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Risk Factors of Rheumatoid Arthritis Development Among Females in North-West of Iran: A Case-Control Study

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Abstract

Background: Given the high prevalence of rheumatoid arthritis (RA) in females of reproductive ages, it seems that hormonal factors might be important in RA pathogenesis.
Objectives: The current study aimed to investigate the association between females' reproductive factors occurring prior to the onset of rheumatoid arthritis and the risk of RA development.
Methods: This case-control study was conducted on 231 patients with RA and 238 controls among females aged 26 - 64 years old from the North-West of Iran. The adjusted risk of RA was assessed using multivariate logistic regression models.
Results: Females $\geq$ 14 years old at menarche, were more likely to be at risk of RA (OR = 1.69; 95%CI: 1.08 - 2.64). Advanced maternal age at first delivery (OR = 1.91; 95%CI: 1.21 - 3.26) and having abortion (OR = 1.97; 95%CI: 1.23 - 2.99) significantly increased the risk of RA. Post-menopausal status increased the risk of developing RA (OR = 2.97; 95%CI: 1.98 - 4.46). Longer duration of breast-feeding was determined as significant protective variable for RA ($P < 0.05$). Subjects with oral contraceptives (OCs) use (OR = 0.36; 95% CI: 0.20 - 0.64), parity (OR = 0.20; 95%CI: 0.06 - 0.70) or large number of children tended to show rather more reduced risk of RA.
Conclusions: The risk of RA increased with delayed menarche, advanced maternal age at first delivery and early age at menopause. However, longer duration of breast-feeding, parity, large number of children and consumption of OCs were found as protective independent variables against RA.

Keywords: Rheumatoid Arthritis, Breast-Feeding, Reproductive History, Oral Contraceptives

1. Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disorder, which is outlined as the main common cause of morbidity from inflammatory arthritis worldwide (1). In this regard, the increasing incidence rate of RA in Iran is remarkable as one of the major challenging issues for public health concern (2). However, no particular attention is paid to studying the etiologic risk factors in the concept of this chronic disorder in Iran (3).

Meanwhile, on the basis of a case-report study conducted in Iran, neonatal lupus (NL) and its main manifestations including skin and liver involvement was observed in infants whose mothers were known subjects of rheumatoid arthritis with positive anti-SSA/Ro (anti-Sjögren-syndrome-related antigen A) antibody. Thus, the presence of certain antibodies contributes as substantial factors in RA development in females and other serious consequences in health status of the infant (4).

An association of severity and long duration of RA with the occurrence of psychological problems are reported. As a result, mental health status can be considered as another contributing factor of RA development (5).

Given that RA predominantly affects females of the reproductive ages twice more than males, other hormonal predisposing factors may be emerged concerning RA pathogenesis (6). The contributions of high estrogen level to the hypothalamic-pituitary-adrenal (HPA) axis in augmentation of inflammatory reactions were addressed in different earlier observations (7). Additionally, estrogen is likely attributed to the upregulated production of auto-antibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptides (anti-CCP) (8, 9), suggesting a possible promoting effect of estrogen on RA development. In other circumstances, a series of epidemiologic data re-

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cently suggested the protective role of high level of estrogen on RA pathogenesis prominently resulted from the significant ameliorating conditions in association with pregnancy and post-partum flares on RA symptoms (10). It is biologically speculated that estrogen might be attributed to the inhibition of IL-1 and TNF-α secretions from macrophage and T-cells and also induction of regulatory T-cells and TGF-β, which altogether results in osteoclast apoptosis and reduction in inflammation and eventually might lead to remission in the disease (8, 9). There is confined evidence with contradictory findings to support the role of estrogen and related reproductive factors (such as age at menarche, age at menopause and age at first delivery) in RA risk, which is subject to a debate.

Age at menarche is a key characteristic of initiating time episode of exposing to increased rates of female hormones may influence the risk of RA (11-14). Nevertheless, females who were at younger ages for menarches were expected to be at higher risk for RA development (6, 15, 16), some researchers described the increasing risk of the disease by being at older ages for the physiological commencing of mense (11-14). Age at menopause is supposed as another key determinant of estrogen exposing period in lifetime to raise the RA incidence (15). However, early age at menopause also increases the risk of RA (10, 17). The association between using oral contraceptives (OCs) and the risk of RA is conflicting as well. Some studies suggested that the use of OCs is protective (18-21). However, several studies have met no significance to demonstrate this association (22-24).

