



Sex steroids and autoimmune rheumatic diseases: state of the art

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Abstract | In autoimmune rheumatic diseases, oestrogens can stimulate certain immune responses (including effects on B cells and innate immunity), but can also have dose-related anti-inflammatory effects on T cells, macrophages and other immune cells. By contrast, androgens and progesterone have predominantly immunosuppressive and anti-inflammatory effects. Hormone replacement therapies and oral contraception (and also pregnancy) enhance or decrease the severity of autoimmune rheumatic diseases at a genetic or epigenetic level. Serum androgen concentrations are often low in men and in women with autoimmune rheumatic diseases, suggesting that androgen-like compounds might be a promising therapeutic approach. However, androgen-to-oestrogen conversion (known as intracrinology) is enhanced in inflamed tissues, such as those present in patients with autoimmune rheumatic diseases. In addition, it is becoming evident that the gut microbiota differs between the sexes (known as the microgenderome) and leads to sex-dependent genetic and epigenetic changes in gastrointestinal inflammation, systemic immunity and, potentially, susceptibility to autoimmune or inflammatory rheumatic diseases. Future clinical research needs to focus on the therapeutic use of androgens and progestins or their downstream signalling cascades and on new oestrogenic compounds such as tissue-selective oestrogen complex to modulate altered immune responses.

Following the early observations made by Philip S. Hench in the 1930s¹ regarding the ameliorating effects of pregnancy and cholestasis on rheumatoid arthritis (RA), rheumatologists have repeatedly reported links between biological sex and the distribution or severity of systemic chronic inflammatory or autoimmune rheumatic diseases. In many rheumatic diseases, the female-to-male incidence ratio is much higher than 1.0 (up to 10.0), and menarche, menses, pregnancy, the postpartum period, menopause and hormone replacement therapies all influence disease activity^{2,3}. Although sound non-endocrine explanations, such as the influence of sex chromosomes^{4–6}, have been used to explain the links between sex and rheumatic diseases, sex steroids were and are the most important explanatory factors for understanding sexual dimorphism in rheumatic diseases.

Generally, oestrogens have roles in both enhancing and inhibiting immune reactions (BOX 1), whereas androgens (BOX 2) and progesterone exert suppressive effects on many immune reactions^{7–21}. Moreover, a common final steroid conversion pathway is shared between oestrogens and androgens (intracrinology) at the site of inflamed tissue that is similar in men and women, which helps to explain the propagation of local inflammatory diseases in men²².

Before 1980, research into sexual dimorphism in autoimmunity was epidemiological and clinical with a focus on human diseases and animal models of autoimmunity. Between 1980 and the middle of the 2000s, in vitro studies on the effects of sex steroids on cytokine secretion from, the proliferation of and the function of various human immune cells were added to animal studies^{2,7,8,23}. Then, from 2005 onwards, new factors (described in detail in later sections) emerged via multi-omics data generation in immunology that became targets of sex steroid research^{7–21}, including investigations into microbiota that started in the 2000s in the periodontitis and inflammatory bowel disease research fields.

In this Review, we provide an update to previous review articles^{7–21} and present new developments in the field of sex steroid research and novel concepts for basic and clinical research and randomized controlled trials (RCTs) in autoimmune rheumatic diseases. We incorporate data on several autoimmune and inflammatory rheumatic diseases, including RA, systemic lupus erythematosus (SLE), systemic sclerosis (SSc), ankylosing spondylitis (AS) and psoriatic arthritis (PsA). However, although sex steroids have an important role in osteoarthritis, this condition is not covered in this Review.

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<https://doi.org/10.1038/s41584-020-0503-4>

Key points

- Oestrogens have both pro-inflammatory and anti-inflammatory effects, acting as stimulators of B cell-mediated immune responses but inhibitors of pro-inflammatory macrophages and some T cells.
- In contrast to oestrogens, androgens and progesterone have immunosuppressive and anti-inflammatory effects.
- In men and postmenopausal women with rheumatic diseases, increased androgen-to-oestrogen conversion in inflamed tissues and local oestrogen metabolite synthesis support disease.
- Pregnancy, sex hormone replacement therapies and oral contraceptives can negatively or positively affect the severity of autoimmune rheumatic diseases, depending on the respective predominance of oestrogens or androgens (and progesterone).
- Sex-dependent differences in gut microbiota may lead to genetic or epigenetic changes in local gastrointestinal inflammation, systemic immunity and susceptibility to a range of rheumatic diseases.
- Therapies with androgens and progestins, selective oestrogen receptor modulators and tissue-selective oestrogen complex need to be tested more rigorously in autoimmune rheumatic diseases.

Genetics of sex steroid signalling

The past 10 years have provided new information on genetic variation in sex steroid receptors, sex steroid receptor binding sites and enzymes and cofactors related to sex steroid generation that help to explain several aspects of rheumatic diseases, including susceptibility, autoimmunity and severity (TABLE 1). The role of sex chromosomes is not covered in this Review (reviewed elsewhere^{4–6}) and, to the best of our knowledge, no new genetic markers in the progesterone receptor or progesterone signalling pathways have been reported in the past decade. Importantly, not all of the genetic studies mentioned in the following subsections are adequately powered according to current standards, and we realize that some of the studies mentioned will need to be replicated in larger samples.

Box 1 | Known effects of oestrogens on immune responses

Oestrogens have a dichotomous effect *in vivo* and *in vitro*: physiological or low concentrations are pro-inflammatory but high concentrations (for example, in the periovulatory or pregnancy range) are anti-inflammatory⁸. At high concentrations, oestrogens inhibit T helper 1 (T_H1) cells, T_H17 cells (via oestrogen receptor- α (ER α), but have the opposite effect via ER β ⁷⁰), M1 macrophages, dendritic cells, neutrophils, microglia, vascular smooth muscle cells and fibroblasts *in vitro* via inhibition of NF- κ B (reviewed elsewhere^{7,8,11,12,18}). Oestrogens at high concentrations also support the function of regulatory T cells and the secretion of IL-4, IL-10 and transforming growth factor- β , which stimulates T_H2 cell cytokine pathways (reviewed elsewhere^{7,8,11,12,18}). However, these effects can aggravate asthma and can worsen disease in patients with active systemic lupus erythematosus or antiphospholipid syndrome and in pregnant women with these conditions^{218,219}.

Oestrogens also demonstrate beneficial anti-inflammatory effects in many animal models of rheumatic diseases, although their effects can be favourable or unfavourable (sometimes in the same model) depending on the prevailing immune reaction; when B cells dominate, oestrogens stimulate the disease, and when T cells dominate, they can inhibit disease^{8,220}. Oestrogens at high concentrations (such as in the periovulatory to pregnancy range) inhibit some of the later steps of T cell and B cell lymphopoiesis *in vivo*^{8,131,136,221}. They upregulate CD22 and the pro-survival molecule Bcl-2 in B cells and increase the amount of B cell activating factor (reviewed elsewhere^{7,8,11,12,18}), which is expected to worsen disease in patients with active systemic lupus erythematosus or antiphospholipid syndrome. Oestrogens also stimulate many B cell-mediated immune processes at a wide range of hormone concentrations *in vivo* and *in vitro*, mainly (auto) antibody generation in rheumatic diseases; B cell-dependent autoimmune diseases are supported by the presence of any amount of oestrogen (reviewed elsewhere^{8,11,12,18}).

