Out of balance: the role of evolutionary mismatches in the sex disparity in autoimmune disease

Sarai M. Keestra a,b,*, Victoria Male c, Gul Deniz Salali d

a Amsterdam UMC, University of Amsterdam, the Netherlands
b Department of Global Health & Development, London School of Hygiene and Tropical Medicine, UK
c Department of Metabolism, Digestion and Reproduction, Faculty of Medicine, Imperial College London, UK
d Department of Anthropology, University College London, UK

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ABSTRACT

Over the past century autoimmune disease incidence has increased rapidly in (post-) industrialised, affluent societies, suggesting that changes in ecology and lifestyle are driving this development. Epidemiological studies show that (i) 80% of autoimmune disease patients are female, (ii) autoimmune diseases co-occur more often in women, and (iii) the incidence of some autoimmune diseases is increasing faster in women than in men. The female preponderance in autoimmunity is most pronounced between puberty and menopause, suggesting that diverging sex hormone levels during the reproductive years are implicated in autoimmune disease development. Using an evolutionary perspective, we build on the hypotheses that female immunity is cyclical in menstruating species and that natural selection shaped the female immune system to optimise the implantation and gestation of a semi-allogeneic foetus. We propose that cyclical immunomodulation and female immune tolerance mechanisms are currently out of balance because of a mismatch between the conditions under which they evolved and (post-) industrialised, affluent lifestyles. We suggest that current changes in autoimmune disease prevalence may be caused by increases in lifetime exposure to cyclical immunomodulation and ovarian hormone exposure, reduced immune challenges, increased reproductive lifespan, changed reproductive patterns, and enhanced positive energy balance associated with (post-) industrialised, affluent lifestyles. We discuss proximate mechanisms by which oestrogen and progesterone influence tolerance induction and immunomodulation, and review the effect of the menstrual cycle, pregnancy, and contraceptive use on autoimmune disease incidence and symptoms.

Introduction

Over the past 150 years, life expectancy in (post-) industrialised, affluent societies has increased concurrently with advances in public health, medicine, nutrition, and sanitation [1]. Whilst incidence of infectious diseases has consequently declined, the prevalence of degenerative and chronic diseases, detrimental to quality of life and long-term health, is increasing [2]. After cardiovascular disease and cancer, autoimmune diseases are now the most common disease category in the United States, with 5–8% of the population affected [3]. Autoimmune disorders are caused by an immune response erroneously launched against an individual’s own body because of the loss of immune non-reactivity, also known as immune tolerance, for self-antigens [4]. More than eighty autoimmune diseases have been identified and the worldwide prevalence is estimated at approximately 4.5% [5]. In recent decades autoimmune disease incidence has rapidly increased in (post-) industrialised, affluent societies, at rates of between 3.7 and 7.1% annually [6], suggesting that contemporary changes in our ecology and lifestyle are driving this trend.

As the category of autoimmune disease encompasses a wide range of disorders, resulting from diverse aetiologies and affecting a variety of bodily systems, there are only few epidemiological studies that have aggregated autoimmune disease incidence. However, when looking at these reports it is striking that (i.) approximately four out of every five autoimmune disease patients is female [3,7], (ii.) the incidence of some inflammatory autoimmune diseases patients is female [3,7], (ii.) the incidence of some inflammatory autoimmune diseases, most notably multiple sclerosis (MS), is increasing faster in females than males [8], and (iii.) the co-occurrence of several autoimmune diseases in one individual is more
common among women than men [9]. Furthermore, when comparing autoimmune diseases first presenting themselves in early adulthood to those with a childhood onset, an increase in the female propensity to develop autoimmune diseases can be noticed for some disorders following the pubertal transition (Fig. 1) [10,11], whilst an opposite shift in the sex disparity is seen following menopause when the female incidence gap narrows again for some but not all autoimmune diseases [10,12,13] (see Fig. 2).

Evolutionary medicine suggests that the transition to life in an evolutionary novel environment associated with a post-industrialised, affluent lifestyle may have significant repercussions for psychological and physiological functioning as these contexts are fundamentally different from those in which we evolved, causing an evolutionary mismatch [14]. Making use of Tinbergen’s four questions in biology, covering both ultimate and proximate explanations for health and disease, evolutionary medicine allows for the integration of insights into the developmental plasticity and evolutionary significance of biological traits with the proximate molecular mechanisms underlying them [15–17]. Such an approach sheds new light on the biological paradox that women are on the one hand more likely to experience a breakdown of tolerance to specific self-antigens in autoimmune disease, whereas they must also be able to tolerate the presence of a semi-allogeneic foetus during nine months of gestation in order to reproduce successfully. Sir Peter Medawar, one of the pioneers of transplantation science, was the first to suggest that research into immunomodulation and tolerance during pregnancy may enhance our understanding of the tolerance mechanisms that also play a role in the development of autoimmune disease [18]. He suggested that in response to pregnancy, which he likened to the implantation of an allograft, mothers dampen down their immune responses indiscriminately to prevent immunological rejection of the offspring. Although research has shown that pregnant mothers are not systematically immunosuppressed nor the foetus immunologically inert [19], understanding immunomodulation during pregnancy may still offer novel insights into the propensity of women to develop autoimmune diseases during their lifetime more often than men. Explanatory Box 1 gives an overview of all proximate mechanisms that may predispose and trigger autoimmune disease in women and that have been previously proposed to underlie the sex disparity in autoimmune disease.

