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Reproductive health and rheumatoid arthritis

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Abstract

Introduction The prevalence of Rheumatoid Arthritis (RA) has been steadily increasing over the last thirty years, particularly among women. Due to the conflicting results of various studies on the link between rheumatoid arthritis and reproductive health, we have undertaken this study to explore their relationship.

Methods This cross-sectional study utilized primary data from 5557 women involved in the Fasa Persian Cohort in the years 2013 to 2018. The study examined the frequency of RA and its association with various factors related to reproductive health, including age at first pregnancy, number of alive children, history of abortion, and infertility. SPSS software was utilized for data analysis, with the significance level set at $p < 0.05$.

Results 5557 women with an average age of 48.6 ± 9.5 years participated. Of these women, 7.2% were diagnosed with rheumatoid disease, with an average onset age of 38.2 ± 15.2. The study did not find a significant correlation between RA and factors such as number of pregnancies, age at first pregnancy, duration of breastfeeding and number of children.

Conclusion The study suggests that the experience of RA is independent of gynecological, obstetric factors, or reproductive life. This finding may provide reassurance to women affected by RA.

Keywords Reproductive health, Rheumatoid arthritis

Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease that primarily affects the joints. The burden of RA has increased globally over the past 30 years and is projected to continue rising [1].

Rheumatoid arthritis (RA) primarily affects women; In fact, being female is considered a risk factor for this disorder [2–4]. RA, the most common chronic systemic autoimmune disease, exhibits a female-to-male prevalence ratio greater than 4 before age 50, and below 2 after 60 [3, 5, 6]. Such a gender tendency raises questions about the possible relationship between immune

dysregulation, hormonal fluctuations, and reproductive health [2–4].

Approximately 50% of RA cases occur during the reproductive years, emphasizing the importance of understanding the effect of hormonal and reproductive factors on disease development [6]. There are much evidence regarding the impact of estrogen and progesterone, the two main female sex hormones, on the immune system, and several molecular mechanisms have been proposed [3]. However, studying the influence of female hormonal factors on RA is complex. Pregnancy, breastfeeding and parity of any number have been shown in some studies to be protective, while the incidence and severity of RA is higher in the postpartum period and perimenopause [6–8]. Women with RA are more likely to have coexisting reproductive disorders such as infertility, endometriosis, and premature ovarian insufficiency, or to develop them later on [9]. There is also a known connection between

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RA and abortion as well as polycystic ovary syndrome (PCOS), although the evidence is somewhat controversial [9].

During the peak incidence of rheumatoid arthritis (RA), which typically occurs during the female reproductive period, women often confront significant decisions concerning pregnancy and the potential for having a child; and the stress experienced by RA patients may somewhat influence their reproductive choices [9]. Therefore, it is essential to have a comprehensive understanding of how RA is associated with female reproductive factors in order to provide the best possible care and consultation for women. Despite progress, controversies still exist [3]. Understanding the impact of reproductive factors on the development and trajectory of RA is important. This knowledge informs society and guides medical expectations. Tailoring preventive interventions for high-risk populations may mitigate disease burden and improve outcomes [10]. This article explores the intricate connections between rheumatoid disease (RA) and reproductive factors, shedding light on potential implications for patient care and preventive strategies.

Methodology

This cross-sectional study was conducted on baseline data of Fasa PERSIAN cohort, which is one of the 22 active cohorts in Iran. It started its activity in 2013 and includes about 10,000 people aged older than 35 from Sheshdeh and Qare-Balagh villages in Fasa (south east of Iran) [11].

The entire female population of the Fasa PERSIAN cohort was included in the study.

Subjects with incomplete information on study variables or any history of malignant gynecologic diseases were excluded.

Rheumatoid arthritis was recorded in check list of diseases completed by the individual or in annual follow-ups, as self-reported that was confirmed by a doctor base on American College of Rheumatology and European League criterias on 2010.