Considering the ambiguous role of reproductive factors in RA pathogenesis, it is tempting to explore potent risk factors among nominated characteristics related to the cumulative estrogen exposure against the risk of RA. Particularly investigation among Iranian females, who experience a cultural transition of bearing fewer children from conventionally crowded families, might provide better insights in this area.

Also, despite the high prevalence of RA in Iran, no study addressed the hormonal risk factors for RA.

2. Objectives

The current case-control study aimed to investigate the association of different potent reproductive parameters with the risk of RA development among females in North-West of Iran.

3. Methods

3.1. Study Subjects

A hospital-based and matched case-control study was conducted from May 2011 to May 2012 in Tabriz, the North-West of Iran. Outpatients from the neighboring provenances including Hamadan, Ardabil, East and West Azerbaijans referred to specialists' clinic in Sina hospital affiliated to Tabriz University of Medical Sciences, Tabriz, Iran. The case group consisted of 231 patients with RA, who fulfilled the inclusion criteria. Eligibility principles for the subjects included documentation of RA according to the American College of Rheumatology (ACR/EULAR criteria 2010) classification, aged 26 - 64 years and written informed consent. Patients who had serious comorbidity such as other chronic inflammatory disorders and autoimmune diseases, (such as systemic lupus erythematosus, intestinal bowel syndrome, Behcet Disease, etc.), severe liver or kidney dysfunction, any sort of malignancies or receiving chemotherapy, hormonal therapy and radiotherapy, benign neoplasms, trauma, chronic hormonal complications (polycystic ovary syndrome, diabetes mellitus, adrenocorticotropin hormone-related disorders, hyperprolactinemia, hyperparathyroidism, Cushing syndrome, hypoglycemia), severe allergic reactions and patients with super obesity (BMI > 40), pregnancy or lactation were excluded from the present study. The hospital-based control groups included 238 normal subjects randomly assigned in this study. Controls were matched to the subjects in case group on available data, i e, age (mean $\pm$ three years) and the place of residence (city or village). Age of the controls at the time of interview were matched to their age at diagnosis for the cases. The normal subjects did not have any history of RA, other inflammatory-related chronic disorders, gynecological and endocrinological diseases and also fulfilled the inclusion criteria as mentioned above. They were recruited from family caregivers in skin, surgery and rhinology wards and Specialists Referral Clinic affiliated to Tabriz University of Medical Sciences, Tabriz, Iran.

The patients with RA and the control group entered the study by convenience sampling and randomized sampling methods, respectively. Randomized sampling was performed in a frame of 750 healthy subjects considering fraction ratio = 3.2.

Sample size was 187 subjects, calculated on the basis of the results of Reckner Olsson et al. (12), on the variable of Parous status of exposed and non-exposed population to environments (P_1 = 0.396, P_2 = 0.508). The following formula was applied to calculate the sample size, in which: n, represents sample size, α = 0.05 (type 1 error), β = 20% (type 2 error), and ΔP = 0.05 was expected to test the difference of the two population proportions.

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$$n = \left[Z_{1-\frac{\alpha}{2}} + Z_{1-\beta}\right]^2 \times \left[P^1 \times \left(1-P^1\right) + \left(P^2\left(1-P^2\right)\right)\right] \frac{}{\Delta P^2} \quad (1)$$

All the procedures were approved by the research ethics committee of Tabriz University of Medical Sciences (ethical approval code: 5/46/176, date: May 10, 2012), and performed according to the Helsinki humanity research declaration (2008). During the experiments, all the personal information was kept confidential and other ethical and considerations of humanity were performed as well.

The whole set of answers on date and type of menopause (natural or induced by bilateral oophorectomy), age at menarche, date of hysterectomy (if positive), date of the first menstruation, age at menarche (puberty; years), maternal age at first delivery (years), the number of previous live-born children, abortion(s), the number of breast-fed children and the duration were recorded in the questionnaire. Well-trained interviewers were conducting face to face interviews with each subject. The interviewer administered questionnaires related to reproductive events and timings only to the period before the development of their RA. Duration of estradiol exposure variable is a term used for being in reproductive life span (25). Age at menarche and first delivery were stratified in tertiles. Early menarche was defined as the first menstruation before age of 13 years. The median age at menopause was determined at 48 years old. These borderlines were all identified in the control sample population. Non-responders to each variable were not considered in the concerning analysis. The history of OCs use, and non-steroid anti-inflammatory drugs (including the starting time, frequency of daily use and the duration of usage) were also ascertained through combination of open- and closed-structured questions.