We propose that increased lifetime exposure to reproductive hormones and number of menstrual cycles might alter central and peripheral tolerance mechanisms and contribute to an increase in autoimmune disease incidence in women living in (post-) industrialised, affluent contexts. Natri et al. [20] have previously hypothesised that as a

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**Fig. 1.** Sex ratios in autoimmune diseases incidence during childhood versus those that are likely to appear during early adulthood, the reproductive years or after menopause. N.B. that some of the autoimmune diseases with childhood onset have an infectious aetiology. Interestingly autoimmune disorders that appear in early adulthood and more often occur in women, also more frequently co-occur with other autoimmune diseases. Comparing the last graph on the bottom left with the first graph on the top right, one can see that after menopause the sex disparity in autoimmune disease incidence is more similar to that seen before the onset of the reproductive years. Please note that in the publication by Beeson [10] these graphs are based on, teenagers up to age 15 were counted as ‘children’. Considering that most girls undergo menarche before age 15, this might skew the graphs’ ability to demonstrate the influence of the reproductive transition itself on autoimmune incidence. The graphs are a visualisation of data taken from Beeson [10]; MS data from Chitnis [11].
result of natural selection on pregnancy and invasive placentation, evolved sex differences in gene content and dosage might contribute to sex-specific immune modulation and underlie the observed sexual dimorphism in autoimmune disease and cancer rates [20]. Alvergne and Höggqvist Tabor [152] have additionally pointed out the cyclical nature of female health, and suggested that the effects of menstrual cycle on the immune function need to be considered when studying autoimmune disease from an evolutionary perspective. Building on these propositions, we hypothesise that cyclical immunomodulation through female sex hormones contributes to the observed sex disparity in autoimmune disease incidence and symptoms. Using an evolutionary ecology framework, we discuss the effect of ovarian steroids on the regulation of the adaptive immune system at different stages of female reproductive lifespan. We also discuss how recent alterations in reproductive patterns, lifestyle, and the consequent increase in the lifetime exposure to ovarian steroid hormones, might have exacerbated the sex disparity in autoimmune disease in recent decades. We furthermore predict that when populations start adopting a (post-)industrialised, affluent lifestyle characterised by energetic affluence [21,22], the sex disparity in autoimmune diseases may further increase. We specifically review the pathways by which sex hormones modulate lymphocyte development and differentiation during menstrual cycle and pregnancy, discussing the role of puberty and menopause in sex difference in autoimmune disease incidence. By doing so we provide evidence for the hypothesis that reproductive hormone levels shape autoimmune disease incidence and symptoms during a female’s reproductive lifespan by modulating tolerance mechanisms and immunoregulation during the menstrual cycle and pregnancy. Finally, we highlight some relevant findings regarding the influence of ecological pressures on ovarian hormones in women, based on which we suggest new avenues for autoimmune disease research.

Evolutionary mismatches and the prevalence of autoimmune disorders

We propose that the observed increase in autoimmune disease prevalence and patterns might be caused by a mismatch between the ecological conditions in which immune tolerance and cyclical immunomodulation mechanisms originally evolved in and modern (post-)industrialised, affluent lifestyles (Fig. 3). Here, we summarise these mismatches, which may lead to higher lifetime exposure to ovarian steroids and cyclical immunomodulation and may contribute to the observed increased incidence in autoimmune diseases amongst women in (post-)industrialised, affluent contexts, focussing on: 1) increased reproductive lifespan, 2) changing reproductive patterns, 3) fewer immune challenges, 4) positive energy balance.

Increased reproductive lifespan

Currently, girls living in (post-)industrialised, affluent environments often undergo menarche earlier than previous generations [23,24], and are therefore exposed to the cyclical changes in tolerance and immunomodulation for a longer period of time. In (post-)industrial contexts, age of first menstruation has declined dramatically over the past two centuries concurrent with improved quality of early life environments and decreases in infant mortality rates [25]. This, along with a potential upward secular trend in age of menopause, has increased female reproductive lifespan [26]. Girls that undergo menarche before age
Explanatory Box 1
An overview of proximate mechanisms that may contribute to the sex disparity in autoimmunity