The following variables are recorded: current age, years of education, socio-economic status(classified as low, middle, and high), marital status (classified as single, married, widowed, and divorced), obstetric history including gravidity, stillbirth, abortion, age at first pregnancy, alive child numbers and total breastfeeding duration (in months), gynecologic history including history of infertility, hysterectomy, and oral contraceptive pills(OCP) use more than one cycle, physical activity (MET; minutes/week), body mass index (BMI), waist circumference (in centimeter), calorie intake(per day), cigarette, other tobaccos, and opium use as a regular usage. Quantitative variables are described using mean and standard deviation, while qualitative variables are described using frequency and percentage. Univariate analysis was done by using chi-square, independent sample T test, Pearson correlation test and one-way analysis of variance (ANOVA). Logistic and linear regression model were used to adjust confounding variables Variables were correlated with rheumatoid arthritis and start age of disease in univariate analysis with p-value<0.2 enter to these models.

Data analysis was done by SPSS 25 software at a significance level of 0.05.

Results

Among the 5557 women in the Fasa PERSIAN cohort study, the average age of the participants was 48.6±9.5 years. 7.2% of the participants had rheumatoid disease, and the average age at which rheumatoid disease started was 38.2±15.2. 81.9% of the participants were married, and the average years of education was 3.7 years.

We analyzed the socio-demographic characteristics and reproductive factors of participants based on the presence or absence of rheumatoid disease. (Table 1) Reproductive factors such as number of pregnancies, abortions, live child number, infertility, contraceptive use and breastfeeding duration were analyzed with respect to the RA affliction. The mean pregnancy numbers in non-RA and RA groups were 5.15±3.16 and 5.93±3.34, respectively. Age at first pregnancy in non-RA and RA group was 20.45±4.88 and 19.43±4.04 respectively. Among the non-RA group, the live child number was 4.77±2.67; and 5.6±2.76 among the RA group.

Our findings indicated that RA was significantly correlated with waist circumference ($p<0.001$) but not correlated with BMI, calorie intake, and physical activity. Our analysis also revealed that among reproductive factors, RA was significantly correlated with pregnancy number, first pregnancy age, breastfeeding duration, and alive child number (p-value of <0.001) but was not correlated with abortion number, history of hysterectomy, stillbirth, infertility, and contraceptive use. In addition, our analysis showed a significant correlation between years of education and RA (p value<0.001). Marital status did not reveal any significant correlation with RA in our study. Cigarette, tobacco and opium use did not have any significant correlation with RA.

In the regression model (Table 2), it was observed that the years of education have correlations with RA in that people without rheumatoid disease had higher years of education (p value=0.02).

Other variables such as pregnancy number, first pregnancy age, alive child number, abortion number, stillbirth, breastfeeding duration, waist circumference, BMI, and cigarette smoking had no significant statistical correlation with having or not having RA.

Table 1 Socio- demographic characteristics and reproductive factors of participants of study

	No Rheumatoid disease	Rheumatoid disease	P value
Years of education mean ± SD	3.77 ± 3.4	2.85 ± 2.75	< 0.001
Marital status n(%)			0.39
single	265(94)	6(17)	
married	4227(92.9)	323(7.1)	
widow	581(91.4)	55(8.6)	
divorce	82(91.1)	8(8.9)	
Socioeconomic status n(%)			0.75
low	1720(92.8)	133(7.2)	
middle	1707(92.4)	140(7.6)	
high	1726(93)	129(7)	
Waist circumference	96.02 ± 11.43	97.93 ± 12.04	< 0.001
BMI (kg/m2	26.82 ± 4.78	27.33 ± 5.15	0.05
Calorie intake(cal)	2838.77 ± 1110.07	2890.5 ± 1146.44	0.36
Physical activity (MET min/week)	38.41 ± 6.51	38.78 ± 8.13	0.36
Pregnancy number	5.15 ± 3.16	5.93 ± 3.34	< 0.001
Alive child number	4.77 ± 2.67	5.6 ± 2.76	< 0.001
Abortion number	0.44 ± 0.81	0.52 ± 0.79	0.09
First pregnancy age	20.45 ± 4.88	19.43 ± 4.04	< 0.001
Breast feeding duration (months)	90.08 ± 57.38	104.17 ± 58.57	< 0.001
Hysterectomy n (%)			0.25
yes	203(91.4)	19(8.6)	
no	4952(92.8)	384(7.2)	
Still birth n (%)			0.13
yes	701(91.8)	63(8.2)	
no	3997(93)	302(7)	
Infertility n (%)			0.50
yes	1349(92.7)	106(7.3)	
no	3573(92.7)	283(7.3)	
Used contraceptive n (%)			0.31
yes	3432(92.9)	263(7.1)	
no	1723(92.5)	140(7.5)	
smoke Cigarette n (%)			0.07
Yes	253(90.4)	27(9.6)	
no	4902(92.2)	376(7.1)	
Other tobacco usage n (%)			0.31
yes	58(90.6)	6(9.4)	
no	5096(92.8)	397(7.2)	
Opium usage n (%)			0.23
yes	41(89.1)	5(10.9)	
no	5114(92.8)	398(7.2)	