Oestrogen receptors. In a targeted gene analysis, patients with RA possessed several relevant single nucleotide polymorphisms (SNPs) in sex steroid-associated genes²⁴. The researchers included two patient groups, a cohort of patients with RA from Spain and Portugal and patients from the Dutch Rheumatoid Arthritis Monitoring registry²⁴. The combined analysis revealed an association between the *ESR2* (which encodes oestrogen receptor- β (ER β)) genotype rs1271572T/T and a reduced risk of erosive arthritis. Furthermore, patients with seropositive RA carrying the *CYP1B1* genotype rs10012G/G or the *CYP2C9* genotype rs1799853T/T had a significantly reduced risk of developing bone erosions²⁴ (TABLE 1). As the cytochrome P450 enzymes CYP1B1 and CYP2C9 catalyse the conversion of oestrogens to immunomodulatory hydroxy-oestrogens, these SNPs, as well as the SNP in *ESR2*, can have important roles in disease progression in RA.

Studies have also been conducted in SLE, and evidence exists that variants of *ESR1* (which encodes ER α) are linked to SLE susceptibility or severity. According to a meta-analysis, the *ESR1* PvuII polymorphism is associated with susceptibility to SLE in many populations, and the *ESR1* XbaI GA genotype is associated with susceptibility to SLE in Asian populations²⁵. Another important factor in SLE is ubiquitin-conjugating enzyme E2 L3 (UBE2L3), which targets proteins for ubiquitin-mediated degradation. A variant of *UBE2L3* has been linked to SLE susceptibility in several genome-wide association studies (GWAS) in different populations²⁶. The presence of the SLE-risk polymorphism rs140490 in the promoter region of *UBE2L3* causes an increased expression of UBE2L3 in B cells and monocytes *ex vivo*. Additionally, this polymorphism promotes an increase in the number of circulating plasmablasts and plasma cells in patients with SLE²⁶. But what has this polymorphism got to do with sex steroids? Because UBE2L3 regulates the transcriptional activity of oestrogen, androgen and progesterone receptors in a hormone-dependent manner, the ubiquitin conjugation activity of UBE2L3 potentiates transactivation of steroid hormone receptors²⁷. UBE2L3 is hormone-dependently recruited to promoters that are responsive to oestrogen receptors and progesterone receptor. Depletion of endogenous UBE2L3 reduces the transcriptional activity of progesterone receptor, suggesting that this protein is necessary for the proper function of sex steroid hormone receptors²⁷. These data show a clear link between a well-known SLE susceptibility gene product and sex hormone receptor functioning.

In the past few years, oestrogen receptors have also become targets of pharmacogenetic studies owing to the occurrence of functionally relevant polymorphisms of these receptors. A case-control study in three European populations that included 1,985 patients with RA who were receiving TNF inhibitor therapy showed that an *ESR2* (GGG) haplotype was associated with an increased chance of having a good response to TNF inhibitor therapy²⁸. These new data on oestrogenic pathway genes explain a portion of the genetic risk for RA and SLE and should stimulate geneticists to include further sex steroid pathways in their future analyses.

Box 2 | Known effects of androgens on immune responses

In contrast to oestrogens (BOX 1), androgens such as testosterone are mainly anti-inflammatory in vivo and in vitro, with the exception of their role in neutrophil generation. Androgens reduce NF- κ B and Toll-like receptor 4 expression and decrease the secretion of cytokines such as TNF, IL-1 β and IL-6 by monocytes and macrophages and IL-33 by mast cells in vivo and in vitro (reviewed elsewhere^{10,13,16,17,19,20}). Androgen therapy in men with hypogonadism reduces serum concentrations of IL-1 β and TNF, increases concentrations of IL-10 and decreases thymic T cell output. Androgens also inhibit B cell lymphopoiesis and (auto)antibody production in vivo, as well as T helper 1 cell differentiation, by reducing IL-12 and IFN γ in vivo and in vitro (reviewed elsewhere^{10,13,16,17,19,20}).

Androgens are often reduced in the serum of patients with autoimmune or inflammatory rheumatic diseases^{7,16} owing to the conversion of anti-inflammatory androgens to pro-inflammatory oestrogens in inflamed tissue (intracrinology in local cells)^{22,222–225}. In inflammatory diseases, cytokines such as TNF, IL-1 and IL-6 stimulate the aromatase enzyme (which is necessary for the biosynthesis of oestrogens) in immune cells and fibroblasts, a phenomenon first observed in breast cells¹⁶¹.

Biopharmaceutical medical products can also interfere with sex steroid regulation or generation. The neutralization of TNF and IL-6 with biologic therapies can improve altered hormone axes^{162,226,227}. In addition, TNF inhibitor therapy protects both a mother with rheumatoid arthritis (RA) and her fetus during pregnancy, which, among other aspects, can be interpreted as a sign of hormonal normalization²²⁸. Men with RA profit more from biologic therapies than women²²⁹, mostly because blockade of androgen-to-oestrogen conversion with TNF inhibitors maintains the physiologically high serum concentrations of androgens in men. Interaction with sex steroids is also an important aspect of leflunomide therapy in RA because this drug inhibits cytokine production by macrophages more strongly when androgens are given in parallel²³⁰.

Androgens and androgen receptors. Opposed to oestrogens stand androgens, with their well-known immunosuppressive activities. New data from patients with RA have revealed a polymorphism in *CYP5A* on chromosome 18, which encodes cytochrome B5 and determines the amount of androgens that are converted from precursor hormones²⁹. Cytochrome B5 is an important supportive cofactor of the second lyase step of the P450c17 enzyme in androgen production in all tissues where prohormones such as pregnenolone are converted to downstream androgens, including in synovial fibroblasts in patients with RA²⁹. The results of large GWAS from the Wellcome Trust Case Control Consortium and the North American Rheumatoid Arthritis Consortium revealed RA-associated polymorphisms in *CYP5A*: rs1790834 (odds ratio (OR) 0.83; $P = 0.0073$) and rs1790858 (OR 0.44; $P = 0.0095$), respectively^{30,31}. Although the associations between these SNPs and RA did not reach the statistical significance required in these GWAS, a targeted approach in a Slovakian cohort that included 521 patients with RA and 321 healthy individuals confirmed the association between rs1790834 and RA at a significant level ($P = 0.0041$)²⁹. The SNP rs1790834, which is localized in intron 1 of *CYP5A*, showed a protective effect (OR 0.63; 95% confidence interval (CI) 0.46–0.86) similar to the previous GWAS. This protective effect was confined to rheumatoid factor (RF)-positive and anti-citrullinated protein antibody (ACPA)-positive women with RA²⁹. The protective allele doubled the expression of *CYP5A* mRNA, resulting in a 2–3-fold increase in cytochrome P450c17 enzyme activity, an increased density of cytochrome B5-positive cells in RA synovial tissue and increased androgen concentrations in pregnenolone conversion studies in synovial

fibroblasts in vitro²⁹. In other words, a genetic predisposition to produce more androgens seems to provide protection against RA.

CAG repeats in AR, which encodes the androgen receptor, have also been linked to autoimmune diseases. AR is a ligand-dependent transcriptional regulator with 8 exons located on the X chromosome. The first exon of AR contains polymorphic trinucleotide (CAG) $_n$ repeats ($n = 9–37$) that encode polyglutamine, which result in a shorter ((CAG) $_9$) or longer ((CAG) $_{37}$) protein. The number of CAG repeats (and therefore the number of polyglutamine residues) is inversely correlated with the transcriptional activity of the androgen receptor³². Thus, CAG repeats have been a target for genetic studies in several rheumatic diseases. Although the concept of lower androgen activity with a higher number of CAG repeats is fascinating, studies have not yet revealed a clear association with RA^{33–37}, SLE^{38–40} or AS^{41,42}. The sample sizes in these studies of heterogeneous populations were small, leading to limited statistical power; studies with large sample sizes are needed to define the role of CAG repeats in AR in autoimmune rheumatic diseases.