A wide range of molecular mechanisms have been identified that may contribute to a higher autoimmune disease prevalence in women than in men, which can be subdivided in both predisposing and triggering factors (Figure 2). Whereas predisposing factors contribute to the development of immune cells that aberrantly recognise self-antigens as foreign in the first place, trigger factors may cause the subsequent activation of these autoreactive immune cells. For example, skewed X-chromosome activation in women may cause autoreactive T-cells for certain X-linked genes escape tolerance induction processes during thymic development [155], whereas differential exposure to environmental-, dietary-, social-, and stress-related factors, may subsequently play a role in triggering autoimmune disease [17,156]. Several predisposing and triggering factors also directly relate to female reproductive functioning. For example, the bidirectional exchange of cells during pregnancy may predispose women to develop autoimmunity following pregnancy when immune responses are launched to remove foreign foetal cells (microchimerisms) from the body [157,158], whilst men and women also display different immune profiles during the reproductive years under the influence of pregnancy and sex hormones more generally. Research has further shown that women exhibit stronger humoral and cellular immune responses than men as the ‘female’ sex hormones oestrogen and progesterone favour the survival of the adaptive immune system’s B-cells and T-helper- (Th) cells [11,54,145,146]. Using an evolutionary medicine approach, we evaluate the effects of the ovarian steroids oestrogen and progesterone on the adaptive immune system’s tolerance mechanisms in particular, describing pathways by which sex hormones influence the development and symptoms of autoimmune disease in women during the reproductive years.

Fig. 3. The Out of Balance Hypothesis. This figure outlines various factors that can increase our lifetime exposure to ovarian steroid hormones and cyclical immunomodulation. Although originally increases in lifetime oestrogen exposure have been implicated in the development of reproductive cancers, we propose that high lifetime exposure to ovarian steroid hormones, especially oestrogen, can also have a profound impact on the immune system and subsequent autoimmune disease development. This figure uses information from the following sources: Jasienska [62], p. 15, Natri et al. [20] and Núñez-de la Mora and Bentley [135].

twelve may also experience higher serum oestradiol levels during their menstrual cycles [27]. Longer lifetime exposure to ovarian cyclicity and its associated hormones can impact autoimmune disease development as research has suggested that earlier age of menarche causes multiple sclerosis (MS) symptoms to occur earlier and be more severe [11,28,29].

Changing reproductive patterns

In comparison to the contemporary natural fertility populations as a
reference point for the female reproductive patterns for most of human evolution, women in (post-) industrialised societies spend a longer period cycling before first pregnancy, have fewer children, and spend less time breastfeeding [30]. Compared to modern-day foraging populations, the mean age of menarche in (post-) industrialised, affluent context is nearly four years earlier, and affluent women in the United States spend approximately twelve years cycling before having a first child, compared to only three years in contemporary hunter-gatherer populations [30]. Whereas women from subsistence populations breastfeed for approximately 17 years over their reproductive lifespan, the total years of lactation in American women is only 0.5 [30]. Indeed, research among Dogon women in Mali suggests that women in natural fertility populations only cycle regularly if they are infertile, with fertile females experiencing about 100 menstrual cycles over their lifetime compared to more than 300–400 hundred in women living in (post-) industrialised, affluent contexts in the United States [31]. Women are exposed to sharp increases and decreases of regulatory lymphocytes during each menstrual cycle [32], which means that delayed pregnancy exposed to sharp increases and decreases of regulatory lymphocytes compared to more than 300–400 hundred in women living in (post-) industrialised, affluent contexts in the United States [31]. Women are exposed to sharp increases and decreases of regulatory lymphocytes during each menstrual cycle [32], which means that delayed pregnancy exposed to sharp increases and decreases of regulatory lymphocytes.

Fewer immune challenges

Peripheral tolerance can be influenced by changes in microbial exposure, which also affects reproductive ecology and thereby ovarian steroid levels. Proponents of the hygiene hypothesis, recently renamed as the “Old Friends Hypothesis”, have suggested that the transition to modern urban lifestyles depletes populations in (post-) industrialised, affluent contexts of the environmental input from co-evolved microbial organisms during early development, as a result of which their immune systems have become deregulated [35–38]. Pathogen exposure can also lead to more anovulatory cycles and oestrogen dysregulation [39], but in sanitised urban environment this occurs less frequently. Additionally, a decrease in early life immune stressors may alter timing of maturation and menopause as well as ovarian hormone levels during the reproductive lifespan [40]. For example, Bangladeshi women that came to the U.K. as children were observed to have an earlier age of menarche and higher progesterone levels than women who remained in Bangladesh [41], which Nunez-de la Mora and collaborators have suggested to potentially be the result of fewer immune challenges during development and better sanitation and health care access in London compared to Sylhet.

Positive energy balance

Positive energy balance and increased adiposity associated with a (post-) industrialised, affluent lifestyle can also have distinct effects on the immune system, ovarian steroid levels, and reproductive lifespan. Adiposity increases the bioavailability of sex steroids in the blood [42] and enhances the local oestrogen production in adipose tissue [43]. A sedentary lifestyle with reduced physical activity is associated with higher oestradiol levels during the menstrual cycle of women of reproductive age, thereby contributing to a higher lifetime cumulative exposure of this hormone [44]. Obesity might also cause a subclinical chronic inflammatory state, exacerbating autoreactive Treg [45] Th17 [46] cells instead of Tregs [45,46]. Leptin, a key adipokine which is twice as high in women than in men, also promotes the Th1 differentiation and inhibits Treg proliferation, thereby affecting peripheral tolerance [47]. Some studies have additionally found that a combination of low birth weight, early menarche, and excess weight in adulthood also leads to elevated oestradiol levels measured over a single menstrual cycle [48,49]. Although there is some research on the correlation between obesity and autoimmunity [47], no study has addressed the potential combinatorial effect of obesity and hormonal changes occurring during reproductive transitions on peripheral tolerance. For example, it could be that the combined effects of excess adiposity and ovarian steroid exposure may contribute to increasing sex disparities in autoimmune disease incidence starting with puberty. As predicted, women that experienced childhood obesity, early menarche, and overweight in adulthood are at higher risk for developing certain inflammatory, Th1/Th17 mediated autoimmune diseases, such as MS [8,29]. Understanding the combined effect of excess adiposity during menopause might especially be relevant because of the existence higher total and unopposed oestrogen levels during this reproductive transition [50,51] and reduced peripheral tolerance due to the ageing of the immune system [52].

