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EDITORIAL

Complex role of oestrogens in the risk and severity of rheumatoid arthritis in menopause

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INTRODUCTION

In their original article, Park *et al* investigated the differences in terms of clinical outcomes between early menopause (EM) (<45 years) and usual menopause (UM) (≥45 years) in a large nationwide cohort of patients with rheumatoid arthritis (RA), highlighting the impact of EM on longitudinal changes in RA activity and patient-reported outcomes (PROs).[1]

As a result, the EM group demonstrated a higher disease activity and worse PROs for global assessment, fatigue, sleep disturbance and health-related quality of life than UM group in a 5-year follow-up period.

Therefore, for the first time, the study investigated the association between age at menopause and clinical impact in patients with RA using validated disease activity indices and PROs during their follow-up.[1]

The clinical results of the analysis suggest possible pathophysiological interpretations based on the complex role played by oestrogens in immune response and in particular in the higher risk and severity of RA disease activity during menopause.

Indeed, onset and progression of chronic autoimmune rheumatic diseases such as RA are more commonly observed in women rather than men and are correlated with ageing and menopause, the last characterised by the permanent cessation of ovulation with subsequent hypo-oestrogenaemia.[2]

The partial loss of the immunomodulatory effects exerted by oestrogens is an important factor responsible for the negative clinical outcomes observed in patients with RA during menopause.[3]

Consequently, the decrease in oestrogen concentrations after menopause could contribute to the reported negative effects on disease progression and severity in patients affected by RA.[4]

Dichotomous effects of oestrogens on immune response

Male and female gonadal hormones have important proinflammatory and anti-inflammatory effects on the immune system, as clearly demonstrated by in vitro and in vivo (both animal and human) studies of different pathological conditions.[3]

Androgens have direct and indirect anti-inflammatory effects on immune system with a significant lower risk of developing autoimmune rheumatic diseases in men than women.[5]

By contrast, oestrogens exert both complex proinflammatory and anti-inflammatory effects that may differ depending on the cell type mainly involved in the specific autoimmune disease onset and progression (ie, T or B cells) and on the doses or concentrations involved (exogenous and/or endogenous sources).[6]

Usually, oestrogens exert proinflammatory effects on B cells and anti-inflammatory effects on T cells, especially at high concentrations, by inhibiting T helper 1 (TH1) cells, TH17 cells via oestrogen receptor-α (nevertheless, an opposite effect can be observed via oestrogen receptor-β) and on macrophages.[3 7 8] Additionally, oestrogens seem to support regulatory T cells and TH2 cell-associated cytokines production (interleukin (IL)-4, IL-10 and transforming growth factor-β).[3 7 8] However, low endogenous oestrogen concentrations may increase the risk of developing autoimmune rheumatic diseases mainly driven by T cells.

Conversely, both low and high concentrations of oestrogens are recognised to stimulate B cells, and B cell-dependent autoimmune diseases like systemic lupus erythematosus (SLE) at any dose of oestrogens.[3]

Role of oestrogen fluctuations during the major physiological female events

Analysing the results of the study of Park *et al* on disease outcomes in postmenopausal women affected by RA, we should consider

Table 1 Phases of a woman's physiological life and effects on risk and disease activity of rheumatoid arthritis

Conditions	Effects on rheumatoid arthritis
Before menopause	
Early menarche (< 9 years old)	Increased risk of developing disease[19]
Oral contraception (with low concentration of oestrogens or with progestins)	Unchanged risk of developing disease[22]
Pregnancy	Reduced disease activity[3]
Breast feeding–post partum	Increased disease activity[14]
Nulliparity–multiparity	Unaffected risk of developing disease for nulliparity–multiparity[12]
After menopause	
Early menopause (<45 years old)	Increased risk of developing disease[17]
Menopause	Increased risk of developing disease or worsening[16]
Hormone replacement therapy	Not associated with disease flare[26] and potentially protective[20 25]

that pregnancy, post partum and menopause are clinically relevant to enhance the risk of developing or worsening autoimmune rheumatic disease outcomes, being influenced by physiological changes in several hormones, including oestrogens (see table 1).[1 8 9]

The complex fluctuations of serum oestrogens along with other female hormones (ie, progesterone and prolactin) in such conditions strongly limit conclusions for a deeper understanding of the influence of these hormones on immune response.

However, the immune modulatory activities exerted by oestrogens play essential roles and may address the clinical outcomes during pregnancy or menopause in women affected by the most diffuse autoimmune rheumatic diseases.[10]

Modifications of the maternal immune system during pregnancy enable both the tolerance towards the fetus and the defence against infections, and these modifications induce almost a natural improvement in disease activity as observed in patients with RA.