Epigenetics of sex steroid pathways

Epigenetics encompasses functionally relevant changes to the genome and gene products without changes in the nucleotide sequence, examples of which include DNA methylation at CpG sites, histone modifications and regulation of mRNA translation by microRNAs. These epigenetic changes can endure multiple cell divisions and last for several generations⁴³. Depending on environmental conditions, epigenetic changes can occur early in life, leading to long-term imprinting of transcriptional and translational activity⁴³.

Sex steroids can influence epigenetic modulation of immune responses in autoimmune rheumatic diseases. In one study, patients with SLE or RA had increased expression of *ESR1* mRNA and ER α protein in peripheral blood mononuclear cells, which was associated with DNA demethylation within the proximal promoter region of *ESR1* (REF.⁴⁴). Demethylation in the target region was higher in those with SLE or RA than in healthy individuals but was comparable in men and women. Thus, oestrogens, together with increased amounts of ER α via *ESR1* promoter demethylation, are linked to the upregulation of ER α -dependent genes, which can add to the sex bias in autoimmune diseases. In another study, women with SLE showed an oestrogen-dependent genome-wide DNA hypomethylation in CD4 $^+$ T cells⁴⁵. This effect was paralleled by oestrogen-dependent inhibition of DNA methyltransferase 1 in vitro. All effects were neutralized by an ER α antagonist, which again shows the demethylating effect of oestrogens in SLE.

MicroRNAs are epigenetic regulators that control inflammation and immune responses⁴⁶. Oestrogens can upregulate and downregulate different microRNAs that directly interfere with immune responses⁴⁷. In one study, the interaction of ER β with oestrogen controlled microRNA-155 (miR-155)⁴⁸, an important epigenetic regulator known to have a significant role in immune activation in RA and other autoimmune diseases⁴⁶. Silibinin, a major constituent of the extract

Table 1 | Genetic associations between sex steroid signalling and autoimmune rheumatic diseases

Gene	Gene product	Genetic variant	Disease	Association	Odds ratio (n), 95% CI	P value	Ref.
ESR1	Oestrogen receptor- α	PvuII CC + CT versus TT	SLE	Increased susceptibility and severity in all populations ^a	1.33 (2,494), 1.19–1.49	<0.001	²⁵
		XbaI GA versus AA	SLE	Increased susceptibility and severity in Asian populations ^a	1.27 (1,437), 1.10–1.47	0.001	²⁵
ESR2	Oestrogen receptor- β	GGG haplotype	RA	Increased chance of having a good response to TNF inhibitor therapy	0.64 (1,285), 0.49–0.83	0.00090	²⁸
		rs1271572T/T	RA	Reduced risk of erosive arthritis ^b	0.52 (899), 0.36–0.76	0.00074	²⁴
CYP1B1	Cytochrome P450 1B1	rs10012G/G	RA	Reduced risk of erosive arthritis ^b	0.38 (899), 0.23–0.61	0.000081	²⁴
CYP2C9	Cytochrome P450 2C9	rs1799853T/T	RA	Reduced risk of erosive arthritis ^b	0.16 (571), 0.06–0.46	0.0007	²⁴
CYB5A	Cytochrome B5	rs1790834	RA	Reduced susceptibility in women	0.63 (434), 0.46–0.86	0.0041	²⁹
UBE2L3	Ubiquitin-converting enzyme E2 L3 ^c	rs140490	SLE	Increased susceptibility	1.22 (3,936), 1.12–1.33	2.92E-06	²⁷

CI, confidence interval; RA, rheumatoid arthritis; SLE, systemic lupus erythematosus. ^aData from a meta-analysis. ^bIn rheumatoid factor-positive RA.

^cUbiquitin-converting enzyme E2 L3 is necessary for the proper function of sex steroid hormone receptors.

of the milk thistle and a natural ligand of ER β , upregulated ER β expression, induced apoptosis, inhibited proliferation and reduced the expression of IL-17 and TNF (through ER β binding) in T cells from healthy donors and from patients with active RA⁴⁸. Silibinin functioned as an epigenetic modifier by decreasing the expression of miR-155 in vitro⁴⁸, showing that the ER β pathway is closely linked to epigenetic regulation. The therapeutic effect of silibinin has also been demonstrated in RA synovial fibroblasts in vitro via inhibition of the NF- κ B pathway and in rats with collagen-induced arthritis⁴⁹. Oestrogen-regulated microRNAs and those that are differentially expressed between sexes also have effects in SLE⁵⁰. Many of these microRNAs have effects on immune responses and inflammation, and are relevant in different cell types such as fibroblasts, granulocytes, monocytes and mixed splenocytes. Similarly, oestrogen-regulated microRNAs are differentially expressed in male and female lupus-prone mice, which spontaneously develop lupus-like disease^{50,51}.

Another important element of autoimmunity is autoimmune regulator (AIRE), which is required for autoantigen presentation in the thymus. The presence of AIRE leads to negative selection of self-reactive T cells and, thus, to self-tolerance⁵². Deficiency in AIRE leads to the monogenic autoimmune disease autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (APECED)⁵². In a ground-breaking study, Dragin et al. demonstrated a role for sex steroids in AIRE expression⁵³. Women after puberty expressed less AIRE than men, and oestrogen treatment resulted in downregulation of AIRE expression in cultured human thymic epithelial cells, human thymic tissue grafted into immunodeficient mice and murine fetal thymus organ cultures⁵³. In addition, oestrogens increased the number of methylated CpG sites in the AIRE promoter⁵³, which is an epigenetic way to inhibit AIRE expression. Suppression of AIRE by oestrogens can be a strong factor for sexual dimorphism in rheumatic diseases because AIRE downregulation leads to a generally increased disposition for autoimmune phenomena (as occurs in APECED).

Sex steroids and immune responses

Important elements of sex steroid effects on immune responses that have been previously ascertained using immune cell cultures and animal experimentation are discussed in BOX 1 (for oestrogens) and BOX 2 (for androgens) and provide the basis for understanding the role of sex steroids in immunity and autoimmune diseases. The mechanisms discussed in the following sections focus on studies from the past 10 years.

Oestrogen signalling pathways. Different roles for oestrogens have been delineated that can influence susceptibility to and the severity of autoimmune diseases. Oestrogens have complex pro-inflammatory and anti-inflammatory roles that differ depending on the cells being investigated and on the doses or concentrations involved (FIG. 1).

During a normal immune response, activation-induced cytidine deaminase (AID) deaminates cytosines at immunoglobulin gene loci in B cells, initiating somatic hypermutation and class switch recombination. This process is an important step in the production of high-affinity IgG (auto)antibodies, and one that can be modulated by oestrogens (FIG. 1). The oestrogen-ER α complex binds to the promoter of AICDA (encoding AID), which increases AICDA mRNA and AID expression, thus causing a rapid increase in somatic hypermutation and class switch recombination at the immunoglobulin locus in vitro⁵⁴. Importantly, outside of B cells and the immunoglobulin locus (for example, in mammary and ovary cells), oestrogen-induced AID expression is also increased and leads to oncogene upregulation and DNA instability. These results⁵⁴ suggest that oestrogens can induce not only autoimmunity via AID but also oncogenesis in susceptible cells. Other data in mice show a similar oestrogenic effect on class switch recombination. Chromatin immunoprecipitation-sequencing data from mouse B cells demonstrate that ER α binds to oestrogen response elements on DNA near the class switch site (S μ) of the immunoglobulin heavy chain locus⁵⁵, suggesting that oestrogens directly regulate class switch recombination.