Below we explore the current state of the evidence that underlies these predictions and may strengthen our proposition that the observed increase in autoimmune disease prevalence and changing incidence patterns might be caused by a mismatch in immune tolerance and cyclical immunomodulation mechanisms.

Proximate mechanisms by which ovarian steroids influence tolerance and cyclical immunomodulation

Various steps during the normal development and maturation of adaptive immune cells prevent the development of autoimmunity by inducing immune tolerance to healthy bodily tissues through deleting or neutralising autoreactive immune cells [53]. These mechanisms can be subdivided in central and peripheral tolerance depending on whether they take place during the early development of the adaptive immune cell in the thymus or only after they have been released into the circulation. Whereas reduced central tolerance may cause autoreactive lymphocytes to escape stringent selection processes during development and enter the circulation, reduced peripheral tolerance can cause the subsequent activation of these autoreactive cells. As we will describe, oestrogen and progesterone can influence both central and peripheral tolerance, thereby influencing autoimmune disease risk, and affecting immunomodulation, specifically balances between T regulatory and Th17 cells. In Explanatory Box 2 we offer an overview of the adaptive immune system and associated cytokines and explain the difference between humoral and cellular arm of the immune response, which is essential for understanding predictions regarding changes in patterns in autoimmune disease incidence.

Immune tolerance during reproductive transitions: the role of AIRE

During development in the thymus, T cells undergo a complex negative selection process in which T cells with too high affinity for self-antigens are deleted, whereas those with weak interactions develop into normal T cells [Fig. 3a] [54,55]. Those with an intermediate auto-reactivity are positively selected to form long-lived population of native Tregs harbouring the ability to suppress other immune cells [53,54,56–58]. Central tolerance induction is enabled by the transcription of the autoimmune regulator (AIRE), which stimulates medullary thymic epithelial cells (mTECs) to express tissue-specific self-antigens (TSA) from various places around the body, allowing the training of immature T cells [53,59]. Genetic deficiencies or defects in AIRE transcription factor makes the carriers more likely to have multiple, co-occurring autoimmune diseases, and autoreactive T cells and autoantibodies [59].

Oestradiol, the main oestrogen hormone during the menstrual cycle, may influence the process of central tolerance induction via AIRE [54]. Due to the involvement of T-follicular-helper cells in their maturation, B cell tolerance is thereby affected as well [59,60]. In healthy individuals,
Explanatory Box 2
Cellular and humoral immunity and associated T-helper cells and cytokines

Autoimmune diseases can broadly be classified as originating from the humoral arm of the adaptive immune response, encompassing B cells and antibodies, or as being mediated by cellular immunity, comprising immune cells such as cytoytic T cells and macrophages [71,159] (Fig. 4 & Table 1 [4,7,69,98,107,117,160–164]). This classification is based on the way that different types of cytokines mediate the differentiation of T-helper (Th) cells into different types which coordinate the healthy immune response [122,165]. Cytokines enable cross-communication and coordination between innate and adaptive immune responses [166], which is how the immune system is able to effectively eliminate unwanted intruders. Anti-inflammatory cytokines promote Th2 differentiation and are responsible for activating the humoral immune system vital for protection against extracellular parasites [71,167]. Cellular immune responses, facilitated by Th1 and Th17 cells, are important for the eradication of cells infected by intracellular pathogens and viruses and are activated by pro-inflammatory cytokines (71,159). Finally, specialised T regulatory cells (Tregs) supervise the functions of effector Th cells by suppressing immune responses, playing a key role in autoimmunity [166,168].

![The Adaptive Immune System](image)

**Fig. 4.** An overview of the human adaptive immune system and its associated cytokines. The adaptive immune system can roughly be subdivided into humoral and cellular responses, which are mediated by Th2 or Th17 and Th1 cells respectively. Tregs supervise the activities of the different immune responses and play an important role in the regulation of the immune system. Illustration drawn based on [164,168,169, b0170 b0165,171].

**Table 1**
Cytokines and their effects. Immune cells secrete various cytokines with different functions, which have either stimulatory or inhibitory effects on the cellular or humoral arms of the immune system. Tregs suppress and control the different responses and are important in the maintenance of peripheral tolerance.

