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Review

The role of female hormonal factors in the development of rheumatoid arthritis

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Abstract

RA is the most common chronic systemic autoimmune disease, with a higher prevalence in women, suggesting female hormonal factors play a role in the development of the disease. However, many controversies still exist. The aim of this review was to appraise data from recent research concerning female hormonal factors and their association with RA disease development. The study of female hormonal factors is challenging because serum levels may differ throughout a woman's lifetime and interact with various environmental, immunological, genetic and endocrine factors influencing the development of autoimmunity. As some female hormonal factors may be potentially modifiable, understanding their impact on RA development is clinically relevant and may result in specific preventive interventions in high-risk populations.

Key words: rheumatoid arthritis, women's health, risk factors, female hormonal factors, reproductive factors

Rheumatology key messages

- Factors related to decline in ovarian function and oestrogens bioavailability contribute to RA development.
- Hormonal factors differentially influence the development of RA in premenopausal and post-menopausal women.
- The role of female hormonal factors in RA preclinical phases is yet to be understood.

REVIEW

Introduction

Most autoimmune diseases are more prevalent in women [1, 2]. RA, the most common inflammatory rheumatic disease, is no exception, with a female to male ratio above 4 before 50 years old and below 2 after the age of 60 [3–7]. The peak of RA incidence takes place during the fifth decade of life [7, 8], around the age of menopause in women [9]; however, in ~50% of patients the disease starts during the reproductive years [10]. Moreover, the disease activity and progression of RA tends to be more severe in women compared with in men [11].

The aetiopathogenesis of RA is only partially understood. Our current understanding is that in genetically susceptible individuals, environmental factors induce specific post-translational modifications, which in turn initiate a pathologic activation of the immune system that eventually leads to the clinical onset of the disease [4, 12]. The immune onset of the disease can be demonstrated long before the first clinical symptoms of RA by the development of autoimmunity associated with RA, such as ACPAs [13–16]. The immunological onset is typically followed by the so-called preclinical phases of the disease (see Fig. 1), such as 'symptoms without clinical arthritis' or 'unclassified arthritis,' before the eventual onset of classifiable RA [17].

The increased prevalence of RA in women suggests that female hormonal factors play a role in the development of the disease. Several research approaches have been used to investigate the role of sex hormones in the development of RA. While initial studies only compared the prevalence of RA in women and in men [7, 18, 19], more recent studies have focused on specific reproductive factors and sex hormones, such as oestrogens and androgens; however, their role in the development of RA remains far from clear [20, 21].

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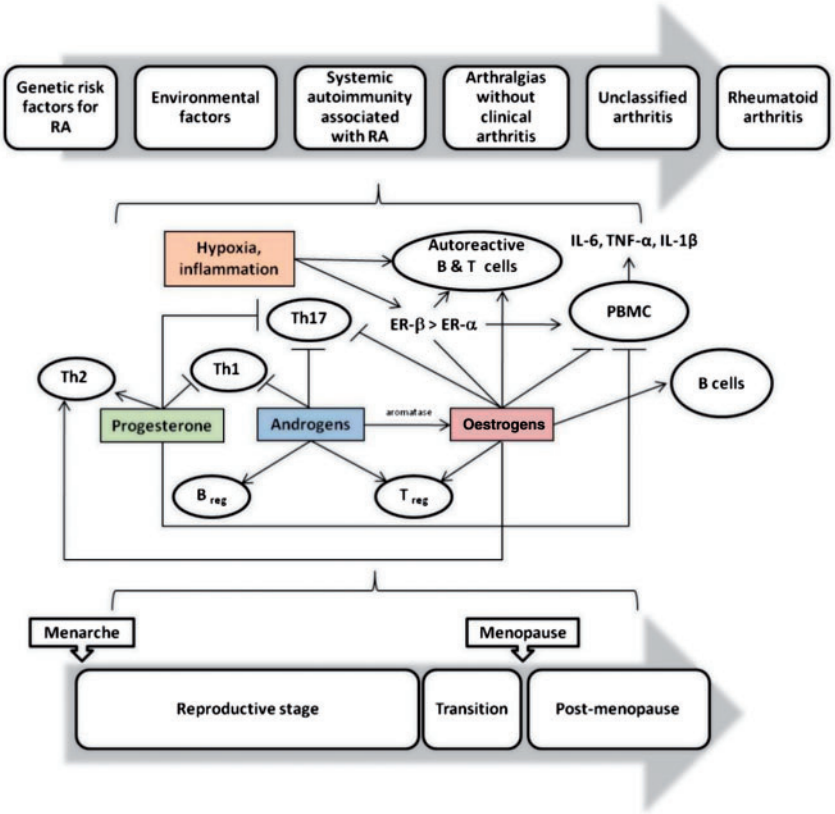
Fig. 1 Potential oestrogen, progesterone and androgens mechanisms influencing the preclinical phases and onset of RA