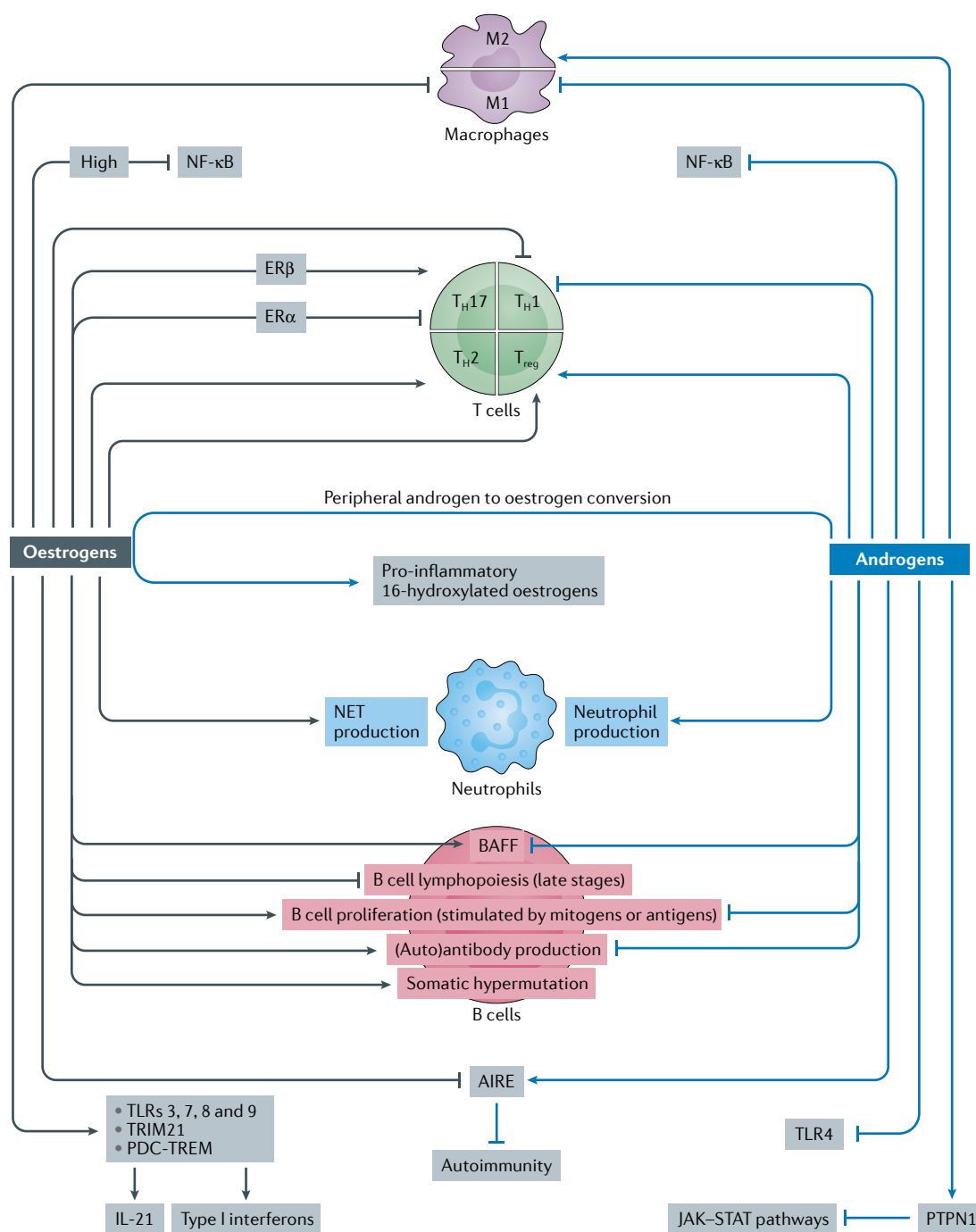


Fig. 1 | Effects of oestrogens and androgens on immune function. Sex steroids have important pro-inflammatory and anti-inflammatory effects on the immune system, as revealed by studies in animal models, in cells and in the clinic. Generally, oestrogens exert pro-inflammatory effects on B cells and anti-inflammatory effects on T helper 1 (T_H1) cells, T_H17 cells (via oestrogen receptor- α (ER α), but have the opposite effect via ER β ⁷⁰) and macrophages, and through regulatory T (T_{reg}) cells and T_H2 cell-associated cytokines. By contrast, androgens mainly have direct and indirect anti-inflammatory roles in immune function, with the exception of their effect on neutrophil production. In particular, oestrogens and androgens have opposing effects on autoimmune regulator (AIRE; an important factor in autoantigen presentation in the thymus, deficiency of which leads to autoimmune disease) and B cell activating factor (BAFF; an important factor in B cell lymphopoiesis and mature B cell clonal expansion), but similar effects on T cells and macrophages. In inflamed tissue, cells more readily convert androgens to oestrogens. The word 'high' indicates that this effect only occurs at oestrogen concentrations that occur during pregnancy (above 3–5 nmol/l), otherwise, all effects occur at oestrogen concentrations of 0.05–1.00 nmol/l. JAK, Janus kinase; NET, neutrophil extracellular trap; NF- κ B; nuclear factor- κ B; PDC-TREM; plasmacytoid dendritic cell-specific receptor; PTPN1, tyrosine-protein phosphatase non-receptor type 1; STAT, signal transducer and activator of transcription; TLR, Toll-like receptor; TRIM21, tripartite motif-containing 21.

Research from the past decade indicated that the type I interferon pathway is important in rheumatic diseases, which led to the development of biologic therapies directed against type I interferons^{56,57}. Important links have been established between oestrogens and Toll-like receptors (TLRs) or type I interferons in patients with SLE¹⁵ (FIG. 1). In microarray analyses of peripheral blood mononuclear cells from patients with SLE, oestrogens upregulated endosomal TLR8, an effect that could be blocked by ER α antagonists⁵⁸. Oestrogen also upregulated other endosomal TLRs, including TLR3, TLR7 and TLR9 (REF.⁵⁸). Given that these pathways are decisive in type I interferon-dependent regulation of immunity, these findings can help to explain sexual dimorphism in SLE via oestrogens and type I interferons.

One of the cytokines induced via endosomal TLRs (TLR7 and TLR9) is IL-21. In patients with SLE, oestrogens upregulate IL-21 via the activation of mitogen-activated protein kinase in CD4⁺ T cells⁵⁹. This oestrogen stimulation also increases antibody production by B cells *in vitro*⁵⁹. Another molecule that regulates antiviral responses and supports the production of type I interferons downstream of TLRs 3, 7 and 9 is tripartite motif-containing protein 21 (TRIM21), which was first described as an autoantigen in patients with SLE⁶⁰. *TRIM21* expression is increased by oestrogens via an ER α -dependent pathway, and the inhibition of ER α in monocytes decreases IL-23 expression *in vitro*⁶⁰. This decrease in expression is important in SLE because IL-23 stimulates T helper 17 (T_H17) cells, which have a role in SLE disease manifestations⁶¹. These results suggest that *TRIM21* is a novel oestrogen-regulated gene with a role in rheumatic diseases. Oestrogen-dependent support of TLR mechanisms has also been shown in lupus-prone mice. ER α deficiency reduced type I interferon activity and the number of MHC class II-positive plasmacytoid dendritic cells in the spleen of lupus-prone mice⁶². After *in vitro* TLR9 stimulation, ER α -deficient mice also had reduced expression of PDC-TREM, a modulator of TLR-mediated interferon production in plasmacytoid dendritic cells⁶². Collectively, these data convincingly demonstrate the supportive role of oestrogens for type I interferon production *in vitro*.