<table>
<thead>
<tr>
<th>Cell of origin</th>
<th>Cytokines</th>
<th>Stimulate</th>
<th>Inhibit</th>
<th>Function</th>
</tr>
</thead>
<tbody>
<tr>
<td>Th1</td>
<td>IFNγ</td>
<td>Th1, macrophages</td>
<td>Th2, Th17</td>
<td>Intracellular pathogens</td>
</tr>
<tr>
<td>Macrophages</td>
<td>IL-1, IL-6, IL-12, IL-18, IFNα, IFNγ</td>
<td>Inflammation, fever, acute phase response, plasma cell formation</td>
<td>N/A</td>
<td>N/A</td>
</tr>
<tr>
<td>Th17</td>
<td>IL-22, IL-17</td>
<td>Neutrophils, antimicrobial peptide-production</td>
<td>Th1, Th2</td>
<td>Extracellular bacteria, fungi</td>
</tr>
<tr>
<td>Treg</td>
<td>TGFβ, IL-10</td>
<td>Tregs</td>
<td>Th1, Th2</td>
<td>Suppression/Inhibition</td>
</tr>
<tr>
<td>Th2</td>
<td>IL-4, IL-5, IL-13</td>
<td>Th2, B cells</td>
<td>Th1, Th17</td>
<td>Extracellular parasites</td>
</tr>
</tbody>
</table>
AIRE expression is epigenetically down-regulated by oestradiol but up-regulated by the androgen dihydrotestosterone (DHT) [54]. As a consequence, females express less AIRE in their mTECs during the reproductive period, causing differences in central tolerance after the hormonal sexual dimorphism of the pubertal transition [54,61]. As AIRE is important in preventing autoimmunity, we would predict that under the influence of increases in oestradiol, women will be more likely to develop an autoimmune disease than men and to suffer from co-occurring autoimmune diseases. An increase in lifetime ovarian steroid exposure as predicted by our hypothesis might affect mechanisms of central tolerance induction through oestrogen-mediated down-regulation of AIRE expression in the thymus, as a result of which negative selection of autoreactive immune cells is reduced under a threshold that makes women more susceptible for autoimmunity and developing co-occurring autoimmune diseases [54,62].

**Tolerance during the menstrual cycle: the role of inflammation**

If autoreactive lymphocytes escape the stringent selection processes during development and start circulating around the body, specialised Tregs and B regulatory cells are usually still able to suppress them [54,63] (Fig. 5b). In absence of necessary co-stimulatory ‘danger’ molecules autoreactive lymphocytes are neutralised, and under the influence of increased oestradiol, women will more likely be able to develop an autoimmune disease than men and to suffer from co-occurring autoimmune diseases. An increase in lifetime ovarian steroid exposure as predicted by our hypothesis might affect mechanisms of central tolerance induction through oestrogen-mediated down-regulation of AIRE expression in the thymus, as a result of which negative selection of autoreactive immune cells is reduced under a threshold that makes women more susceptible for autoimmunity and developing co-occurring autoimmune diseases [54,62].

**Tolerance during pregnancy: the importance of Th cell balances**

Similar to the luteal phase of the menstrual cycle, pregnancy is characterised by an anti-inflammatory Th2/Treg immune profile. During early pregnancy, the progesterone increase stimulates the preferred differentiation of naïve T-helper cells into humoral immunity promoting Th2 cells [73], whereas at the same time hCG and oestrogen induce Tregs expansion at the implantation site and in the blood [74–77]. Research suggests that appropriate Th1/Th2 and Th17/Treg balances might be important for successful gestation of a semi-allogeneic foetus, as the peripheral blood and decidua of women with unexplained recurrent spontaneous abortion have a reduced Treg proportion compared to Th17 cells [78]. In women with preeclampsia, another disorder of pregnancy, Treg and Th2 cell numbers are declined in the umbilical cord blood [79]. Elevated Th1 and Th17 percentages, higher inflammatory cytokine ratios, and decreased Treg percentages in early pregnancy are in contrast associated with developing preeclampsia later in pregnancy [80]. Although further research is necessary to verify whether women with a strong innate pro-inflammatory cytokine profile before pregnancy are more likely to develop preeclampsia later on, the optimal balance between Th cells as well as pro- and anti-inflammatory...
The ovarian cycle causes fluctuations in inflammation, alters the balance between cellular and humoral responses, and influences autoimmune disease symptomatology

**Fig. 6.** Human cyclical immunity. This figure represents the ovarian cycle, which can be subdivided in the follicular and the luteal phase. It shows the developing egg, ovulation, the corpus luteum, and its degeneration, and concurrent changes in ovarian and pituitary hormone levels. The third panel depicts the uterine menstrual cycle and its phases, including the growth and decline of the uterine lining. Finally, the lower panel shows how the ovarian cycle may influence cell-mediated and humoral immunity. The arrows highlight some inflammatory occurrences in the menstrual cycle during the humoral mediated phase, which are (i.) the inflammatory process at ovulation just after the egg is released and (ii) the inflammatory processes involved in decidua differentiation at the start of the reproductive window (days 20–23). Low oestrogen levels during the follicular phase favour Th1/Th17 differentiation, whereas in the luteal phase high progesterone and oestrogen promotes Th2 responses. Consequently symptoms of cellular-mediated autoimmune diseases ameliorate during the luteal phase in most women whereas those of humoral autoimmune diseases worsen during this period. This figure was inspired by Alvergne & Tabor [85].