Information of body mass index (BMI, measured weight in kilograms divided by squared meters of height (kg/m^2) at diagnosis as the primary measure of total adiposity were calculated. Weight (to the nearest 0.1 kg) and height (to the nearest 0.5 cm) were measured in a standard position using a calibrated scale (Seca, Germany) and a wall-meter respectively. according to the world health organization (WHO), overweight was defined as BMI between 25 and 29.9 kg/m^2, while obesity as BMI greater than 29.9 kg/m^2 (26).

3.2. Statistical Analysis

Statistical analyses were conducted using the SPSS statistical package (SPSS Inc., version 11.5). Independent sample T-test was used to compare the continuous data between the case and control groups. Linear histogram and boxplot were used to observe the normality of data distribution (skewness and kurtosis) and detecting the outliers, respectively. The association of independent categorized reproductive factors with RA as dependent outcome was analyzed using Chi-squared statistics test. Multivariate conditional logistic regression analysis was carried out to calculate odds ratios with 95% confidence intervals (OR, 95% CI). Authors adjusted for potent confounding variables correlated with hormonal status or RA pathogenesis (in univariate analysis). As a whole, these intercorrelated covariates were considered in the model of adjustment to alleviate the effect of potential confounders, that is estradiol exposure duration (months), smoking status (yes or no), menopausal status (premenopausal or postmenopausal), age at diagnosis (years), BMI, maternal age at first delivery, OCs usage and frequency of pregnancies. All statistical analyses were two tailed and P values below 0.05 or a 95% CI not including 1.0 were considered significant.

4. Results

The demographic characteristics and gynecological age of subjects in the case and control groups are summarized in Table 1. The mean of age at diagnosis was not different significantly between the case (40.7 $\pm$ 12.1 years) and control (41.4 $\pm$ 10.8 years) groups. In comparison to controls, subjects with RA were more likely to be older at menarche ($P < 0.01$), and younger at onset of menopause ($P < 0.01$). The time course of estradiol exposure was markedly longer in subjects with RA (342 $\pm$ 106 months) than those of the controls (317 $\pm$ 110 months) ($P < 0.05$).

The gynecologic age and menopausal status in the case and control groups are compared in Table 2, and OR and 95%CI for the association of corresponding variables with RA risk are also shown. Late age at menarche significantly increased the risk of RA. This significant association between higher strata of age at menarche and RA was also denoted after adjustment for confounders, i e, age at diagnosis, BMI, maternal age at first delivery and duration of estradiol exposure (OR = 2.20; 95% CI: 1.25 - 4.11). A significant increased risk of RA was also observed with late age at first delivery (OR=1.91; 95% CI: 1.21 - 3.26). Risk of RA was greater for those who were $\geq$ 21 years old at first delivery compared with the ones aged $\leq$ 18 years. After adjustment for some confounders (such as age at diagnosis, BMI and duration of estradiol exposure), the risk of RA increased in association with advanced maternal age at first delivery (OR = 2.67; 95% CI: 1.32 - 5.56) (Table 2). Post-menopausal females were in higher risk of being RA rather than pre-menopausal ones (OR = 2.97; 95%CI: 1.98 - 4.46). This association was more remarkable, even after adjustment for relevant confounders (Table 2).

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Table 1. Demographic Characteristics and Gynecological Age Status in the Case and Control Groups[a]

Characteristics	Case	Control	P Value
Age at diagnosis, y	40.7 ± 12.1	41.4 ± 10.8	0.480
Age at menarche, y	13.9 ± 1.8	13.4 ± 1.7	0.002
Maternal age at first delivery, y	20.9 ± 4.5	20.2 ± 4.7	0.135
Age at menopause, y	43.4 ± 13.8	47.8 ± 6.1	0.006
Duration of estradiol exposure (month)	342 ± 106	317 ± 110	0.021
Place of residence			
City	72 (15.4)	80 (17.1)	0.161[b]
Village	171 (36.6)	144 (30.8)	

[a]Values are expressed in mean ± standard deviation.
[b]Pearson Chi-square test; the relative frequency of subgroups was shown in parenthesis (%).