Arrows indicate stimulatory effect; lines with a bar at the end indicate inhibitory effect. Oestrogens at periovulatory to pregnancy levels stimulate B cells and the Th2 response, promote autoreactive B and T cell survival [20] and enhance the function of T_{reg} cells. Oestrogens inhibit IL-6, TNF-α, IL-1β production and the induction of Th17 cells. ER $-$ β is predominant in hypoxia and inflammation. Androgens inhibit the Th1 response, induce regulatory B cells and suppress differentiation to Th17 cells and PBMC activity [39]. Progesterone stimulates Th2 responses and suppresses differentiation to Th1 and Th17 cells [52]. All these phenomena must be placed in the various phases of ovarian aging (at the bottom)[22]. ER-β: Oestrogen receptor β; B_{reg} and T_{reg}: regulatory B and T cells; Th1: $CD4^+$ T helper type 1 cells; Th2: $CD4^+$ T helper type 2 cells; Th17: $CD4^+$ T helper type 17 cells; PBMC: peripheral blood mononuclear cells.

Many controversies remain regarding the role of female hormonal factors in RA. The aim of this study was to review recent research about the putative role of female hormonal factors in the development of RA. Some fundamental research concepts related to sex hormones are presented in order to highlight clinical research findings.

Strategy

We searched PubMed and Google Scholar for original articles and systematic reviews in English, published from 1 January 2000 to 29 February 2016. We also reviewed relevant references cited in those articles, published prior to the delimited period of time. We used the search terms 'Rheumatoid arthritis', 'development', 'female hormones', 'sex steroids', 'reproductive' and 'risk factors'. In addition each factor was used separately with the above terms, 'pregnancy', 'breastfeeding', 'oral contraceptives', 'hormone replacement therapy', 'parity', 'menopause', 'age at menopause', 'preeclampsia', 'endometriosis' and 'polycystic ovarian syndrome'.

Female hormonal factors

The term female hormonal factors encompass reproductive characteristics or events associated with changes in serum sex hormone levels, mainly oestrogens and progesterone, that women experience throughout their lifetime [22, 23]. Events, such as pregnancy, post-partum, breastfeeding, menopause or the use of exogenous sex steroids [such as oral contraceptives (OCs) or hormone replacement therapy (HRT)] produce changes in the hormonal milieu.

In a broad manner, it has been suggested that oestrogens have a pro-inflammatory and androgens exert an anti-inflammatory effect [24]. More specifically, oestrogens could have different effects on different immune cells, depending on serum concentration, reproductive

stage or ovarian ageing phase (reproductive, menopausal transition or post-menopausal), expression of oestrogen receptors (ERs) or intracellular metabolism [20, 22].