Immune responses might be important for successful gestation. The expansion of Tregs suppressing cellular responses against the semi-allogeneic offspring, might at the same time enhance the peripheral suppression of autoreactive immune cells during gestation [81]. Combined with the shift towards a Th2, anti-inflammatory immune profile, this would predict that during pregnancy the symptoms of autoimmune disease patients might improve for those suffering from cell-mediated, inflammatory autoimmune disease such as RA or MS, whereas those with an antibody mediated, humoral autoimmune disease would experience exacerbations of their symptoms.

**Reproductive hormone levels influence autoimmune disease symptoms and incidence**

Hormonal changes during the menstrual cycle influence the symptoms of women with autoimmune diseases. In some women suffering from the relapsing-remitting form of MS, an inflammatory, cell-mediated autoimmune disease of the nervous system, symptoms ameliorate during the luteal phase in which cellular immunity is more suppressed, but worsen again during the premenstrual decline in sex hormone levels [82–84]. This cyclical effect seems however to be limited to a subgroup MS patients [83,84]. On the opposite side of the autoimmune disease spectrum, the surge in anti-inflammatory cytokines and the stimulation of the Th2 cells during the luteal phase affect patients suffering from humoral autoimmune disease differently [69,85]. Women with systemic lupus erythematosus (SLE), a humoral autoimmune disease caused by autoantibody production towards various organ systems, experience an exacerbation during the luteal phase of the menstrual cycle when Th2 responses dominate, with 80% of symptomatic flares occurring during this period [86]. The complex dynamics by which reproductive hormone changes associated with the menstrual cycle influence the symptoms of autoimmune diseases warrant further investigation, also to understand why these effects occur only in a subset of patients.

As predicted based on this review of the role of ovarian steroids on immunomodulation, the increase in anti-inflammatory cytokines and a Th2/Treg immune profile during gestation pregnancy has an ameliorating effect on the symptoms of RA, a cell-mediated autoimmune disease. Marked disease remission in up to 75% of pregnant patients with active RA, often to such an extent that medication can be drastically reduced [17,87,88]. This was already reported in the scientific literature as early as 1938 [88]. However, postpartum, when oestrogen and progesterone concentrations fall, 90% of these patients experience a revival in disease activity concurrent with a shift back to a stronger cellular response [70,89,90]. In contrast, women with Graves autoimmune thyroiditis, a humoral autoimmune disease mediated by TSH-receptor auto-antibodies [91,92], experience a worsening of their disease early in pregnancy, but have their symptoms improve again later on, probably due to the positive effects associated with Treg increases [93,94].

Acknowledging the importance of these observations, biomedical research has long focused on finding potential treatments for alleviating the symptoms of autoimmune diseases using exogenous hormone administration, especially testing the benefits of oestradiolin mouse models of MS. For this disorder, oestradiol administration has been shown to decrease disease severity and even delay disease-onset [95,96]. Similarly, a case-control study in humans found MS incidence to be 40% lower in women who took hormonal contraception in the last three years, suggesting that high exogenous oestrogen levels may even delay the incidence of the first clinical attack of this cell-mediated inflammatory autoimmune disease [95,97]. However, on the other end of the spectrum, studies suggest that exogenous hormone administration might increase the incidence of developing humoral autoimmune disease such as SLE, with combined oral contraceptive starters being at a heightened risk [98,99]. The risk of developing SLE increases with greater concentrations of ethinyloestradiol in the pill formulation and is higher in women using first- or second-generation contraceptives that are known to have higher oestrogen doses compared to more modern drug formulations [99,100]. As predicted by our hypothesis, postmenopausal exogenous oestrogen use also increases women’s SLE risk, and randomized, double-blind controlled trial of hormone replacement therapy in SLE patients slightly increases the risk of mild to moderate flares [101–103]. Oestrogen levels therefore influence not only symptoms of autoimmune disease, but might also be a contributing factor to autoimmune disease incidence, possibly by affecting central and peripheral tolerance induction mechanisms.

Changes in endogenous sex hormone levels during the reproductive transition of puberty may also increase the incidence of autoimmune disease in women, shifting the sex ratio towards female preponderance. A Finnish cohort study found that girls during childhood are not more likely to present with type 1 diabetes T1D than boys overall [104], yet at age thirteen 87.5% of newly diagnosed T1D patients in the same cohort was female, coinciding with the age of menarche in the country [105]. Generally considered to be a childhood onset disease, T1D actually peaks at several points during the lifespan - during childhood (ages of 5–7), around puberty, and in the fifth decade around menopause.
suggested a role for shifting sex hormone levels during reproductive transitions in triggering autoimmunity [106,107]. Even in autoimmune diseases that are predominantly female, changing oestrogen levels associated with reproductive transitions may widen the incidence gap between women and men. For example, before puberty SLE already affects 3–4 girls for every boy, but during the childbearing years the incidence gap increases to as much as 9–20 females for every male [85,108,109]. A Chinese study furthermore found that although during the reproductive period SLE incidence was 13.3(f):1(m), the sex disparity in late onset, post-menopausal SLE was only 3.2(f):1(m) [110], which is remarkably similar to pre-pubertal numbers. Similarly, the sex ratio of RA, a cell-mediated autoimmune disease characterised by chronic inflammation of bone and cartilage [69], is 6(f):1(m) during the childbearing years but approaches 1(f):1(m) again for older ages of onset [111,112]. These epidemiological studies suggest that concurrently with the sexual dimorphism of reproductive hormone levels during the childbearing years, a change in autoimmune disease incidence takes place, and that changes in endogenous levels of ovarian steroids might affect autoimmune disease incidence.

