# Pregnancy Outcomes and Contraceptive Use in Women with Rheumatoid Arthritis: A Comparative Study

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***Background.*** *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 measures.*

***Objective*** *– to assess the pregnancy outcomes in women with RA prior and after the diagnosis and compare them with those in women with no chronic illness, to evaluate contraceptive practices and contraceptive method efficacy with the use of concomitant rheumatic medications (methotrexate, leflunomide).*

***Patients and Methods.*** *Female patients diagnosed with RA according to ACR/EULAR 2010 classification criteria were compared with apparently healthy female controls matching in age in this case-control study. Data were collected by questionnaires and interviews. The questionnaires included demographic data and pregnancy outcomes, mode of delivery, contraceptive methods used by patients against the background of methotrexate and leflunomide therapy.*

***Results and discussion.*** *One hundred patients with RA were included. The mean age of the patients and controls was 38.4±5.1 and 36.7±4.5 years, respectively. The live births significantly decreased in female patients with RA compared to the controls and the period before the diagnosis (p=0.01, p=0.002, respectively). Caesarean section frequency was higher in the control group compared to patients with RA (p=0.001). But in patients with RA, frequency of caesarean section increased after the diagnosis (p=0.021). Frequency of unplanned pregnancy significantly decreased after the diagnosis of RA compared to the period before the diagnosis (p<0.001). About 75.4% of patients had the desired number of children in their family before the diagnosis, and 24.6% feared the effect of RA on themselves and their children. 81% of 100 women with RA used methotrexate, 43.2% of them received rheumatological consultation regarding the contraceptive methods, and 56.8% did not. 30.86% of patients treated with methotrexate used ineffective contraceptive methods, 27.16% – long-acting reversible methods, 14.81% – effective contraceptive methods, and 24.69% did not use any contraceptive methods. 19% of RA patients used leflunomide, and 73.7% of them received rheumatological consultation regarding the type of contraceptive methods, 36.84% used effective methods of contraception, 31.58% – long-acting reversible methods, 15.79% – ineffective contraceptive methods and 15.79% did not use any contraceptive methods.*

***Conclusion.*** *There is a decrease in live births and an increase in preterm birth frequency as well as caesarean sections in Iraqi female patients with RA. There is lack of knowledge about the importance of contraceptive methods efficacy in relation to teratogenic medications (methotrexate, and leflunomide).*

***Keywords:*** *rheumatoid arthritis; leflunomide; methotrexate; tumor necrosis; factor-alpha.*
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## Introduction

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

Conceiving a child is a major life event. RA is one of the most common chronic inflammatory joint diseases that affect women of childbearing age; about one third of women with RA experience fertility problems and have a prolonged time to pregnancy [4]. A study done in 2018 showed 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), whereas poorly controlled disease at conception increases the risk of intrauterine growth restriction, caesarean section, preeclampsia, and fetal loss among pregnant women [6].

Given these considerations, in 2014, the American College of Rheumatology (ACR) published information for female patients that included the ollowing 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***. Female patients diagnosed with RA according to the 2010 ACR / European Alliance of Associations for Rheumatology (EULAR) RA classification criteria, or diagnosed previously according to the ACR revised criteria of RA 1987 with a history of at least one pregnancy were included in the study of pregnancy outcomes. Age-matched healthy controls with at least one pregnancy were selected from

outpatients and inpatients in the wards of Rheumatology Unit / Baghdad Teaching Hospital.

Patients were selected for a contraceptive study group, and their data on contraceptive practices were analyzed in relation to RA medications used (methotrexate, leflunomide). This study was carried out from December 2019 to July 2020.

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

***Inclusion criteria***. Female patients diagnosed with RA aged between 16–49 years with a history of at least one pregnancy.

***Exclusion criteria for the contraceptive study group:***

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

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

***Definitions used*** *[8]:*

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

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

Miscarriage: when pregnancy loss occurred before 28 weeks of gestation.

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

Preterm delivery: labor occurring after completing 37 weeks of gestation.