Another oestrogen-stimulated pathway is that mediated by TNF-like weak inducer of apoptosis (TWEAK), a member of the TNF ligand superfamily that has a pro-inflammatory role in SLE, particularly in lupus nephritis⁶³. *TWEAK* expression in the kidneys and urinary TWEAK concentrations are increased in patients with SLE who have kidney disease^{64,65}. In lupus-prone mice, oestrogens increased TWEAK mRNA and protein, which could be blocked by specific ER α antagonists⁶³, suggesting that TWEAK is a new factor that can help to explain sexual dimorphism in SLE.

IL-17 is known to be important in inflammatory arthritis in both humans and animal models⁶⁶, and data now suggest that oestrogens affect this central pathogenic cytokine. Although the inhibitory effect of oestrogens on T_H17 cells was known in humans and animals (FIG. 1), it was not known that oestrogens induce T_H17 cell retention in lymph nodes. This fact has now been demonstrated, and it is thought that the CC-chemokine

receptor 6–CC-chemokine ligand 20 pathway, which is involved in T_H17 cell migration, might be a decisive factor⁶⁷. An oestrogen-dependent decrease in IL-17 might happen through inhibition of the transcription factor ROR γ T, which is mediated by binding of an inhibitory complex consisting of ER α and repressor of oestrogen receptor activity (REA, also called prohibitin-2) to the ROR γ T promoter⁶⁸. ER β has also received attention in relation to IL-17. Silibinin, a natural agonist of ER β , upregulated ER β expression, induced apoptosis, inhibited proliferation and reduced expression of IL-17 (and TNF) through ER β binding in T cells from healthy individuals⁴⁸. However, the inhibitory influence of oestrogens on IL-17 and T_H17 cell differentiation is not unopposed; a T_H17 cell propagating role has been proposed for oestrogens in patients with allergic asthma who have airway inflammation⁶⁹. The reasons for this discrepancy are presently not known, but the general importance of the T_H2 cell pathway in asthma, as opposed to the T_H1 pathway that predominates in inflammatory arthritis, might be involved in these diverse results. In addition, one study demonstrated that activation of ER β stimulates IL-17-producing cells in a model of experimental thyroiditis⁷⁰. Thus, the effects of oestrogens on T_H17 cells or IL-17 secretion are still a matter of discussion.

Another important oestrogen-dependent effect is post-translational modification of the Fc portion of IgG, which can influence macrophage activity through Fc receptors. For example, the attachment of terminal sialic acid residues to IgG can mediate anti-inflammatory effects in macrophages⁷¹. In postmenopausal women with RA, treatment with oestrogens substantially increased the sialylation of the Fc portion of IgG⁷¹, suggesting that sialylation is a possible mechanism by which oestrogens inhibit antibody-dependent macrophage activation through Fc receptors.

Androgen signalling pathways. Studies on androgen signalling pathways from the past decade have clearly shown the anti-inflammatory influence of this sex steroid. Inducing tolerance is a crucial factor in preventing autoimmunity and, as previously mentioned, AIRE is important for promoting immune tolerance. In contrast to oestrogens, which inhibit AIRE⁵³, androgens recruit androgen receptors to AIRE promoter regions and consequently enhance AIRE transcription⁷² (FIG. 1). In mice and humans, thymic AIRE expression is higher in males than in females, and androgen administration and male sex were protective against autoimmunity in an AIRE-dependent manner in a mouse model of multiple sclerosis⁷². Similar effects have not yet been shown in models of rheumatic diseases. Another important factor in immune tolerance is CD4⁺CD25^{hi}FOXP3^{hi} regulatory T (T_{reg}) cells, which have a decisive role in preventing autoimmunity⁷³. Importantly, in one study, androgens increased *FOXP3* expression in T cells from women during the ovulatory phase of the menstrual cycle, but did not increase *FOXP3* expression in T cells from men⁷⁴. The *FOXP3* locus possesses a functional androgen response element suitable for androgen receptor binding, which leads to changes in the acetylation status

of histone H4 and, thus, to the activation of *FOXP3*. The authors of the study⁷⁴ concluded that their results point to a direct role for testosterone in the expansion of *FOXP3*⁺ *T_{reg}* cells in women, but not in men (FIG. 1).

Androgens were already known to exert inhibitory effects on B cell lymphopoiesis via stromal cells⁷⁵. These data fit nicely with the concept that mature B cells do not possess the androgen receptor, whereas precursor B cells do¹⁶, which renders the precursor cells sensitive to the direct inhibitory influence of androgens. When looking at B cell activating factor (BAFF), a similar inhibitory picture to androgens emerges. Studies in patients with PsA have revealed that high serum concentrations of testosterone in men are associated with low serum concentrations of BAFF⁷⁶, indicating that androgens have an inhibitory influence on BAFF (FIG. 1). This concept has subsequently been supported by further evidence from *in vitro* and *in vivo* experiments⁷⁷. Importantly, the opposite is also true and oestrogens upregulate BAFF in women^{78,79}. These results suggest that androgens block B cell clonal expansion and class switch recombination via BAFF inhibition, whereas oestrogens exert opposite effects via BAFF.

Another role for androgens lies in regulating tyrosine-protein phosphatase non-receptor type 1 (PTPN1), which is involved in cell growth, differentiation, mitosis and immune function⁸⁰. Androgens, through interactions with the androgen receptor, bind a conserved region of *PTPN1*, which causes upregulation⁸¹. Androgen deprivation in patients with prostate cancer led to down-regulation of PTPN1, demonstrating the relevance of this pathway *in vivo* in humans⁸¹. PTPN1 inhibits Janus kinase 2 (JAK2) and tyrosine kinase 2 (TYK2)⁸⁰, particularly in CD4⁺ T cells *in vitro*⁸¹. These PTPN1-blocked kinases are part of the JAK–signal transducer and activator of transcription (STAT) signalling pathway, which is involved in T_H1 cell-mediated immune responses and the production of IL-12 and IFN γ ⁸¹. Given that inhibition of the JAK–STAT pathway is clinically relevant for the treatment of rheumatic diseases, these results⁸¹ are important as they show that endogenous testosterone inhibits JAK–STAT signalling in men, but not so much in women. Androgens might support the effects of exogenous JAK inhibitor therapy, or it could be possible that men might require lower doses of JAK inhibitors than women, but this is presently unknown. The role of PTPN1, and whether this molecule might be a suitable target for therapy in rheumatic diseases, have not yet been explored.

Progesterone signalling pathways. In general, progesterone supports many anti-inflammatory and immunoregulatory pathways (summarized extensively elsewhere^{14,15,21}). A current understanding of the effects of progesterone on immune responses, including previous discoveries and the updates discussed below, is summarized in FIG. 2.

