables	Groups		p- value
	Patients N(39) before diagnosis	Patients N(39) after diagnosis	
	No. of pregnancies N(154) %	No. of pregnancies N(95) %	
Planned pregnancy	22.7	74.7	0.342
Unplanned pregnancy	77.2	25.3	0.000

IV- Women stop to get pregnancy after diagnosis

In the remaining 61 women with rheumatoid arthritis who don't have children after diagnosis divided into two groups regarding the decision not to get pregnant, 75.4% have completed their family before the diagnosis and 24.6% have fear from the effect of rheumatoid arthritis on themselves and their children. The mean age at diagnosis of women who completed their family is above 30 years and women who fear to get pregnant is less than 30 years 38.3 ± 4.5 , 28.9 ± 5.8 respectively and

have more children before diagnosis than women who fear to get pregnant after diagnosis 5 VS. 2 and also the mean of disease duration is more in the women who completed their family shown in table 5.

Table 5. The characteristics of women stop to get pregnancy after diagnosis.

Variables	Groups	
	Complete the familyN (46)	Fear of Rheumatoid arthritis N(15)
Age at diagnosis (Mean $\pm$ SD)years	38.3 $\pm$ 5.8	28.9 $\pm$ 4.5
No. of children at diagnosis(Mean)	5	2
Disease duration (Mean $\pm$ SD) years	6 $\pm$ 4.5	1.6 $\pm$ 0.8

SD: Standard deviation

Contraceptive methods in relation to current use of methotrexate and leflunomide

In 100 women with rheumatoid arthritis 81% using methotrexate, 43.2% receive rheumatological consultation regarding the contraceptive methods and 56.8% don't receive any rheumatological consultation. The type of contraceptive method in relation to the methotrexate use 30.86% using not effective methods, 27.16% using long acting reversible methods, 14.81% using effective contraceptive methods and 24.69% don't receive any contraceptive methods. On the other hand 19% using leflunomide and 73.7% receive rheumatological consultation regarding the type of contraceptive methods, 36.84 % using effective methods of contraception, 31.58% using long acting reversible methods, 15.79% using not effective contraceptive methods and 15.79% not using any contraceptive methods. So the percentage of patients who receive rheumatological consultation regarding contraceptive methods is higher inleflunomide group than methotrexate group 73.7% compared to 43.2%, as shownin table 6 A,B.

Table 6.A. Types of contraceptive methods with current use of drugs.

Types of contraceptive methods	Patients on MTX		Patients on Leflunomide	
	N 81	%	N 19	%
Highly effective	2	2.47	0	0
Long acting reversible	22	27.16	6	31.58
Effective	12	14.81	7	36.84
Not effective	25	30.86	3	15.79
No contraceptive	20	24.69	3	15.79

MTX: methotrexate

Table 6.B. Rheumatological consultation regarding methotrexate, leflunomide

Rheumatological consultation	Patients on MTX		Patients on Leflunomide	
	N (81)	100%	N (19)	100%
With consultation	35	43.2	14	73.7
Without consultation	46	56.8	5	26.3

MTX: methotrexate

Discussion

Pregnancy outcome

In large cohort studies, pregnancy outcomes in women with RA had been less favorable in comparison with a normal healthy population. There are often small differences from the general population [10]. In this study, there is a decrease in the frequency of live birth after the diagnosis of RA when compared with healthy control and before the diagnosis of RA. This is agreed by the study done by Eudy *et al.* in 2018 [11] in which live birth after diagnosis when compared with healthy control 67% vs. 53% ($p=0.004$) also before and after diagnosis 70% vs. 63% ($p=0.04$). The frequency of preterm delivery in RA group is increased when compared with healthy control 5.3% vs. 4% which agreed with the study done by Skomsvoll *et al.* in 1999 [12] in which frequency of preterm delivery in RA group when compared with healthy control 7.1% vs. 5.6% and also agreed with the study done by Norgaard *et al.* in 2010 [10] in which preterm delivery in RA compared to healthy control 9.2% vs. 6.2%. There is increase in preterm delivery after diagnosis of RA in compare before diagnosis 5.3% vs. 2.6% ($p=0.142$) which agrees with the study done by Eudy *et al.* in 2018 [11] that showed that there is increase in preterm delivery after diagnosis of RA 16% vs. 0% ($p=1$). The increased incidence of preterm delivery in RA women may be related to prednisolone use which shortened gestation age in the study done by de Man *et al.* in 2009 [13]. In study done by Smith CJ *et al.* in 2018 [14] mentioned that active RA at enrollment and any time during pregnancy was associated with preterm delivery, corticosteroid use in every trimester associated with an approximate 2 to 5-fold increased risk for preterm delivery, independent of disease activity.