Oestrogens have both stimulatory and inhibitory effects on the immune system [25]. Oestrogens at periovulatory to pregnancy levels stimulate B cells and the Th2 response and support the survival of auto-reactive T and B cell clones [20, 26]. On other hand, oestrogens could inhibit cell-mediated responses [26–28], such as the differentiation to Th17 cells (see Fig. 1) [29–32]. Oestrogens, including the most potent 17β-estradiol (E2), bind to ERs, whose distribution varies in different tissues. A preponderance of ER-β over ER-α has been observed in RA synovial tissue [33, 34]. Inflammation or hypoxia can increase cellular expression of ER-β and stimulate the production of TNF-α and IL-6 by peripheral blood mononuclear cells (PBMCs) [20, 26, 34]. The rapid decline in ovarian function and in circulating oestrogens at menopause is associated with spontaneous increases in pro-inflammatory cytokines, such as IL-6, TNF-α and IL-1β [35–37]. Adding E2 at periovulatory levels to PBMC from postmenopausal women *in vitro*, inhibits the release of these three pro-inflammatory cytokines in a dose dependent manner. On the other hand, E2 do not have a consistent effect on PBMC derived from men or premenopausal women [38].

Other hormones, such as androgens, progesterone or prolactin, exert effects on the immune system. Androgens, also present in women, inhibit PBMC activity [39], and Th1 and Th17 differentiation [40, 41]. Low serum levels of gonadal androgens (androstenedione, testosterone and dihydrotestosterone) and adrenal androgens (dehydroepiandrosterone sulphate) have been detected in both women and men with RA [42, 43]. In a small case–control study of women in preclinical phases of RA, serum androstenedione levels were significantly lower compared with in healthy controls [44]. In men with RA, dehydroepiandrosterone sulphate concentrations were lower compared with in healthy controls, while E2 levels were higher [45]. In addition, the conversion of androgens to oestrogens is increased in RA patients, because inflammatory mediators stimulate aromatase activity in peripheral tissues [46–49]. The ratio of oestrogens to androgens in the SF is significantly elevated in both male and female patients with RA [49]. Progesterone stimulates Th2 responses [20] and suppresses the differentiation of Th1 and Th17 cells [50–52]. Rapid progesterone withdrawal causes an upregulation of the expression of IL-1β, and TNF-α [53]. Prolactin decreases apoptosis of B cells, allowing autoreactive B cell survival [54]. Few studies have focused on cross-talk between immune and endocrine signalling pathways. Fig. 1 displays potential mechanisms through oestrogen, progesterone and androgens that could be altered and eventually influence the development of RA.

Female hormonal risk factors for RA

Several female hormonal factors have been described as risk factors for RA development, some of them related to oestrogen exposure (such as the use of HRT or OCs), others with low levels of oestrogen, such as earlier age at menopause [55, 56], and other factors related to multiple hormonal changes, such as polycystic ovary syndrome (PCO) [57], parity or post-partum [58]. Findings from clinical research have been inconsistent and have not confirmed uniform effects of the various reproductive and hormonal factors.

Parity

Having more than one pregnancy increased the risk of ACPA-negative RA in women of reproductive age (18–44 years) [Odds Ratio (OR) = 2.1 (95% CI: 1.4, 3.2)], particularly if the first pregnancy was before age 23 [OR = 2.5 (95% CI: 1.5, 4.1)], in participants of the Swedish Epidemiologic Investigation of RA cohort [58].

Postpartum

In the post–partum, incident RA cases are significantly more frequent, with an incidence rate ratio of 1.7 (95% CI: 1.1, 2.7) in the 24 months after delivery [59]. In a cohort study, a high risk of developing RA was observed in the first year post-partum [OR = 3.8 (95% CI: 1.5, 9.9)] compared with in subsequent years (P = 0.004) [60]. Looking in more detail at the timing of RA incidence during the post-partum period, the increased risk of RA was highest during the first 3 months [OR = 5.6 (95% CI: 1.8, 17.6)] and reduced during the subsequent 9 months [OR = 2.6 (95% CI: 0.8, 7.9)] [61]. The increased risk of RA during the post-partum has been hypothesized to be related to the increased levels of prolactin. However, the association of RA with prolactin has been inconsistent [44, 62, 63]. Rapid progesterone withdrawal is another explanation proposed for the increased risk of RA after delivery [53].