Similar to other sex steroids, progesterone also has effects on B cells and can interfere with autoantibody production (FIG. 2). A study in which the authors introduced a disruptive progesterone receptor gene mutation into lupus-prone mice showed that expression of

the progesterone receptor suppresses the emergence of highly pathogenic class-switched IgG2c autoantibodies⁸². In this respect, the progesterone receptor has opposite effects to ER α , as ER α supports the production of autoantibodies. Progesterone receptor-deficient lupus-prone mice also developed more rapid proteinuria than wild-type lupus-prone mice⁸². These results support the concept that progesterone inhibits autoantibody generation. Similarly, AID, which stimulates somatic hypermutation at the immunoglobulin locus of B cells, is strongly stimulated by oestrogens, whereas progesterone shows opposing effects. Progesterone, in complex with the progesterone receptor, reduces AID production by binding to the *AICDA* promoter and inhibiting transcription⁸³. The binding site of this complex is close to the binding site for NF- κ B, which might lead to steric hindrance of NF- κ B binding.

The anti-inflammatory effects of progesterone extend to neutrophil extracellular trap (NET) formation, which is inhibited by this sex steroid⁸⁴ (FIG. 2). By contrast, oestrogens stimulate NET production. Progesterone also regulates the ability of neutrophil elastase to translocate from the cytoplasm to the nucleus⁸⁴. Thus, progesterone can block important neutrophil functions and, as neutrophils have a pro-inflammatory role in many rheumatic diseases, this ability enables progesterone to reduce inflammation. Similar to androgens, it remains unclear why RCTs with progestins (synthetic hormones that activate the progesterone receptor) are not underway in rheumatic diseases.

Microbiota and sex steroids

Following the first studies into the links between the gut microflora, HLA-B27 and a rat model of spondyloarthritis⁸⁵, a link between gut microbiota and autoimmunity has been more firmly established^{86–88}. Interestingly, women and men tend to have different gut microbiota, sex hormones can affect these microbiota, and microbiota can influence sex hormone endocrinology⁸⁹. However, not much progress has been made in deciphering the unambiguous role of sex steroids in gut microbiota-related effects on autoimmunity. The relationship between the gut microbiota and autoimmunity has been presented elsewhere⁸⁷, so we focus on direct sex steroid hormone effects on microflora.

The sexually dimorphic microbiome has been termed the ‘microgenderome’, and its influence on immunity has been summarized elsewhere⁹⁰. To date, most studies have been performed in rodents, but sex differences in gut microbiota have also been clearly shown in humans. Microbiota at different body sites in humans can be categorized into so-called ‘community types of bacteria’⁹¹. Biological sex was associated with different community types in the stool, on the tongue, in the right retroauricular crease and in the right antecubital fossa. Analysis showed that characteristics related to an individual’s life-history are associated with different community types⁹¹. Various studies in humans and animals have also shown that sex-related differences in the microbiota occur across the lifespan of an individual⁹². For example, hormone replacement therapy (HRT) can change the colonization of vaginal bacteria in postmenopausal women,

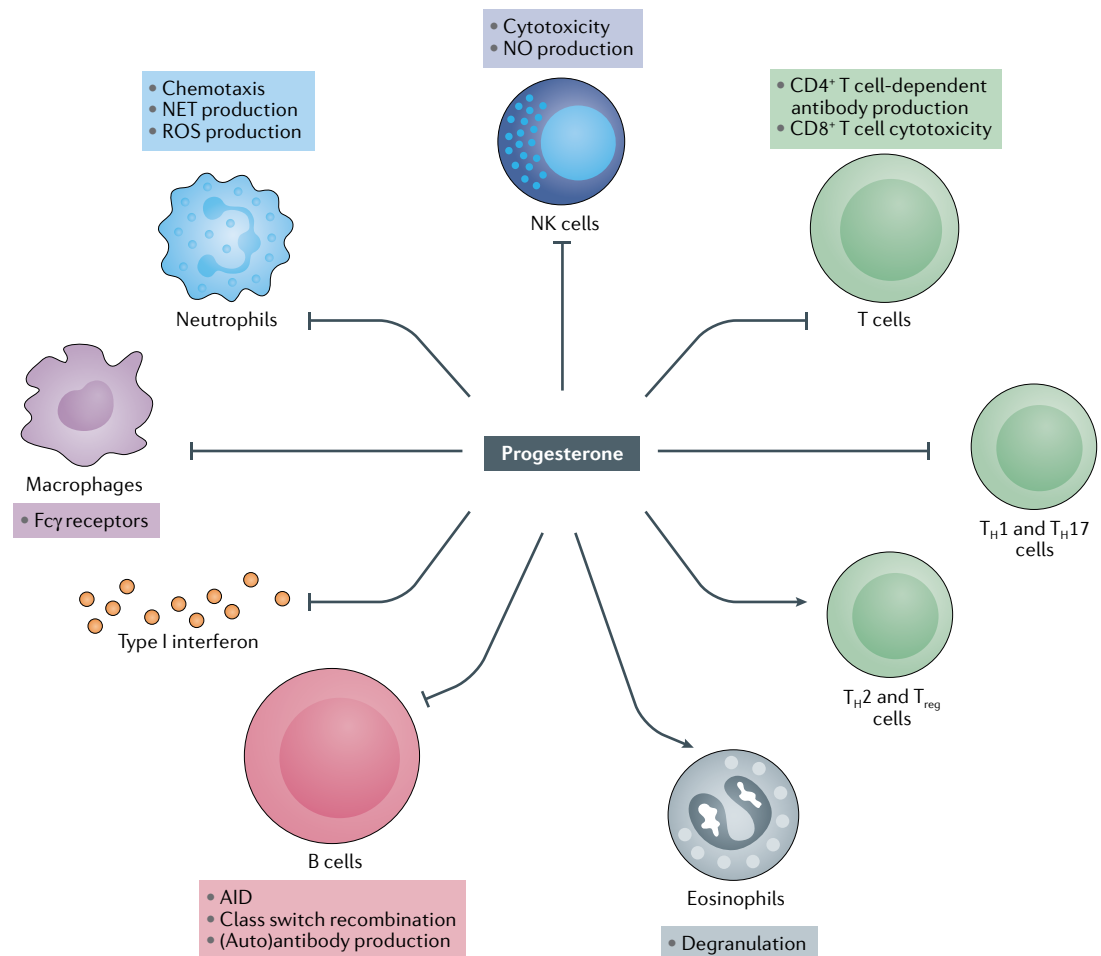


Fig. 2 | Effects of progesterone on immune function. Progesterone has uniformly anti-inflammatory effects, with the exception of T helper 2 (T_H2) cell-supporting pathways and eosinophil degranulation, which can have roles in atopic diseases and in T_H2 cell-mediated autoimmune diseases. In contrast to oestrogens, which stimulate activation-induced cytidine deaminase (AID) to support immunoglobulin class switching in B cells, progesterone inhibits this enzyme, thereby reducing somatic hypermutation and autoantibody production. A general blockade of natural killer (NK) cells, neutrophils and macrophages are other characteristics of this hormone. NET, neutrophil extracellular trap; NO, nitric oxide; ROS, reactive oxygen species; T_{reg}, regulatory T cell.

and the gut microbiota of ovariectomized female mice, which is similar to that of male mice, can be restored to a female-like pattern by oestrogen treatment⁹². The presence or absence of ERβ also influences gut microbiota composition in mice⁹³. When fed a complex diet containing oestrogenic isoflavones, the abundance of Bacteroidetes was higher in ERβ^{+/+} mice than in their ERβ^{-/-} littermates (28.7% versus 20.4%, respectively), whereas the abundance of Proteobacteria was lower in ERβ^{+/+} mice than in ERβ^{-/-} mice (13.8% versus 21.0%, respectively)⁹³. These results demonstrate that the presence of ERβ can change the abundance of prominent phylotypes within the murine autochthonous gastrointestinal microbiota. Given that Bacteroidetes were related to regulatory immune function⁹⁴, these oestrogen-related changes might be beneficial in autoimmune diseases.