Mode of delivery

There is an increase in the frequency of C-section in healthy control when compared with women with RA this may explained by increasing the frequency of C-section in Iraq which is studied by Shabila NP in 2017 [15] that mentioned that the overall rate of C-section in Iraq increased from 18.0% in 2008 to 24.4% in 2012 which is far above the recommended rate. In the current study, 33.3% of healthy control women have university degree while 2.6% of women with RA have it and in the study done by Gilbert A *et al.* [16] showed an increased frequency of C-section in those with a university degree ($p=0.03$) compared with women whose maximum education was a high school diploma. On the other hand, there is an increase in the frequency of C-section in women after diagnosis of RA when compared before diagnosis which agrees with a study done by Aljary H *et al.* in 2018 [17] that showed that increased the frequency of C-section in RA 42.16% vs. 32% ($p=0.001$). There are many causes behind increase the frequency of C-section in women with RA as a high rate of labor induction, prematurity, and mal presentation which is reported among RA complicated births [10].

Pregnancy loss

There is no significant difference in overall pregnancy loss between women with RA after diagnosis when compared before diagnosis and with healthy control women which is agreed with the study done by Eudy *et al.* in 2018 [11] which

show no significant difference between pregnancy loss in women with RA and healthy control ($p=0.9$) and before diagnosis ($p=0.4$) but there is an increase in the frequency of spontaneous abortion in women with RA with healthy control which is agreed with the study done by Wallenius M *et al.* in 2015 [18]. The increased risk of spontaneous abortion in women with RA may be contributed to the administration of medication at time of conception as methotrexate, also planning of pregnancy may present women with RA for prenatal care earlier in gestation age, and this may lead to an erroneously higher rate of reported early spontaneous abortion than in general population [18].

Planned pregnancy

The increased frequency of the planned pregnancies after diagnosis of RA and decreased frequency of the unplanned pregnancies. This result goes in line with study done by Galappatthy *et al* [8] that showed increase percentage of the planned pregnancies after RA to the unplanned pregnancies 75% vs. 25%, and also agree with study done by Eudy *et al* in 2018 [11].

Women who stopped to get pregnancy after diagnosis

In women with RA who stop to get pregnant, 24.6% of women fear getting pregnant and have fewer children when compared with those who completed their family before diagnosis. This result agrees with a study done by Katz PP in 2006 [19] that showed 20% of women with RA fear to get pregnant after diagnosis and those not less likely to have any pregnancy or any children, but had significantly fewer pregnancies and children. The remaining 75.4% of women who complete their family prior diagnosis which agrees with a study done by Clowse ME *et al.* in 2012 [20] that found 578 women with RA, more than 60% that finished their children prior to diagnosis. Women who fear getting pregnant are younger than those who complete her family with fewer children which is agreed with a study done by Clowse ME *et al.* in 2012 [20]. There are other causes in RA related that women not to get pregnant as infertility, and subfertility.

Contraceptive methods in relation to current use of methotrexate and leflunomide

Teratogenic medications are often prescribed to women of childbearing age with autoimmune diseases. Many studies suggest that appropriate use of contraception among these women is low, potentially resulting in high-risk unintended pregnancies [21]. Among patient using methotrexate, 27.16% using long-acting reversible methods, 14.8% using effective methods, and 55.55% (using ineffective methods or no contraception). This disagrees with the study done by Eudy *et al* in 2016 [11] that mention the percentage of patients on methotrexate using long-acting reversible, effective, and (ineffective methods or no contraception's) is 44%, 32%, 24% respectively, in this study this may be explained by: 56.8% of patients don't receive contraceptive counseling about the type of contraceptive methods from their rheumatologist, factors related to patient and her partner preference, and financial issues (23,24).

Women with rheumatoid arthritis on leflunomide 36.84% using effective contraceptive methods, 31.58% long-acting reversible, and 31.58% using (Not effective methods or no methods) this is agreed with the study done by Banas T *et al.* in 2014 [22] that mentioned 48.4% using effective methods and 33% do not use any contraceptive method. When comparing the effectiveness of contraceptive methods of patients using leflunomide is higher to those using methotrexate this may be due to that 73.7% of patients on leflunomide receive consultation about the type of contraceptive methods.

Conclusions

There is a decrease in the live births and an increase in the frequency of preterm birth and caesarean section in Iraqi female patients with rheumatoid arthritis. There is lack of knowledge about the importance of contraceptive methods regarding efficacy in relation to Teratogenic medications (methotrexate, and leflunomide).

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Conflict of interesting

None

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