Breastfeeding

A long duration of breastfeeding (self-reported breastfeeding for >17 months) was associated with an increased risk of developing RA [OR = 5.7 (95% CI: 1.8, 17.9)] in a case–control study that included 70 RA women and 280 matched controls [23], but this finding has not been confirmed by most other studies [55, 64–67].

Menopause

Factors related to menopause, particularly an early age at menopause, have been consistently associated with an increased risk of RA. In an analysis of the Nurses' Health Study (NHS) cohort, being post-menopausal increased the risk of seronegative-RA [hazard ratio = (HR) = 2.1 (95% CI: 1.5, 3.1)], particularly with an early age at menopause [<44 years, HR = 2.4 (95% CI: 1.6, 3.5)] [68]. An independent cohort confirmed this finding, with an earlier age at menopause (<40 years) more than doubling the risk of RA [OR = 2.5 (95% CI: 1.4, 4.5)] [56]. In a cross-sectional study, early age at menopause (defined as <45 years) was also associated with subsequent development of RA [OR = 2.4 (95% CI: 1.3, 4.4)] [55]. Another cross-sectional study, confirmed that early

age at menopause (<45 years) was associated with RF-positive RA [OR = 2.2 (95% CI: 1.3, 3.8)] [69].

PCO

PCO, the most common endocrine disorder among women of reproductive age, is characterized by ovarian dysfunction and hyperandrogenism. PCO is associated with chronic anovulation, low serum progesterone levels and longer unopposed estrogenic phases [70, 71]. In a prospective cohort, self-reported diagnosis PCO was associated with RA, with a relative risk (RR) = 2.6 (95% CI: 1.1, 6.3) [57]. This finding could illustrate the complex nature of hormonal effects on the immune system.

Endometriosis

Endometriosis is associated with increased local concentrations of oestrogens due to increased expression of aromatase in the ectopic endometrium, activation of peritoneal macrophages and increased cytokine production, with a predominance of Th1/Th17 response [72, 73]. In the large prospective cohort of the NHS, laparoscopically confirmed endometriosis was found to be significantly associated with subsequent RA, with an HR = 1.4 (95% CI: 1.1, 1.9) [74]. However, this association was attenuated after adjustment by hysterectomy and oophorectomy, suggesting a possible confounding effect by surgically induced menopause.

OCs and HRT

Studies have found differences in the role of OCs when comparing ACPA-positive and ACPA-negative RA. A matched case–control study reported an increased risk for ACPA-positive RA to be associated with OCs use [OR = 1.7 (95% CI: 1.1, 2.6)] [75]. The association of OCs with ACPA-positive RA was confirmed in another study reporting increased risk of ACPA-positive RA, in particular in shared-epitope homozygotes, with an OR as high as 44.6 [76]. HRT was significantly associated with RA development, with a RR = 1.5 (95% CI: 1.0, 2.0), in a prospective study of >30 000 women aged between 55 and 69 years, with 158 incident cases of RA [57].

Anti-oestrogen agents

Selective oestrogen receptor modulators (SORMs) are competitive inhibitors of oestrogen binding to ER and can have agonist or antagonist properties in different target tissues [77]. Aromatase inhibitors (AIs), reduce endogenous production of oestrogen by 50–90% [78]. A large study based on a national database for breast cancer assessed the incidence of RA following treatment with SORMs or AIs. Both treatments were associated with a cumulative, dose-dependent, increase in the incidence of RA, with an OR = 1.3 (95% CI: 1.1, 1.4) in the first 12 months and 2.4 (95% CI: 1.9, 3.0) for >12 months of SORMs treatment and = 1.3 (95% CI: 1.2, 1.4) and 1.9 (95% CI: 1.6, 2.1) for AI treatment, respectively [79]. These findings strongly support a risk of RA associated with the use of anti-oestrogen agents.

Protective female hormonal factors for RA

Some female hormonal factors have been described as protective factors. However, some (such as parity, breastfeeding, use of HRT or OCs) have been found to be both protective and risk factors for RA development.