Meanwhile, in linear regression, the relationship between variables and the age of onset of RA was investigated. However, there was almost no relationship between the two except for education level & marital status (p values of 0.001 & 0.03 respectively). (Table 3)

Discussion

In this cross -sectional study women had average age of more than 45 years; 7 out of 100 of them were found to be suffering from RA. The average body mass index of the population was in the overweight range. Additionally,

the average number of pregnancies was more than 5, and the number of live children was over 4. The average age of RA onset was 38.2 years. The average age at first pregnancy was 20.37 years within our population.

This study showed that the number of pregnancies, the age of the first pregnancy, the duration of breastfeeding, the number of children, the number of abortions, and stillbirths, had no statistically significant correlation with RA. However, a review article by Alpízar and colleagues highlighted controversies in different studies regarding whether these factors are associated with RA. Some

Table 2 Logistic regression model for rheumatoid arthritis

	B	S.E.	*P* value	OR	95% CI for OR	
					Lower	Upper
Years of Education	−0.050	0.022	0.0250	0.951	0.910	0.994
Pregnancy Number	−0.190	0.204	0.352	0.827	0.554	1.234
Alive Childbirth Number	0.242	0.206	0.241	1.273	0.850	1.908
First Pregnancy Age	−0.026	0.015	0.072	0.974	0.947	1.002
Abortion Number	0.238	0.215	0.269	1.268	0.832	1.934
Breast feeding Duration	0.000	0.001	0.964	1.000	0.997	1.003
Waist Circumference	0.016	0.010	0.125	1.016	0.996	1.036
BMI	−0.008	0.024	0.753	0.993	0.947	1.040
Smoke Cigarette	0.115	0.218	0.597	1.122	0.732	1.719
Has Stillbirth	−0.258	0.298	0.387	0.773	0.431	1.386
Constant	-3.213	0.711	0.000	0.040		

Table 3 Linear regression model for age of rheumatoid arthritis

	Unstandardized coefficients		Standardized coefficients	*P* value
	B	Std. Error	Beta	
(Constant)	26.888	7.848		0.001
Use Contraceptive Drug	-2.243	1.635	−0.068	0.171
Smoke Cigarette	0.074	2.733	0.001	0.978
Marital Status	3.664	1.764	0.100	0.039
Years of Education	-1.012	0.311	−0.185	0.001
Pregnancy Number	0.066	0.720	0.014	0.927
Alive Childbirth Number	1.547	0.844	0.285	0.068
Breast feeding Duration	0.005	0.017	0.019	0.775
Physical activity	−0.041	0.089	−0.021	0.648

studies suggested a protective effect, while others considered them as risk factors for developing RA [6].

Our study supported previous research findings regarding the relationship between years of education and rheumatoid arthritis (RA). Years of education had an inverse relationship with RA. Previous studies have shown an association between higher levels of education and a decreased risk of RA; However, the findings have been inconsistent, and the reasons behind this association remain unclear [12].

In our analysis, we found that marital status did not show a significant correlation with RA. It seems to be more of a prognostic factor rather than a causal or protective factor [13]. Many studies have shown that married individuals tend to have fewer health problems and lower mortality rates compared to those who are not married, including divorced, widowed, separated, or never married individuals [13]. Being in a well-adjusted or nondistressed marriage seems to be associated with less pain and better functioning for individuals with RA [14].

