Gynecological/Obstetric Background and Rheumatoid Arthritis: A Cross-sectional Study in Brazilian Patients

Antecedentes ginecológicos/obstétricos e artrite reumatoide: Um estudo transversal em pacientes brasileiros

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Abstract

Objective To study a sample of rheumatoid arthritis (RA) patients for their gynecological/obstetric history and compare them to controls to determine their influences on number of pregnancies, menarche, menopause and reproductive years following RA onset.

Methods This is a cross-sectional study of 122 RA patients and 126 controls. Patients and controls were questioned about age of menarche, age of menopause, number of pregnancies and abortions. Reproductive years were calculated as the difference between age at menopause and age at menarche. For comparison, we used the Mann-Whitney, unpaired t, chi-squared, and Spearman tests. The adopted significance was 5%.

Results In the RA patients with disease beginning in the postmenopausal years, the period of reproductive years (age at menopause – age of menarche) showed a positive correlation with age at disease onset (ρ = 0.46; 95% confidence interval [CI] = 0.20–0.55 with p = 0.0008). The number of pregnancies was higher in patients with postmenopausal disease onset when compared with those with premenopausal disease onset (median of 3 with interquartile range [IQR] = 2–4 versus median of 2 with IQR = 1–3; p = 0.009), and RA patients had more pregnancies than controls (p = 0.0002).

Conclusion The present study shows that, in our population, the duration of reproductive years and the number of pregnancies are linked to the onset of RA.

Keywords ► rheumatoid arthritis ► pregnancies ► menarche ► menopause ► postmenopause

Resumo

Objetivo Estudar uma amostra de pacientes com artrite reumatoide (AR), com investigação da história ginecológica e obstétrica, comparando-a com controles, visando conhecer suas influências no número de gestações, menarca, menopausa e anos reprodutivos no início da AR.

Métodos Trata-se de um estudo transversal de 122 pacientes com AR e 126 controles. Pacientes e controles foram questionados sobre idade da menarca, idade da menopausa, número de gestações e abortos. Os anos reprodutivos foram calculados com a
introduction
Rheumatoid arthritis (RA) is the most common connective tissue disease, with a prevalence of 1% in the general population. Similar to other connective tissue diseases, RA has a female predominance; the ratio ranges from 4 women to 1 man, when the disease begins in the reproductive years, to 2 to 1, when it initiates after 60 years. Hormonal influences have been considered to play a role in this female preponderance as estrogens are considered to be agents with proinflammatory activity and capable of activating B cells. 

Rheumatoid arthritis and female reproduction have been linked in the literature for decades, and the decrease in its symptoms during pregnancy is well recognized, with exacerbation of the disease in the postpartum period. The gynecological and obstetrical history have been studied in this context; however, contradictory results have been obtained. According to an epidemiological investigation in a Swedish context, the patients with RA had a female predominance; the ratio ranges from 4 women to 1 man, when the disease begins in the reproductive years, to 2 to 1, when it initiates after 60 years. 

The results were analyzed with the help of the software Graph Pad Prism version 6.01 (Graph Pad Software, San Diego, CA, USA). To analyze the data distribution, the Shapiro-Wilk test was used. The central tendency of parametric data was expressed in mean ± standard deviation (SD) and of non-parametric data as median and interquartile range (IQR). For comparison of numerical data (age, age of menarche, menopause, number of pregnancies, and number of abortions), we
Table 3 Comparison of rheumatoid arthritis patients with disease onset prior and postmenopause

<table>
<thead>
<tr>
<th>Variables</th>
<th>Fertile women (n)</th>
<th>Postmenopausal women (n)</th>
<th>Abbreviations: IQR, interquartile range; n, number.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (IQR)</td>
<td>40 (31.45-51.0)</td>
<td>56 (46.0-68.0)</td>
<td>0.0001</td>
</tr>
<tr>
<td>Median age at menarche (years) (IQR)</td>
<td>13 (12.1-14.7)</td>
<td>12 (11.0-14.0)</td>
<td>0.02</td>
</tr>
<tr>
<td>Median number of pregnancies (n) (IQR)</td>
<td>8 (7.25-9.25)</td>
<td>8 (7.00-8.25)</td>
<td>0.05</td>
</tr>
<tr>
<td>Four children or more (n)</td>
<td>26/122 (21.3%)</td>
<td>10/125 (8.0%)</td>
<td>0.43</td>
</tr>
<tr>
<td>Three children (n)</td>
<td>32/122 (26.2%)</td>
<td>55/125 (44.0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Two children (n)</td>
<td>32/122 (26.2%)</td>
<td>55/125 (44.0%)</td>
<td>0.009</td>
</tr>
<tr>
<td>One child (n)</td>
<td>23/122 (18.8%)</td>
<td>28/125 (22.4%)</td>
<td>0.009</td>
</tr>
<tr>
<td>Nulliparas (n)</td>
<td>0</td>
<td>12/125 (9.6%)</td>
<td>0.009</td>
</tr>
</tbody>
</table>

Table 4 Comparison of rheumatoid arthritis patients with positive rheumatoid factor (n) and postmenopausal disease onset. The correlation of the number of reproductive years with age at menopause in RA patients with postmenopausal onset was done with the Spearman test. The adopted significance was 5%.