Therefore, pregnancy and its related increase of oestrogen levels are commonly considered protective elements against disease flares in patients with RA, as shown by a lower disease activity at the beginning of pregnancy (table 1).[11]

However, gravidity did not show to be a potential risk factor for RA development in healthy women (table 1).[12]

On the other hand, post partum and breast feeding are linked to disease flares in almost all rheumatic diseases, including RA.[13]

The immunomodulatory action exerted by the steroidal hormones produced by the placenta during pregnancy expires in the post partum leading to disease flares, as commonly observed in patients with RA. More specifically, it is the increased production of the pituitary hormone prolactin, along with the pineal hormone melatonin, that enhances the inflammatory reactions.[14 15]

Equally, menopause is often linked to the worsening of ongoing rheumatic disease outcomes, observed also in RA, which is related to the dramatic decrease in gonadal steroids production, especially oestrogens, that occurs during this phase (table 1).[16] Moreover, it has been reported that EM is also associated with an increased risk of developing RA.[17]

In addition, in a recent study, postmenopause and EM were found mainly associated with seronegative RA, rather than seropositive RA, supporting potential differences in the aetiology of RA subtypes.[18]

Both oestrogen's roles in physiological female conditions at the early menarche as well as the cyclical increase in oestrogen levels during menstrual cycles are associated with the increased risks of developing RA.[3 19] Therefore, their potential role in increasing the risk of RA development should be taken into account.

These physiological conditions were not evaluated in the study of Park *et al* for both groups of postmenopausal patients with RA (EM and UM), but they should also be considered as potential further modifiers of the immune response.

Oestrogen doses and serum concentrations modulate immune cell reactivity and related clinical outcomes

The study of Park *et al* adds important clinical aspects, supporting that reduced lifetime exposure to oestrogens and related low serum concentrations, as reported in EM, contribute to most of the severe disease outcomes and comorbidities in postmenopausal women with RA.[1] However, no data have been reported regarding the hormonal serum concentrations in EM and UM patients in the above-mentioned study.

Conversely, recent data reported that lifetime oestrogen exposure, including cumulative endogenous and exogenous exposures, seems associated with a decreased risk of RA in postmenopausal women.[20]

A previous study concluded that early onset of menopause, compared with UM, is associated with seropositivity in women with early RA.[21]

Similarly important are the different modulatory effects exerted in RA by oestrogens, based on their doses, for example, in case of oral contraceptive use or hormone replacement therapy (HRT).

In particular, regarding the role of oral contraceptives and their effects on the risk and/or influence on the outcomes in inflammatory rheumatic diseases such RA, the results have been for long time controversial.[3]

Nowadays, at least in RA, it has been concluded that the new generations of oral contraceptives, which have a lower oestrogen content and more protective progestins

than the previous ones, seem to exert a small protective effect in European women (table 1).[22]

Such results are expected also for the use of oral contraceptives in SLE, since this autoimmune condition is mainly driven by B cell activation, which is enhanced by oestrogens.

Likewise, HRT increases the risk of worsening SLE disease activity, according to the HRT-SELENA trial.[23] Moreover, HRT was found to induce mild-to-moderate flares in this disease.[23]

By contrast, HRT in menopause might have generally protective effects in RA that is mainly driven by T cells, with a small but significant increased risk of disease worsening in patients with seropositive RA that are accordingly characterised by prevalent B cell activation (table 1).[24–26]

In conclusion, in the study of Park *et al*, no significant differences were observed between menopausal groups regarding previous or current use of HRT, even if it was found employed more frequently in EM, as expected.[1]

Oestrogens, menopause and cancer risk

Oestrogens not only modulate immune responses but are also involved in the development and spread of malignant tumours enhancing the progression of a range of hormonally responsive tumours, including in female breast and other gynaecological cancers.[27]

For example, in patients with breast cancer, the inhibition of androgen-to-oestrogen conversion by aromatase inhibitors has been found associated with an increased risk of RA.[28]

Same results were found from literature review of case reports that reported positive associations between aromatase inhibitor use and RA.[29]

Remarkably, the use of aromatase inhibitors does not induce a complete deficiency of endogenous oestrogens, but causes low tissue/serum concentrations, at which oestrogens might potentially still exert proinflammatory effects on T cells.[6]

In a recent study, the prevalence of colorectal cancer was found significantly lower in women with EM than in those with UM.[30] Likewise, focusing on age in both groups, an older age was shown to be a risk factor for colorectal cancer.[30] 31

Conversely and as expected, the prevalence of uterine or cervical cancer was found in the large study of Park *et al* significantly higher in the younger EM-RA group (66.0% vs 38.1%, p<0.001), and more patients in the EM group underwent surgical menopause (46.9% vs 7.2%) than those in the UM-RA group for related reasons.[1]

As a matter of fact, in this analysis, the EM group of patients with RA, having higher prevalence of neoplastic disease than the UM group, may have reported more negative PROs and consequently showed to have more severe disease outcomes.

CONCLUSIONS

The investigation of Park *et al* suggests that age at menopause should be considered a major factor in interpreting RA disease outcomes when treating postmenopausal patients with RA.

Gonadal oestrogen production ends at menopause: more specifically, at that time, lower serum concentrations of oestrogens arise from peripheral tissue production by aromatases.

The reduction of the immunomodulatory actions exerted by oestrogens in RA menopause seems involved in the negative clinical outcomes of the disease, with different intensity in EM versus UM.

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