In our study, we did not find a link between waist circumference and body mass index (BMI) with rheumatoid arthritis (RA). However, a review and meta-analysis showed that overweight and obese individuals have a higher risk of developing RA compared to those with a

normal BMI [15]. Specifically, women with a waist circumference greater than 102 cm had 2–3 times the risk of developing RA, while those with a waist circumference greater than 88 cm did not show the same association [16]. This association may not have been observed due to the cross-sectional nature of our study. Regarding physical activity, Azeez and colleagues found that exercise led to reductions in weight, waist circumference, and BMI in RA patients [17]. Low-intensity leisure-time physical activity (LTPA) was inversely associated with BMI, while moderate/vigorous LTPA showed an inverse relationship with both BMI and waist circumference [18].

The analysis of our population did not show a significant correlation between smoking and rheumatoid arthritis (RA), even though smoking is widely recognized as a significant risk factor for the development of RA [19]. The prevalence of smoking was 6% in the RA group and 5% in the non-RA group. Likely due to the low prevalence of smoking in this rural society, no significant relationship between smoking, tobacco use, and rheumatoid arthritis was observed. Cigarette smoking is associated with the risk of chronic inflammatory diseases (CIDs) like RA [20]. Heated tobacco products (HTPs) are being promoted as a potentially less harmful alternative to traditional cigarettes, but their impact on CIDs is still under ongoing research [20]. In literature, opioids are generally considered for pain management and are not regarded as a risk factor or a protective factor [21].

The age of disease onset was only correlated with marital status and years of education, not any other mentioned variables.

The average age of onset of rheumatoid arthritis in our population was 38.2 years, and the average age at first pregnancy was 20 years. This suggests that the participants in our society completed their reproductive history and family formation before developing rheumatoid arthritis. Therefore, it can be inferred that initiating and completing the reproductive history at a younger age for females does not seem to have an impact on the

incidence of rheumatoid arthritis. We believe that the high average age of disease in our society has led to a lack of correlation between women's reproductive factors and RA. This is because the majority of women's history of childbearing occurs before the average age of the disease in our population, especially considering that the age of marriage and pregnancy is lower in our rural population.

The Fasa Persian cohort comprised individuals over 35 years of age. The average age of the participants in our study was over 45 years old, indicating that our study population had nearly completed its reproductive history. This aspect can be considered both a strength and a weakness of our study. The study did not include individuals of childbearing age who had not completed their reproductive history. However, it focused on people who had completed their reproductive history on a cross-sectional basis, thereby strengthening the study. Additionally, the study population was limited to rural areas, so its findings may not apply to urban populations. As another limitation of this study, the study participants may have used their medications during pregnancy and under the supervision of their physicians, but this group was not analyzed as a separate group.

Despite these weaknesses, our study was conducted on a large population. Furthermore, many reproductive factors in a woman's life were included and studied in our research.

Given the higher prevalence of rheumatoid arthritis (RA) in women and the increased incidence of RA in middle age (50–60 years) [4], it is recommended that multi-centered longitudinal studies, encompassing both rural and urban populations and conducted as either prospective or retrospective studies, should be undertaken to establish the exact relationship between reproductive factors and rheumatoid arthritis. Additionally, since there are varying results from studies on the impact of female hormones on rheumatoid arthritis [3] and considering the higher prevalence of this disease in women compared to men, it is advisable to assess testosterone levels in men with rheumatoid arthritis. Low testosterone levels may potentially play a greater role than female hormones in the development of the disease.

Conclusion
According to the findings of this research paper, there is no significant link between reproductive factors and RA, regardless of gynecologic and obstetric history. Additionally, the onset age of RA is not associated with reproductive factors.

Due to the chronic nature of RA and its mental and emotional burden, it is comforting for affected women to know that suffering from RA is unrelated to gynecological and obstetric factors or their reproductive life.

Although longitudinal studies are recommended, women can be advised that having children at a younger age result in better outcomes and fewer consequences on reproductive health following autoimmune diseases, especially rheumatoid arthritis, which is at its peak in middle age.

Declarations

Ethics approval and consent to participate
Manuscripts reporting studies involving human participants. Accordance to the Helsinki Declaration the study protocol was approved by the National and Regional Ethics Committee of FUMS (code: IR.FUMS.REC. 1402.112) .Written and informed consent was obtained from each participant to enter the first phase of a cohort study and is available on the fa-ncdrc.fums.ac.ir website.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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