Evolutionary perspectives on the sex disparity in autoimmune disease

What can an evolutionary perspective bring to research on the influence of sex hormones on autoimmune disease incidence and symptoms? An evolutionary perspective acknowledges that our bodies are “bundles of compromises” shaped by natural selection with the ultimate purpose of reproducing and passing down our genes to subsequent generations [62,113,114]. Natural selection consequently preferentially acts on traits conferring an advantageous advantage before or during the childbearing years. As a consequence, traits that are detrimental to health in post-reproductive life, including those contributing to increased autoimmune, will still be inherited if they confer an advantage during reproduction or early survival [62,115–119]. Therefore, the regulatory effect of ovarian steroids on central and peripheral tolerance induction in women might have evolved to ensure immune non-reactivity to paternal antigens displayed by the placenta during pregnancy to optimise reproductive success [20], yet these interactions might become deregulated in post-reproductive life. Accordingly, the evolution of placentation in mammals may have led to sex-specific sex hormone levels that affect autoimmune disease incidence.

Finally, an evolutionary medicine perspective highlights the importance of investigating the effect of recent changes in the ecology under which the interactions between the reproductive and immune system originally evolved, which can be considered a ‘mismatch’. Using the concept of WEIRD (Western, Industrialised, Rich, and Democratic) from the field of psychology [21], evolutionary anthropologists have argued that conventional biomedical research currently too heavily relies on participants of European descent living in urban, industrialised contexts, which are not representative of the lifestyle and ecological pressures experienced by our ancestors [133]. Most biomedical research on autoimmune diseases and sex hormones originates from (post-) industrialised, affluent societies that have adopted a Western lifestyle, which is not reflective of the energetic conditions during most of human evolution. Current immunological studies consequently fail to appreciate the existence of substantial variations in reproductive hormone levels between populations, members of the same group, and even between different cycles of the same woman [134]. Gene polymorphisms only partially account for these differences, which are instead the result of variations in age, ecology, and energetic factors that affect metabolic energy availability and their reallocation to vital functions other than reproduction [62,135]. Hormones are key modulators in the optimal investment of energy into these competing physiological functions and influence the timing of life-history events, such as the pubertal transition and menopause [136,137]. They are the mechanism by which organisms adapt cellular functions across different tissues in response to endogenous and exogenous environmental factors [138]. Therefore, gonadal function is sensitive to ecological influences, such as immune challenges, nutrition, and energy expenditure.
Although androgens such as testosterone promote cytotoxic T cell proliferation, compared to women men display lower humoral and cellular immune activity, which are the arms of the adaptive immune system involved in the development of autoimmunity [11,54,145,146].

**AIRE expression, which is implicated in central tolerance, is epigenetically up-regulated by the androgen dihydrotestosterone, as a consequence of which males express more AIRE in their mTECs than females during the reproductive period [25,55].** This may cause a difference in central tolerance after the hormonal sexual dimorphism occurs. Additionally, testosterone may play an important role in autoimmune disease progression and symptoms. In a study of MS patients, women with the lowest testosterone levels as well as men with the highest oestadiol levels experienced more brain lesions [89]. Furthermore, in obese men there is an even more distinct increase in plasma oestrogen levels compared to women [147], altering relative testosterone to oestrogen ratio’s due to excess adiposity. In this context, there is a dearth of studies focussing on the importance of relative hormone ratio’s rather than absolute hormone levels on autoimmune disease risk, whereas for cardiovascular diseases research seems to suggest that determining relative testosterone to oestrogen ratio’s may be a more valuable predictor than looking at either hormone in isolation [148].

Finally, despite an abundance of studies suggesting that hormonal changes over the life span affect autoimmune disease risk in women, no such research has been conducted in men, despite a documented age-related drop in the production of testosterone and other androgens during andropause, whilst oestrogen levels remain similar [149,150].

**Conclusion and future directions**

Of all immunology articles, less than 10% considers the sex of the participants in their analysis [151] and this bias persists in animal model studies [152]. Although compared to other areas of biomedicine autoimmune disease research has already acknowledged that taking sex and parity into consideration is key to understanding the female preponderance in autoimmunity incidence, research on the proximate mechanisms by which reproductive hormones influence tolerance mechanisms and autoimmune disease symptoms would benefit from an evolutionary medicine framework. A key part of this approach is recognising the diversity in sex hormone levels and immunomodulation in response to ecological pressures, and the effect these interactions might have on the immune system of women according to their reproductive life stage and energy balance [122,153].