Pregnancy and parity

Pregnancy has been found to be protective, both for RA development and for activity in already established disease. The protective effect has been attributed to the intense hormonal changes involved (high oestrogen and progesterone concentrations) [20, 80]. A 70% reduction in the incidence of RA onset during pregnancy has been described; however, this did not reach statistical significance [OR = 0.3 (95% CI: 0.0, 2.6)] [61]. In a high-risk population cohort of native Americans, having ⩾6 births was protective against developing RA [OR = 0.43 (95% CI: 0.2, 0.9) [60]. In a prospective case–control study in women with newly diagnosed RA, parity of any number was significantly associated with a lower risk of RA [RR = 0.6 (95% CI: 0.4, 0.8)]; however, gravidity without parity did not confer protection [RR = 1.2 (95% CI: 0.7, 2.0)] [81].

Breastfeeding

Long-term breastfeeding has been consistently found to decrease the risk of RA [55, 64–66]. A systematic review including six studies and 1672 RA cases demonstrated that breastfeeding for between 1 and 12 months and for >12 months is associated with a lower risk of RA, with a clear dose–response effect [OR = 0.8 (95% CI: 0.6, 0.9) for breastfeeding for ⩽12 months, and OR = 0.6 (95% CI: 0.4, 0.7) for breastfeeding for >12 months] [67].

Use of HRT and OCs

HRT and OCS have been described as protective factors. In a study based on data from the Epidemiologic Investigation of RA cohort (EIRA), current use of combined HRT (oestrogen plus progestagens without specified dose) by post-menopausal women aged between 50 and 70 years was associated with a reduced risk of ACPA-positive RA compared with non-users [OR = 0.3 (95% CI: 0.1, 0.7)] [82]. No association was found between oestrogens-only HRT and ACPA-positive RA (OR = 0.8, 95% CI: 0.5, 1.6), nor between any type of HRT used and ACPA-negative RA [82]. Use of OCs has also been found to be protective [83], specifically with a treatment duration of ⩾7 years [OR = 0.4 (95% CI: 0.2, 0.9)] [23]. Other studies have confirmed this finding, with OC use of ⩾8 years being protective for ACPA-positive RA [OR = 0.8 (95% CI: 0.7, 0.9)], and only borderline protective for ACPA-negative RA, OR = 0.8 (95% CI: 0.7, 1.0) [84]. Table 1 summarizes the general characteristics of selected studies with regard to female hormonal factors and risk of RA development.

Table 1 General characteristics of selected studies on female hormonal factors and RA development