Table 2. Gynecological Age and Menopausal Status in the Case (n = 231) and Control (n = 238) Groups and Rheumatoid Arthritis Risk

Variables	Case Group[a]	Control Group[a]	P Value[b]	Crude OR	95%CI	Adjusted OR	95%CI
Age at menarche, y							
≤ 13	117 (27.5)	85 (20.0)	0.059	1.00	-	1.00[c]	-
13 - 14	54 (12.7)	42 (9.9)		1.07	0.66 - 1.75	1.27	0.66 - 2.42
≥ 14	57 (13.4)	70 (16.5)		1.69	1.08 - 2.64	2.20	1.25 - 4.11
Maternal age at first delivery, y							
≤ 18	107 (28.8)	78 (21.0)	0.029	1.00	-	1.00[c]	
18 - 21	50 (13.4)	58 (15.7)		1.51	0.99 - 2.57	1.95	1.05 - 3.62
≥ 21	33 (8.9)	46 (12.4)		1.91	1.21 - 3.26	2.67	1.32 - 5.56
Menopausal status							
Pre-menopause	186 (40.1)	129 (27.5)	0.001	1.00	-	1.00[d]	-
Post-menopause	50 (10.7)	102 (21.7)		2.97	1.98 - 4.46	13.134	5.36 - 32.17
Age at menopause, y							
< 48	24 (15.2)	57 (36.1)	0.576	1.00	-	1.00[d]	-
≥ 48	26 (16.5)	51 (32.3)		0.83	0.42 - 1.62	1.10	0.17 - 7.01

Abbreviations: RA, rheumatoid arthritis; OR, odds ratio; 95%CI: 95% confidence interval.
[a]Values are expressed as observed No. (%).
[b]P value was obtained through Pearson Chi-square statistic test. The models were planned by means of logistic regression analysis and significant ORs with P < 0.05 were indicated.
[c]The multivariate model was adjusted for relevant confounders, i e, age at diagnosis, body mass index (BMI), maternal age at first delivery and duration of estradiol exposure.
[d]The multivariate model was adjusted for age at diagnosis, BMI, maternal age at first delivery, contraceptive usage and frequency of pregnancies.

Table 3 contains data related to reproductive and breast-feeding status of the subjects. Parity was inversely associated with RA risk at OR = 0.20 (95%CI: 0.06 - 0.70). The risk of RA significantly decreased by increasing the number of children. This protective effect was highlighted even after adjustment for relevant confounders (Table 3). A significant association was also observed between having abortion and risk of RA (OR = 1.97; 95% CI: 1.23 - 2.99). Longer duration of breast-feeding was found in a protective factor for RA. In case of breast feeding for more than four months, a lower significant risk of RA was obtained in comparison to those who never breast fed (OR = 0.1; 95% CI: 0.01 - 0.80). There was a significant inverse association between OCs use and the risk of RA (OR = 0.36; 95% CI: 0.20 - 0.64). Indeed, after adjustment for confounders, those who had consumed OCs were at lower risk of RA versus never users (OR = 0.40; 95% CI: 0.02 - 0.90).

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Table 3. Reproductive and Breast-Feeding Characteristics of Case (n = 231) and Control (n = 238) Groups, and Their Association With RA Risk