***Contraceptive methods evaluation [9]***. The patients were asked about the use methotrexate or leflunomide, or both of them; they were also asked if they had discussed contraceptive methods with a rheumatologist, and about 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 (intrauterine devices and implants).
3. Effective methods (oral contraceptive pills and other hormonal methods – patches, rings, depot medroxyprogesterone).
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 methods used by patients in relation to current medications (methotrexate, leflunomide); the effect of educational level on contraceptive methods (primary school, high school, university degree), and if a patient received a rheumatologist's 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 Student's t-test, chi-square test (if Fischer's exact test was not applicable). P value less than 0.05 was considered significant.

## Results

This study included 100 Iraqi female patients with RA. The mean age at the time of the study entry was 39.5±6.7 years, the mean body mass index (BMI) was 26.4±3.2 kg/m$^2$, 59% only finished primary school, 29% – high school, and 12% had a university degree. Thirty-nine out of 100 patients with RA who continued to get pregnant after the diagnosis were compared with 39 healthy controls. The mean age of RA patients at the time of the study was 38.4±5.1 years, that of the control group was 36.7±4.5 years (p=0.123), this difference was not statistically significant. There was no statistically significant difference regarding BMI between the two groups (p=0.9). As for the educational level of the two groups, there was a statistically significant difference (p=0.002) as shown in Table 1.

**Table 1. Baseline characteristics of the studied groups**

| Variables | Groups | | p |
|---|---|---|---|
| | Patients (n=39) | Controls (n=39) | |
| Age, years, M±SD | 38.4±5,1 | 36.7±4.5 | 0.123 |
| BMI, kg/m$^2$, M±SD | 28.9±5.9 | 28.8±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 | |

**Note:** BMI – Body mass index; SD – Standard deviation.

***Pregnancy outcomes***

*Pregnancy outcomes in women with RA compared to healthy controls*. There were 95 pregnancies in 39 women with RA and 148 pregnancies in 39 healthy controls. The frequency of live births in RA group was 67.4%, and in healthy controls – 81.7%, (p=0.01); the difference is statistically significant. The frequency of preterm delivery in RA group and in healthy controls was comparable (5.3% and 4% respectively; p=0.435). The rate of cesarean sections in RA group was lower than in healthy controls: 23.2% vs 48.6%, respectively (p=0.001). There were no statistically significant differences in pregnancy loss (spontaneous abortion, still birth, ectopic pregnancy) between the groups (p=0.4) as shown in Table 2.

*Pregnancy outcomes in women with RA before and after the diagnosis*. The number of pregnancies before the diagnosis of RA was higher than after the diagnosis (154 vs 95, respectively). The percentage of live births after the diagnosis was 67.4% and before the diagnosis – 84.4% (p=0.002). The percentage of preterm delivery before and after the diagnosis did not differ (5.3% and 2.6%, respectively, p=0.142). The percentage of caesarean sections after RA diagnosis confirmation was significantly higher than

**Table 2. Pregnancy outcomes in women with RA in comparison with healthy controls, %**

| Variables | Patients (n=39, 95 pregnancies) | Controls (n=39, 148 pregnancies) | p |
|---|---|---|---|
| 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 | |
| Caesarean section | 23.2 | 48.6 | 0.001 |

**Table 3. Pregnancy outcomes in women with RA before and after the diagnosis, %**

| Variables | Groups | | p |
|---|---|---|---|
| | Before diagnosis (n=39, 154 pregnancies) | After diagnosis (n=39, 95 pregnancies) | |
| 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 | |
| Caesarean section | 16.2 | 23.2 | 0.021 |

**Table 4. The effect of RA on pregnancy planning, %**

| Variables | Groups | | p |
|---|---|---|---|
| | Before diagnosis (n=39, 154 pregnancies) | After diagnosis (n=39, 95 pregnancies) | |
| Planned pregnancy | 22.7 | 74.7 | 0.342 |
| Unplanned pregnancy | 77.2 | 25.3 | <0.001 |

**Table 5. The characteristics of women who stopped getting pregnant after the diagnosis**

| Variables | Groups | |
|---|---|---|
| | The family is complete (n=46) | Fear of RA (n= 15) |
| Age at diagnosis, years, M±SD | 38.3±5.8 | 28.9±4.5 |
| No. of children at diagnosis, Mean | 5 | 2 |
| Disease duration, years, M±SD | 6±4.5 | 1.6±0.8 |

before it (23.2% and 16.2%, respectively; p=0.02). There was no significant difference in pregnancy loss before and after the diagnosis of RA (p=0.985) as shown in Table 3.