Hormonal factors References	Study design	Age (years) baseline	Cases/controls or cohort size	RR, OR, HR (95% CI)	Other observations
OCs					
Pedersen *et al.* [75]	Case–control	18–65	515/769	OR = 1.7 (95% CI: 1.1, 2.6)	ACPA-positive RA OCs ever used
Orellana *et al.* [84]	Case–control	18–75	884/1947	OR = 0.8 (95% CI: 0.7, 0.9)	ACPA-positive RA Treatment ⩾8 years
HRT					
Merlino *et al.* [57]	Prospective cohort	55–69	31 336	RR = 1.5 (95% CI: 1.0, 2.0)	HRT former use
Orellana *et al.* [82]	Case–control	50–70	523/1057	OR = 0.3 (95% CI: 0.1, 0.7)	ACPA-positive RA
Polycystic ovary syndrome					
Merlino *et al.* [57]	Prospective cohort	55–69	31 336	RR = 2.6 (95% CI: 1.1, 6.3)	
Endometriosis					
Harris *et al.* [74]	Prospective cohort/ NHSII	25–42	114 453	HR = 1.4 (95% CI: 1.1, 1.9)	Hysterectomy-adjusted: HR = 1.3 (95% CI: 0.9, 1.7)
Pregnancy					
Silman *et al.* [61]	Case–control	18–40	88/144	OR = 0.3 (95% CI: 0.0, 2.6)	
Post-partum					
Peschken *et al.* [60]	Case–control	46/36	168/400	OR = 3.8 (95% CI: 1.5, 9.9)	12 months postpartum
Silman *et al.* [61]	Case–control	18–40	88/144	3 months postpartum: OR = 5.6 (95% CI: 1.8, 17.6)	4–12 months postpartum: OR = 2.6 (95% CI: 0.8, 7.9)
Parity					
Orellana *et al.* [58]	Case–control	18–44	136/546	OR = 2.1 (95% CI: 1.4, 3.2)	ACPA-negative RA ⩾ 1 pregnancy
Guthrie *et al.* [81]	Case–control	15–64	310/1418	RR = 0.6 (95% CI: 0.4, 0.8)	⩾1 pregnancy
Pre-eclampsia					
Jorgensen *et al.* [85]	Prospective cohort	15–49	1981	HR = 1.9 (95% CI: 1.1, 3.6)	Between women with pre-eclampsia
Breastfeeding					
Berglin *et al.* [23]	Case–control	20–68	70/280	OR = 5.7 (95% CI: 1.8, 17.9)	Breastfeeding ever ⩾17 months
Chen *et al.* [67]	Meta-analysis	16–79	1672/143 670	>12 months OR = 0.6 (95% CI: 0.4, 0.7)	Breastfeeding ever
Post-menopause					
Bengtsson *et al.* [68]	Prospective cohort (NHSI/II)	NHSI/II 30–55/25–40	NHSI/II 121 701/116 430	HR = 2.1 (95% CI: 1.5, 3.1)	Seronegative-RA
Early age at menopause					
Bengtsson *et al.* [68]	Prospective cohort (NHSI/II)	NHSI/II 30–55/25–40	NHSI/II 121 701/116 430	HR = 2.4 (95% CI: 1.6, 3.5)	Seronegative-RA; age at menopause (<44 years)
Pikwer *et al.* [55]	Case–control	44–74	136/544	OR = 2.4 (95% CI: 1.3, 4.4)	Age at menopause (<45 years)
Anti-oestrogen agents, SERMs or AIs					
Chen *et al.* [79]	Prospective cohort	⩾18 with breast cancer	238 880	⩾12 months SERMs/AI OR = 2.4 (95% CI: 1.9, 3.0)/OR = 1.9 (95% CI: 1.6, 2.1)	

AI: aromatase inhibitor' HR: hazard risk; HRT: hormone replacement therapy; NHS: Nurses' Health Study; OCs: oral contraceptives; OR: odds ratio; RR: relative risk; SERM: selective oestrogen receptor modulator.

Controversies

Several studies have found no significant association between specific female hormonal factors and the development of RA. On the other hand, factors such as parity [56, 64, 65, 86], history of pregnancy loss [87], use of HRT [83, 88] or OCs [64, 65] have been found to be both protective and risk factors for the disease. Table 2 provides a summary of risk and protective female hormonal factors for RA in relation to hormonal changes and some of the most important controversies.

A good example of a controversial factor is hormone therapy. OCs use has been reported to decrease the risk of RA [83], but also to increase the risk of ACPA-positive RA [75, 76]. Part of the discrepancy may be explained by an assessment bias of OCs use. Two meta-analyses that investigated the association between OCs and development of RA concluded a non-significant association, but showed a strong heterogeneity between selected studies, partially explained by the source of controls and different effect estimates [86, 90]. The oestrogen dose of OCs or HRT has been significantly reduced over the past decades, and different types and combinations of hormones have been employed, limiting the interpretation of results. Moreover, when OC use is analysed as a dichotomic variable, the effect of oestrogen dose or the time of exposure may be lost [83, 90, 91].

Clinical research on female hormonal factors in RA has been hampered by uncertain definitions for the various reproductive variables, such as early menopause or menarche. In addition, most of the exposures are self-reported outcomes. Furthermore, most studies have not taken into account potential interactions between the various reproductive factors, with other environmental factors or with the stages of reproductive aging of women [22].