In relation to autoimmunity, oestrogens in adult female mice protect against autoimmune encephalitis, prevent disease-associated changes in the gut microbiota and promote the enrichment of bacteria that are associated with immune regulation⁹⁵. In non-obese diabetic

(NOD) mice, which spontaneously develop autoimmune diabetes, androgens are highly protective⁹⁶. Changes in the gut microbiota composition in young, commensally colonized NOD mice confer systemic testosterone changes that are sufficient to oppose genetically programmed autoimmunity in later life⁹⁶. Although autoimmune diabetes occurs more frequently in female-specific than in male-specific pathogen-free NOD mice, germ-free NOD mice do not have this sexual dimorphism⁹⁷. However, the gut microbiota differed between male-specific and female-specific pathogen-free NOD mice, and castration reversed this difference. Gene expression analysis suggested two monocyte-M2 macrophage gene signatures (networks of genes that are dependent on IFNγ and IL-1β) that are involved in protecting male mice from autoimmune diabetes via the microbiota⁹⁷. Humanized transgenic mice carrying susceptibility and resistance HLA-DR genes have been used to investigate the role of the microbiome in inflammatory arthritis. The intestines of arthritis-susceptible mice are dominated by a *Clostridium*-like bacterium, whereas the guts of

arthritis-resistant mice are enriched for members of the Porphyromonadaceae family and *Bifidobacterium*⁹⁸. Arthritis-resistant mice had a dynamic gut microbiome that was influenced by sex and age, whereas arthritis-susceptible mice did not have age or sex differences in their gut microbiomes. Although these results⁹⁸ indicate crosstalk between arthritis susceptibility, the microbiome and biological sex, causality remains unclear.

We feel that great potential exists for important new research in this area, but that the technology required to unravel the interactions between diet, host and gut microbes in sex-biased autoimmunity will require careful development. The translation of findings from animal studies to human disease will also be a great challenge.

Sex steroids and disease risk

Sex steroids affect the risk of developing an autoimmune rheumatic disease in different ways across an individual's lifespan. The effects of sex steroids on SLE, primary Sjögren syndrome (pSS), RA, SSc and AS are summarized in TABLE 2.

Endogenous sex steroids. A lack of endogenous oestrogens (or removal of the same) might influence the risk of developing an autoimmune rheumatic disease. Interestingly, in patients with breast cancer, blockade of androgen-to-oestrogen conversion with aromatase inhibitors induced musculoskeletal pain and was associated with an increased risk of RA compared with tamoxifen therapy⁹⁹. A literature review of case reports similarly reported positive associations between aromatase inhibitor use and RA, pSS, Hashimoto thyroiditis, SLE and antisynthetase syndrome¹⁰⁰. Notably, aromatase inhibition does not lead to a complete lack of oestrogens, but to low concentrations, at which oestrogens might potentially still have pro-inflammatory effects on T cells and M1 macrophages (BOX 1)⁸.

The endogenous adrenal hormone dehydroepiandrosterone sulfate is an important precursor of peripheral anti-inflammatory androgens, and low concentrations of dehydroepiandrosterone sulfate were considered to be a biomarker of disease susceptibility in a study of premenopausal-onset RA in women¹⁰¹. Two other investigations in patients with RA did not confirm these findings^{34,102}, but used different assay methods, making true comparison difficult. A similar study investigating the effects of testosterone concentrations on the risk of developing RA separated the results according to RF status. In 104 men with RA and 174 matched healthy men, lower serum concentrations of endogenous testosterone were predictive of RF-negative RA (OR 0.31; 95% CI 0.12–0.85) and were weakly predictive of RF-positive RA (OR 0.87; 95% CI 0.53–1.43). These results suggest that testosterone changes precede the onset of RF-negative RA in men¹⁰³. The authors of a systematic review¹⁰⁴ of studies in SSc that investigated sex steroid status prior to disease onset concluded that (with the caveat of small sample sizes) women with SSc tend to have lower serum concentrations of androgens and non-significantly higher amounts of oestradiol than healthy women. By contrast, men with SSc had

increased amounts of oestradiol and conflicting results for androgens. In another study, the development of SSc was observed in transgender women who were treated with oestrogens, which indicates a propagating role for this sex steroid in autoimmune disease¹⁰⁵.

Another way to study endogenous sex steroids is via disease-related lack of a hormone. In a retrospective cohort study, analysis of data from 123,460 men with hypogonadism and no history of prior rheumatic diseases from a large nationally representative cohort was matched with data from 370,380 men without hypogonadism¹⁰⁶. Untreated hypogonadism was associated with an increased risk of developing any autoimmune rheumatic disease (hazard ratio (HR) 1.33; 95% CI 1.28–1.38), RA (HR 1.31; 95% CI 1.22–1.44) and SLE (HR 1.58; 95% CI 1.28–1.94). The authors of the study concluded that men with hypogonadism who were not treated with testosterone had an increased risk of developing autoimmune rheumatic diseases¹⁰⁶. The well-known link between hypoandrogenism and Klinefelter syndrome has also been studied in relation to autoimmunity in a UK cohort. Individuals with Klinefelter syndrome were at an increased risk of seven autoimmune diseases: Addison disease (rate ratio (RR) 11.7; 95% CI: 2.4–34.4), type 1 diabetes mellitus (RR 6.1; 95% CI 4.4–8.3), multiple sclerosis (RR 4.3; 95% CI 1.2–11.0), acquired hypothyroidism (RR 2.7; 95% CI 1.8–4.0), RA (RR 3.3; 95% CI 2.0–5.2), pSS (RR 19.3; 95% CI 4.0–57.0) and SLE (RR 18.1; 95% CI 2.2–65.6)¹⁰⁷. Thus, a genetically determined hypogonadal state with low serum testosterone concentrations seems to be autoimmune disease propagating; however, chromosomal aberrations in these individuals might have an additional influence. In another study using the same patient cohort, the use of testicular hypofunction as a proxy for low testosterone concentrations independent of genetic aberrations revealed an adjusted RR of 7.7 (95% CI 2.5–18.1; $P < 0.0001$) for developing SLE following testicular hypofunction¹⁰⁸.

Endocrine disruptors. Endocrine disruptors such as phytoestrogens can be found in a wide variety of foods^{109,110}. Phytoestrogens occur naturally in plants such as clover and soy. Xenoestrogens or industrial oestrogens are synthetic chemicals produced for specific purposes and include pesticides, agrochemicals, plastics, surfactants and detergents. These endocrine disruptors typically bind to steroid receptors, have steroid-like effects and negatively influence hormone-regulated processes^{109,110}. As immune cells have functional nuclear and plasma membrane steroid receptors (mainly for oestrogen), phytoestrogens and xenoestrogens can provoke perinatal faulty hormonal imprinting via epigenetic changes such as DNA methylation and histone modifications^{109,110}. These epigenetic changes can have lifelong consequences, potentially including the epidemiological associations between exposure to these endocrine disruptors and rheumatic diseases¹¹¹.