To fully understand how this diversity in sex hormone profiles can contribute to differences in autoimmune disease incidence, there is also a need for more immunological research to take place outside of (post-) industrialised, affluent settings that are more reflective of the energetic conditions and challenges encountered in our ancestral environment [133]. This is necessary to understand how novel changes in energy balance and lifestyle might affect autoimmune disease development. For example, considering that throughout most of our evolutionary history women engaged in prolonged periods of breastfeeding [30], there is a severe lack of studies that consider the effect of lactation on the mother’s immune profile and consequent autoimmune disease risk. In Tsimane women, lactational amenorrhoea lasts 12–14 months, and after just 7–9 months of regular cycling women may get pregnant again [152]. Preliminary studies suggest that during lactation Tsimane women have an immune profile that is quite distinct from both normal cycling and pregnant women [154]. Yet, it is not properly known how breastfeeding duration influences tolerance mechanisms in women and subsequent autoimmune disease risk.

Although methodologically challenging, future research on autoimmune diseases should particularly focus on understanding possible variation in epigenetic regulation of the AIRE gene in response to ecological pressures and differences in oestadiol levels. Additionally, the effect of pregnancy on mechanisms of central tolerance deserves further attention. Research is also needed on the variation in cyclical immunity in relation to autoimmune disease incidence and symptomatology, specifically looking at fluctuations in Treg/Th17 and inflammatory cytokine ratios across the menstrual cycle in different ecological settings, and the influence in lifetime menstrual cycles on Treg-pool and peripheral tolerance. For this purpose, it is crucial that a more flexible, context dependent approach to immunological research is created based on life history theory and evolutionary principles. This is needed to enhance our understanding of how variations in ovarian hormone levels during different reproductive stages contribute to population level differences in autoimmune disease incidence. Currently no accounts of autoimmune disease exists in subsistence populations, although this cannot be taken as prove of absence of incidence of these diseases outside of (post-)industrialised, affluent contexts, as it is highly likely that under-diagnosis and under-reporting of autoimmune disease symptoms are responsible for the absence of such accounts. Due to their low life expectancy at birth, which is skewed because of infant mortality, it is a common misconception to assume that individuals from subsistence populations may not live long enough to experience chronic diseases associated with ageing [142], such as autoimmune disorders. However, the modal age of death of adults in hunter-gathers is 68–78 years [142–143] and there are many autoimmune diseases whose onset is most frequent at earlier stages of life [10]. Immunological research will benefit from considering the reasons for differences in autoimmune disease incidence in ecologically diverse populations, taking into account evolutionary explanations for variation in sex hormones, immunomodulation, and tolerance mechanisms. As reproductive function affects the body beyond fertility and pregnancy alone, understanding interactions between sex hormones and immune system throughout women’s reproductive history is indispensable for advancing female health.

**Glossary**

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tr>
<td>Andropause</td>
<td>The male equivalent of menopause, characterised by a significant drop in androgen production whereas oestrogen levels remain more stable.</td>
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<tr>
<td>Cellular immunity</td>
<td>Is activated by pro-inflammatory cytokines and regulated by Th1 and Th17 cells. The cellular immune response offers protection against intracellular pathogens such as viruses, as well as fungi and extracellular bacteria.</td>
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</table>
Th1 cells T-helper cells type 1 are important in the cellular immune response. They secrete inflammatory cytokines which regulate the humoral immune response. Autoimmune diseases such as MS.

Th2 cells T-helper cells type 2 are important in the humoral immune response. Th2 cells secrete anti-inflammatory cytokines which regulate the humoral immune response. Autoimmune diseases such as SLE.

Tolerance also known as immunotolerance, this is a state of unresponsiveness of the immune system to antigens derived from the own tissues that may have the capacity to elicit an adaptive immune response.

Tregs T-regulatory cells’ main function is the suppression and regulation of immune responses as well as tolerance. They also play an important role during pregnancy in the tolerance to a semi-allogeneic foetus. There are two types of Tregs, those that are centrally induced and those that originate in the periphery.

Type 1 diabetes autoimmunity causing the progressive loss of insulin-secreting cells pancreatic islets. Cellular autoimmunity diseases with an occasional humoral component, especially in children.

Ultimate explanations according to Tinbergen’s four questions in biology (1963), ultimate explanations ask for the function and phylogeny of a trait or complex biological phenomenon. Ultimate explanations are guiding evolutionary anthropology/biology research and ask ‘what for’ rather than ‘how’. For example, one may ask how did natural selection leave our body vulnerable to developing autoimmune disease?

Unopposed oestrogen levels during the menstrual transition, progesterone levels decline nearly a decade before oestriol levels rapidly fall six months before menopause (age 49-51).

Weird the acronym for Westernised, Educated, Industrialised, Rich, and Democratic was introduced by Henrich and colleagues in 2010 to describe the unusual psychological characteristics of people living in such societies. The term is now increasingly also applied to describe the abnormal physiological features people living in these societies exhibit.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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