*The pregnancy planning before and after the diagnosis of RA.* After the diagnosis of RA 74.7% of women planned pregnancy, and the number of unplanned pregnancies (25.3%) was lower than before the diagnosis (77.2%; p<0.001; Table 4).

*Women who stopped getting pregnant after the diagnosis.* The remaining 61 women with RA who didn't have children after the diagnosis, were divided into two groups regarding the decision not to get pregnant; 75.4% already had the desired number of children (regarded their family as complete) before the diagnosis, and 24.6% feared the effect of RA on themselves and their children. At diagnosis women of the first group had more children than women who feared to get pregnant (mean, 5 vs 2), and their mean age was above 30 years, and less than 30 years, respectively (38.3±4.5 vs 28.9±5.8 years), Table 5.

***Contraceptive methods in relation to current use of methotrexate and leflunomide***

81% of 100 women with RA included in the analysis of contraceptive methods used methotrexate, 43.2% of them received rheumatological consultation regarding the contraceptive methods, and 56.8% did not. 30.86% of patients treated with methotrexate used ineffective contraceptive methods, 27.16% – long-acting reversible methods, 14.81% – effective contraceptive methods, and 24.69% did not use any contraceptive methods. 19% of RA patients used leflunomide, and 73.7% of them received rheumatological consultation regarding the type of contraceptive methods, 36.84 % used effective methods of contraception, 31.58% – long-acting reversible methods, 15.79% – ineffective contraceptive methods, and 15.79% did not use any contraceptive methods. So, the percentage of patients who received a rheumatological consultation regarding contraceptive methods in leflunomide group was higher than in methotrexate group (73.7% and 43.2%, respectively; Table 6, 7).

## Discussion

***Pregnancy outcomes.*** In large cohort studies, pregnancy outcomes in women with RA were less favorable in comparison with normal healthy population, though the differences between RA patients and general population were often small [10].

In this study we revealed a decrease in the frequency of live births after the diagnosis of RA when compared with healthy controls and with patients before the diagnosis of RA. This is in agreement with the study of A.M. Eudy et al. [11] in 2018 in which live birth frequency after RA diagnosis, when compared with healthy controls was 67% vs 53% (p=0.004), and that before and after the diagnosis – 70% vs 63%, respectively (p=0.04). The frequency of preterm delivery in RA group was

comparable with healthy controls – 5.3% vs 4%, which agreed with the study done by J.F. Skomsvoll et al. [12] in 1999 in which the frequency of preterm delivery in RA group compared with healthy controls was 7.1% vs. 5.6%, and also agreed with the study done by M. Norgaard et al. in 2010 in which preterm delivery in RA compared with healthy controls was 9.2% vs. 6.2% [10]. The preterm delivery frequency after the diagnosis of RA was also comparable with that before the diagnosis (5.3% vs 2.6%; p=0.142) which agrees with the study done by A.M. Eudy et al. [11] in 2018 that showed that there was no significant increase in preterm delivery after the diagnosis of RA (16% vs. 0%; p=1.0).

Increased incidence of preterm delivery in RA women may be related to prednisolone use in the study of Y.A. de Man et al. [13] in 2009. C.J. Smith et al. [14] in 2019 mentioned that active RA at the time of enrollment and any time during pregnancy was associated with preterm delivery, corticosteroid use in each trimester was associated with an approximately 2 to 5-fold increased risk for preterm delivery, independent of disease activity.

***Mode of delivery***. There is an increase in the frequency of caesarean sections in healthy controls when compared with women with RA, which may be explained by increasing frequency of caesarean sections in Iraq. N.P. Shabila [15] mentioned that the overall rate of caesarean sections 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 had a university degree, while only 2.6% of women with RA had it, and A. Gilbert et al. [16] showed an increased frequency of caesarean sections in those with a university degree (p=0.03) compared with women whose maximum education was a high school certificate.

On the other hand, there was an increase in the frequency of caesarean sections in women after the diagnosis of RA when compared with that before the diagnosis which agrees with the study done by H. Aljary et al. [17] in 2018 that showed increased frequency of caesarean sections in RA in comparison with controls (42.16% vs 32%, respectively; p=0.001).