<table>
<thead>
<tr>
<th>Variables</th>
<th>Postmenopausal RA patients (n)</th>
<th>Postmenopausal controls (n)</th>
<th>Abbreviations: IQR, interquartile range; n, number.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median age (years) (IQR)</td>
<td>57.2 (51.0-60.5)</td>
<td>55.0 (50.0-60.5)</td>
<td>0.10</td>
</tr>
<tr>
<td>Median age at menopause (years) (IQR)</td>
<td>49.12 (44.45-54.45)</td>
<td>49.12 (44.45-54.45)</td>
<td>0.0008</td>
</tr>
<tr>
<td>Median number of pregnancies (n) (IQR)</td>
<td>8 (7.00-8.25)</td>
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</tr>
</tbody>
</table>

Table 2 Comparison of obstetrical/gynecological history in RA and controls

The comparison of these two samples is on - Table 4.

Table 1 Description of the studied sample of rheumatoid arthritis patients according to the presence of rheumatoid factor (RF).

The description of the RA studied sample is on - Table 1.

The group of 122 RA patients had 290 children (2.3/patient).
postmenopausal disease onset, we found that in controls the median age of menopause was 50 years (IQR = 47.0–51.5), while it was 46.0 (IQR = 42.7–50.0) in RA patients, with \( p = 0.003 \).

**Discussion**

Our results have shown that RA patients had earlier menopause and later menarche than controls, suggesting that reproductive years in RA females are diminished. They also show that, if the number of reproductive years increases, the disease onset is delayed. These results point to a protective role of the length of reproductive years in the occurrence of this disease. Finding an early age for menopause in RA is consistent with previous results. A study with the Nurses’ Health Study (NHS) cohort showed that early menopause increased the risk of RA (HR = 2.1). Another study found that menopause onset at an age earlier than 40 years old more than doubled the risk of RA (odds ratio \([OR]\) = 2.5).\(^{15}\)

Although estrogen is broadly considered to have a proinflammatory activity, its action is much more complex; this hormone may have diverse effects on the immune system, according to its concentration, on tissue receptor expression, and even on the female’s reproductive stage.\(^6\) Estrogens at peri-ovulatory to pregnancy serum levels are capable of increasing B-cell responses, driving antibody secretion in healthy and autoimmune situations.\(^{16}\) At similar levels, it stimulates the secretion of IL (interleukin) –4 and IL-10 and inhibits tumor necrosis factor (TNF) production, downregulating T cell-dependent immunity.\(^6\) The secretion of IL-1β (a proinflammatory cytokine) by monocytes and macrophages is increased at peri-ovulatory to early pregnancy levels; however, it is inhibited at late pregnancy levels.\(^{16}\)

Binding to the different receptors may also modulate the influence of estrogen on the immune system. Synovial cells of RA joints have both estrogen receptors, ER-\(\alpha\) and ER-\(\beta\), with higher density of ER-\(\beta\), which is usually upregulated under hypoxic and inflammatory circumstances such as arthritis.\(^{17}\) Studies in animal models have shown that the use of selective ER-\(\beta\) estrogens may have a repressive effect in the transcription of proinflammatory genes;\(^{16}\) this has led to the attempt to use them in the treatment of RA, unfortunately with negative results.\(^{18}\)

The number of pregnancies has been considered protective for RA by some authors but not by others.\(^{7,8,10}\) In the present work, we found that RA patients have significantly more children than controls. In addition, the number of pregnancies was higher in patients with postmenopausal diagnosis. Altogether, these data suggest that the number of pregnancies is linked positively to this disease appearance. Nevertheless, it is important to remember that the premenopausal women are still fertile, and the number of pregnancies may increase, blurring this difference. Another point to pay attention to and that may have caused possible interpretation bias within this data are that we did not collect information on breast feeding. Although controversial, some authors found that long duration of breast feeding was associated with increased risk of developing RA.\(^{17,19,20}\) Prolactin is considered both a hor- mone and a cytokine; it has an immune stimulatory effect, inhibiting the negative selection of autoreactive B lymphocytes and promoting autoimmunity.\(^{21}\)

The present work has several limitations: its cross-sectional design is one of them; another one is not having data on breast feeding. Also, it would have been interesting to analyze the influence of the gynecological/obstetric background according to the anti-citrullinated peptide (CCP) positivity. However, it does highlight the importance of menarche and menopause ages in the risk of developing RA, showing that more studies in this area could bring important information for the understanding and treatment of this disease.

**Conclusion**

In conclusion, the present study shows that, in our population, the decrease in reproductive years and the high number of pregnancies are linked to the onset of RA.

**Collaborations**

All of the authors contributed with the project and data interpretation, the writing of the article, the critical review of the intellectual content, and with the final approval of the version to be published.

**Conflict of Interests**

The authors have no conflict of interests to declare.

**References**