Association with environmental and genetic factors

Interestingly, in the NHS cohort, hormonal factors were combined with other environmental and familial factors in order to calculate population attributable risk (PAR) for RA. Familial RA was defined as having at least one first-degree relative with a RA diagnosis. Authors reported that PAR was higher (41%), taking into account a group of environmental factors, including smoking (>10 pack-years), low alcohol intake (<5 g/day), overweight, nulliparity and breastfeeding (<12 months) than when taking into account only familial RA (PAR 21%). The combination of nulliparity/breastfeeding <12 months had a PAR for RA of 15% among all women and 25% among women with familial RA. The findings of this study suggest that environmental factors, including female hormonal factors, are responsible for a large proportion of RA risk, and various genetic and environmental factors may interact to increase the risk of disease [92].

Perspectives

Several female hormonal factors have been associated with RA development; however, most findings are inconsistent. The existing clinical research has only considered the final phases of RA disease development, namely established RA, but it may well be that the contribution of female hormonal factors differs in the earlier phases of disease development. For example, currently we do not know what stages of disease development are influenced by oestrogen decline. The role of female hormonal factors in the transition between the preclinical phases needs to be studied in detail. In particular in genetically predisposed women, the balance and effects of

Table 2 Controversies on risk and protective female hormonal factors for RA development

	RA overall	ACPA positive	ACPA negative
Risk factors	High oestrogen[a] Early menarche [64] HRT [57][b] Parity [81][b] Low oestrogen Postpartum stage [5, 59] Early age at menopause [55][b] Nulliparity [89][b] Anti-oestrogens agent treatment [79]	High oestrogen OCs [75][b] High prolactin Breastfeeding [23][b]	High oestrogen Parity [58][b] Young age at first pregnancy [58] Low oestrogens Early age at menopause [68][b] Postmenopausal status [68]
Protective factors	High oestrogen Older age at menopause [57] Parity [60][b] OCs [83][b] Low oestrogen Older age at last pregnancy [57] High prolactin Breast feeding [55, 64–66][b]	High oestrogen HRT [82][b]	

[a]Factors related with high oestrogen exposure. [b]Controversies, described as both risk/protective factors. HRT: hormone replacement therapy; OCs: oral contraceptives.

sex steroids could influence the transition from one phase to the next, such as from the 'systemic autoimmunity associated with RA' to the 'unclassified arthritis' stage.

Furthermore, future research on RA risk should consider the different stages of a woman's life, such as the reproductive or the post-menopausal stage. An interesting approach to the study of female hormonal factors in RA development could be the use of cumulative exposure to sex steroids in women, both endogenous and exogenous, over lifetime [93, 94]. More studies focusing on the interaction between various female hormonal factors and other environmental exposures should be performed.

Conclusions

Female hormonal factors contribute to the development of RA. The post-menopause stage, an early age at menopause, the post-partum period and the use of anti-oestrogen agents are associated with RA onset. All these phenomena have in common an acute decline in ovarian function and/or in oestrogen bioavailability. However, there are controversies regarding other female hormonal factors. The influence of systemic hormonal treatments, including contraceptive and HRT, on RA onset remains unclear. The effect of other factors related to diverse hormonal changes (such as parity, breastfeeding or PCO) is also controversial. The timing of oestrogen exposure also plays a role on RA onset, with female hormonal factors having varying effects during premenopause and postmenopause. Non-hormonal sex-related factors, such as sex chromosomes [95], microchimerism [96, 97] or sex differences in the microbiome [98] may also contribute to RA development.

Overall, the effect of sex hormones on the immune system and their interaction with environmental and genetic factors could explain the higher prevalence of RA in women. As some female hormonal factors are potentially modifiable, understanding their precise role is key for future preventive interventions focusing on women at high risk [99]. However, our current knowledge on the effect of sex steroids on RA development is still insufficient to provide individual recommendations to subjects at high risk.

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