Variable	Case Group[a]	Control Group[a]	P Value[b]	Crude OR	95%CI	Adjusted OR	95%CI
Live born children	3 (0.7)	15 (3.6)	0.006	1.00	-	1.00[c]	-
Nulliparous	198 (47.7)	199 (48.0)		0.20	0.06-0.70	0.12	0.02 - 0.58
Parous							
0	3 (0.7)	15 (3.6)	0.032	1.00	-	1.00[d]	-
1	24 (5.8)	33 (8.0)		0.27	0.07 - 1.05	0.10	0.01 - 1.15
2	54 (13.0)	59 (14.2)		0.22	0.06 - 0.80	0.07	0.01 - 0.88
3	45 (10.8)	35 (8.4)		0.16	0.04 - 0.58	0.05	0.01 - 0.67
$\geq$ 4	75 (18.1)	72 (17.3)		0.19	0.05 - 0.69	0.14	0.11 - 1.84
Abortions							
Never	146 (36.1)	118 (29.2)	0.001	1.00	-	1.00[d]	-
Ever	54 (13.4)	86 (21.3)		1.97	1.23 - 2.99	2.73	1.54 - 4.82
Breast feeding (month)							
Never	1 (0.3)	12 (3.3)	0.001	1.00	-	1.00[d]	-
$\leq$ 3	8 (2.2)	19 (5.2)		0.20	0.02 - 1.80	0.16	0.01 - 1.88
4 - 11	26 (7.1)	30 (8.2)		0.10	0.01 - 0.80	0.04	0.01 - 0.44
12 - 23	75 (20.5)	67 (18.3)		0.07	0.01 - 0.59	0.06	0.01 - 0.65
$\leq$ 24	75 (20.5)	53 (14.6)		0.06	0.01 - 0.41	0.06	0.01 - 0.59
Oral contraceptives usage							
Never	192 (41.9)	204 (44.5)	< 0.001	1.00	-	1.00[d]	-
Ever	45 (9.8)	17 (3.7)		0.36	0.20 - 0.64	0.40	0.02 - 0.90

Abbreviations: RA, rheumatoid arthritis; OR, odds ratio; 95%CI, 95% confidence interval.
[a] Values are expressed as observed No. (%).
[b] The P-value was obtained through Pearson's Chi-square test. Significant ORs with P < 0.05 were indicated.
[c] The multivariate adjusted variables were age at diagnosis, BMI, and duration of estradiol exposure.
[d] The model was adjusted for relevant confounders, i e, age at diagnosis, body mass index (BMI), maternal age at first delivery and duration of estradiol exposure.

5. Discussion

On the basis of the current study findings, advanced age at menarche and maternal first delivery, and early age at menopause are determinants of increasing RA risk. However, longer duration of breast-feeding, parity, large number of children and consumption of OCs were found as protective independent variables against RA.

Advanced age at menarche showed a significant association with RA risk. It was shown that females aged over 14 years of menarche were comparatively at higher risk of RA. Consistently, the current study findings were in line with much recent evidence on juvenile RA suggesting compromised RA with delayed menarche (12, 27). On the other hand, the impairment and delayed sexual maturation was reasonably delineated in subjects with RA (27), which could be likely in concerned with up-regulation of pro-inflammatory mediators and also being polymorphic for some susceptible genes, e g, human leukocyte antigen (HLA) gene (28). Thereby, the reasons for autoimmunity in RA development might predispose individuals to postponed menarche (7).

In the present study, a significant inverse association was also found between parity and the risk of RA. The current study results are in agreement with those of the most previous studies suggesting a predisposing effect of nulliparity in RA disease (19, 29-31). It is denoted that long-term persistence of fetal DNA in the mother's bloodstream (fetal microchimerism) give further description for the preventive role of parity in RA development (30). Additionally, there is convincing evidence that some immunosuppressive proteins in mother's bloodstream is reflected in weighting Th2 versus Th1 responses (32).

The current study findings showed that the menopausal status was significantly associated with increased risk of RA. The increasing body of reports underlined the fact that the onset of RA is coincident with years of menopause onset (16). The time period that is believed

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in diminishing and subsequent halted of the hormonal secretions of ovaries, i e, estrogen and progesterone (16, 33). Perhaps, estrogen deficiency or acute change in its level at menopause may play an important role in the risk of RA development (10, 15). Thus, late age at menopause and consequently delay in hormonal changes might be a protective factor against the risk of RA development (10).

On the basis of the current study findings, the duration of estradiol exposure was fundamentally longer among subjects with RA. This outcome might be concerned with large variation in age at menopause in both case and control groups. Several investigations have described that estrogen may increase the risk of RA through promoting phagocytic activity of immune system and producing antibodies (8, 9). In addition, it is revealed that the balance among sex hormones impaired in synovial fluid of subjects with RA (9). It seems that estrogen to androgen ratio is increasing in favor of exacerbating inflammatory condition (1, 34). The suggested mechanism behind this event might be explained by increasing inflammatory cytokines such as TNF-α, IL1β and IL6 that induce aromatase activity in order to convert androgens to estrogen (9). Subsequently, estrogen predominantly metabolizes to 16α-hydroxyestrone that might cause synoviocyte proliferation which is a hallmark of RA (9). Moreover, 16α-hydroxyestrone found in RA synovial fluid is pro-inflammatory (9, 34, 35).