There are many causes of the increase in caesarean section frequency in women with RA, such as a high rate of labor induction, prematurity, and mal presentation which were reported among RA complicated births [10].

***Pregnancy loss***. There was no significant difference in overall pregnancy loss among women with RA after and before the diagnosis, and between RA women and healthy controls, which agrees with the study done by A.M. Eudy et al. [11] in 2018, that showed no significant difference between pregnancy loss in women with RA and healthy controls (p=0.9) and before the diagnosis (p=0.4), but there was an increase in the frequency of spontaneous abortions in women with RA compared with healthy controls, which agrees with the study done by M. Wallenius et al. [18] in 2015. The increased risk of spontaneous abortions in women with RA may be contributed to the administration of medication, such as methotrexate, at the time of conception; 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 abortions than in general population [18].

**Table 6. Types of contraceptive methods, n (%)**

| Types of contraceptive methods | Patients on methotrexate (n=81) | Patients on Leflunomide (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) |
| Ineffective | 25 (30.86) | 3 (15.79) |
| No contraceptive | 20 (24.69) | 3 (15.79) |

**Table 7. Rheumatological consultation regarding methotrexate, leflunomide, n (%)**

| Rheumatological consultation | Patients on methotrexate (n=81) | Patients on Leflunomide (n=19) |
|---|---|---|
| With consultation | 35 (43.2) | 14 (73.7) |
| Without consultation | 46 (56.8) | 5 (26.3) |

***Planned pregnancy***. We revealed an increased frequency of planned pregnancies and a decreased frequency of unplanned pregnancies after the diagnosis of RA. This result goes in line with the study done by P. Galappatthy et al. [8] that showed an increased percentage of planned pregnancies after RA onset from 25% to 75%, and it also agrees with the study done by A.M. Eudy et al. [11] in 2018.

***Women who stopped getting pregnant after the diagnosis***. 24.6% of women with RA who stopped getting pregnant, feared pregnancy and had fewer children when compared with those who regarded their family as complete before the diagnosis. This result agrees with the study done by P.P. Katz in 2006 [19] that showed that 20% of women with RA feared to get pregnant after the diagnosis, and though RA diagnosis affected their childbearing decisions, they were not less likely to have any pregnancy or any children, but had significantly fewer pregnancies and children.

The remaining 75.4% of women considered their family to be complete prior to the diagnosis which agrees with the study done by M.E. Clowse et al. [20] in 2012 who found that 60% of 578 women with RA had the desired number of children prior to their diagnosis. Women who feared getting pregnant were younger than those who regarded there family as complete, and had fewer children, which agrees with the study done by M.E. Clowse et al. [20] in 2012. There are also other causes related to RA women's decision not to get pregnant, such 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 a high risk of unintended pregnancies [21].

Among the patients treated with methotrexate, 27.16% used long-acting reversible methods, 14.8% – effective methods, and 55.55% – ineffective methods or no contraception. This disagrees with the study done by A.M. Eudy et al. [11] in 2018 that mentioned 44%, 32%, 24%, respectively. This disagreement with the data of the present study may be explained by the fact

that 56.8% of our patients did not receive counseling about the type of contraceptive methods from their rheumatologists, by factors related to patient and her partner preference, and by financial issues.

36.84% of women with RA receiving leflunomide used effective contraceptive methods, 31.58% – long-acting reversible, and 31.58% – ineffective methods or no methods. These results are in agreement with the study done by T. Banas et al. [22] in 2014, which mentioned that 48.4% of patients used effective methods, and 33% did not use any contraceptive method. Patients receiving leflunomide used more effective contraceptive methods than patients using methotrexate. This discrepancy may be due to medical recommendations because 73.7% of patients treated with leflunomide received consultations about the type of contraceptive methods.

**Conclusion**

There is a decrease in live births and an increase in preterm birth frequency as well as caesarean sections in Iraqi female patients with RA. There is lack of knowledge about the importance of contraceptive methods efficacy in relation to teratogenic medications (methotrexate, and leflunomide).

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**Conflict of Interest Statement**

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