Regarding the role of sex steroids in the etiology of RA, it is believed that exogenous steroid hormones such as OCs may play an important role to develop RA as well (18). In this regard, the current study findings showed that OCs use was in an inverse significant association with the risk of RA. Bhatia et al. described that OCs usage can decrease RF autoantibody production in healthy females (36).To date; the underlying mechanism for the protective effect of OCs in the development of RA is less noticed. Estrogen has dual immune-stimulatory and immunosuppressive effects depending on its physiological level (6, 32). Females, who consumed OCs before 1970, were in a lower risk to develop RA (18). Since OCs pills at that time included high doses of estrogen level compared with now. On the other hand, progesterone is an immunosuppressive hormone. This property is partly related to its androgenic effects (18). Thereby, it appeared that the OCs use as exogenous hormone might help to protect individuals against the risk of RA (36).

There was an inverse association between breast-feeding and the risk of RA, which was consistent with other evidence from previous prospective epidemiologic studies (6, 37, 38). Karlson et al. (6) in the large cohort of nurses' health study demonstrated the strong protective role of breast-feeding on RA with significant descending trend across increasing duration of breastfeeding among parous females. In particular, they denoted a significant protective role while the duration of breast-feeding exceeded 24 months, just after taking age, smoking, BMI, parity, OCs usage and other hormonal factors as covariates into account (6). In a prospective cohort older females from Iowa on 158 incident subjects of RA, an inverse association between increasing the number of children breastfed (> 2) and RA risk in an age-adjusted model was also delineated (10). However, only a limited number of studies highlighted the contribution of breast-feeding and its duration in later disease pathogenesis (22). Some researchers show that the increased risk of RA during breast-feeding might in part attribute to higher level of prolactin (15). In addition, there is evidence suggesting that genetic variations in HLA-DRB1 alleles as a strong genetic component in providing susceptibility to RA development in combination with prolactin level (39). Thereby, it seems that among the underlying mechanisms concerning the privileged role of breast feeding on reducing the RA risk later in life is considered as the predisposing genetic variations simultaneously in the upcoming future studies.

The limitation of present study, like other retrospective researches, was the relevant intrinsic error in most question based studies mostly referred to recall bias. Additionally, the current study data in subjects were almost obtained in 24 months later than the disease onset or diagnosis. Therefore, some diagnosis related bias might render possible misclassifications, attempted to alleviate by recalling though reproducible questions. In addition, nutritional factors, physical activity pattern, biochemical hormonal status and genetic predisposition factors were not considered in the analyses and might affect results as confounders. The advantage of the current study was including large enough sample size in a matched case-control study and assessment of the risk factors by trained interviewers (non-self-administering method). The participants in the case group were clinically examined and biochemical tests supported the validity of RA diagnosis. However, there was potential for misclassification in the control group while data, for lack of RA, were documented based on self- or medical-reports. In addition, the case and control groups showed minor demographic differences (Table 1). The inclusion of this representative sample population of females with RA from North-West of Iran (Azeri-language community) could likely provide data with relative less genetic heterogeneity, sunlight exposure and lifestyle related variations.

In conclusion, it is the first study focused on female reproductive factors involved in RA etiology in Iran, which showed an increased risk of RA with delayed menarche, advanced maternal ate age at first delivery and early age at menopause. Females with delayed menarche were more likely to be at higher risk of RA compared with the ones

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aged $\leq$ 13 years old. An inverse association was observed between parity and risk of RA. The protective effect of OCs use on risk of RA was also observed in this study, suggesting the related estrogen and progesterone contents as pro-inflammatory hormones. Besides, the protective effect of breast-feeding was noticed on the risk of RA development later in life.

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Footnotes

Authors' Contribution: Saeed Pirouzpanah, Mehrzad Hajialilo, Alireza Khabbazi and Neda Ghamarzad Shishavan: study design; all authors: data collection and entries; Saeed Pirouzpanah, Mehrzad Hajialilo, Alireza Khabbazi and Neda Ghamarzad Shishavan: writing of manuscript; none of the authors had personal or financial conflicts of interest.

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