Pregnancy, menarche and menopause. Several physiological conditions that are clinically relevant to autoimmune rheumatic diseases, such as pregnancy, postpartum,

Table 2 | Role of sex hormones in autoimmune rheumatic diseases at different life-stages

Factor	Systemic lupus erythematosus ^{107,119,123,124,188–194}	Primary Sjögren syndrome ^{13,107,192,195–200}	Rheumatoid arthritis ^{11,107,120,123,201–209}	Systemic sclerosis ¹⁰⁴	Ankylosing spondylitis ^{2,114,210–217}
Adolescents and reproductive-age adults					
Incidence peak in the reproductive phase	Two peaks at 20–29 and at 40–49 years in F; no peak in M	40–50 years in F and M	25–45 years in F; no peak in M	40–50 years in F and M	15–35 years in F and M
F:M distribution	7:1–15:1	9:1	3:1–4:1	5:1–10:1	1:3
Hypogonadism	Increases risk of developing disease	Increases risk of developing disease	Increases risk of developing disease	Increases risk of developing disease	Case report with a positive association
Early menarche	Increases risk of developing disease	Little influence	Increases risk of developing disease	Increases risk of developing disease	Influence unknown
Pregnancy	Worsens disease	Worsens disease	Protective	Disease remains stable, Raynaud phenomenon and digital ulcers improve	Discordant effects, can improve, remain the same or worsen
Postpartum period	Worsens disease	Unknown	Worsens disease	Worsens disease in 17% of patients	Worsens disease
Parity	Risk increases when nulliparous	Risk increases with parity	No influence	Discordant results, majority of studies say risk decreases with parity	Influence unknown
Breastfeeding	No influence	No influence	Discordant results	Influence unknown	Influence unknown
Oral contraceptive use	No influence in mild disease; risk of developing disease increases; risk of flares increases, particularly, when anti-phospholipid antibodies or thrombosis are present	Two case reports with positive associations	Pre-1990 use was protective owing to higher hormone doses than post-1990; post-1990 use had no effect in North America and a small protective effect in Europe	Effects unknown	No influence
Disease in men compared with women	More severe	More severe; more extraglandular disease	Less severe	More severe kidney disease, more cancer, worse prognosis	More frequent
Post-reproductive-age adults					
Incidence peak	50–59 years in F; >60–70 years in M	Around menopause and andropause	Around menopause and andropause	50–75 years; 90% before 65 years in F and M	None, disease is rare
F:M distribution	≥3:1	Unknown, but less than in the reproductive phase	Near 1:1	5:1–10:1	Unknown
Early menopause	Increases risk	No influence	Increases risk	Influence unknown	Influence unknown
Menopause	Decreases disease severity	Worsens disease; sicca symptoms generally increase	Worsens disease	Decreases skin disease but increases lung disease in diffuse cutaneous SSc	Influence unknown
Hormone replacement therapy use	Increases risk of developing disease somewhat; no major flares; higher incidence of mild-to-moderate flares	Effects unknown	Protective	Hormone therapy in transgender individuals might increase risk of developing disease	Effects unknown

F, female; F:M, female-to-male ratio; M, male; SSc, systemic sclerosis.

menarche (puberty) and menopause, are influenced by physiological changes in several hormones, including sex steroids, which prohibits firm conclusions from being drawn about which of the hormones is mainly affecting immunity. Even glucocorticoids increase during pregnancy, which is important for placental function¹¹². The influence of these different hormonal conditions

in pregnancy has been carefully investigated in RA and SLE, but data in other autoimmune rheumatic diseases are sparse (reviewed elsewhere¹¹³).

Typically, flares are increased during pregnancy in women with diseases such as SLE and pSS, which have a prevalence that is much higher in women, although, interestingly, not in SSc. This flaring of disease speaks

to the pro-inflammatory influence of altered concentrations of oestrogens on these diseases. Pregnancy is generally protective against disease flares in patients with RA or SSc, but results around the influence of pregnancy on AS have been discordant¹¹⁴ (TABLE 2). The protective effect of pregnancy on disease flares is particularly evident if patients had a low disease activity at the beginning of pregnancy^{115–118}. Importantly, the postpartum period is linked to disease flares in almost all rheumatic diseases (TABLE 2). This effect is probably influenced by sex steroid loss, but could also be related to increases in prolactin, which is pro-inflammatory.

Early menarche is associated with increased risks of developing SLE and RA, but there is either little or no influence in other diseases, or the relationship has not been studied (TABLE 2). The cyclic increase in oestrogens during this period is thought to be involved in the increased risks of RA and SLE. Menopause is also often linked to the worsening of rheumatic diseases (TABLE 2), which might be related to the dramatic decrease in sex steroids that occurs at this time. Early menopause is associated with an increased risk of developing SLE¹¹⁹ and RA¹²⁰, a slightly higher risk of cardiovascular disease in RA¹²¹ and with seropositivity in RA¹²².

Sex steroid therapy

Exogenous hormones can also influence the risk of developing an autoimmune disease or the induction of flares. In this section, we discuss oral contraceptives, HRT, oestrogen-only therapy, selective oestrogen receptor modulators (SERMs), androgens and progestin therapy. Looking at the different clinical treatment approaches used to date, it seems that rheumatologists have focused on classical oestrogen therapies (and related adverse effects), such as oral contraceptives and HRT. Most of these studies have been retrospective or epidemiological, with the exception of the SELENA RCT.

Oral contraceptives, hormone replacement therapy and oestrogen-only therapy. The influence of prior oral contraceptive use and HRT on autoimmune rheumatic diseases is summarized in TABLE 2. The use of oral contraceptives slightly increases the risk of developing SLE, but does not substantially influence other chronic inflammatory rheumatic diseases such as AS. In RA, modern contraceptives (which have a lower oestrogen content and more progestins than those used historically) are linked to a small protective effect in European women¹²³. Similar to oral contraceptive use, HRT increases the risk of SLE and, according to the HRT-SELENA trial¹²⁴, induces mild-to-moderate flares in this disease. By contrast, HRT might have protective effects in RA and SSc. The effects of HRT on pSS and AS are not known (TABLE 2).

Targeting oestrogen receptors specifically using agonists of ER α (Org 37663)¹²⁵ or ER β (ERB-041)¹²⁶ failed to demonstrate anti-inflammatory efficacy in RCTs in patients with RA, despite evidence of strong activity in preclinical models of arthritis (BOX 1). Given the known effects of oestrogens in experimental arthritis⁴¹, these studies were disappointing from a clinical perspective. However, these results might indicate that progesterone

in oral contraceptives and HRT is the more important anti-inflammatory ingredient of these drugs. Oestrogen receptor blockade has also been investigated in patients with SLE. The ER α blocker fulvestrant, which is used to treat certain types of breast cancer, has been investigated in a small RCT in which 20 patients with SLE were treated with either fulvestrant or placebo¹²⁷. The SLE disease activity index improved significantly in those individuals who received fulvestrant at 12 months ($P=0.02$) and 15 months ($P=0.002$). Although this study¹²⁷ showed promising results, no other investigations of this or similar drugs in patients with autoimmune rheumatic diseases have been started in the past 10 years.

Novel oestrogen-related therapies and bone health. Bone degradation in the context of chronic inflammation is a well-known problem in rheumatic diseases^{11,128,129}. Similarly, bone degradation is known to occur in the context of menopausal and andropausal loss of sex steroids. Thus, an examination of sex steroids, bone integrity and rheumatic diseases is warranted, which has so far led to new therapeutic approaches that go beyond HRT.

SERMs bind to oestrogen receptors and can simultaneously function as an agonist or antagonist depending on the tissue. SERMs have critical therapeutic roles in several human diseases and include tamoxifen (breast cancer), raloxifene (breast cancer and postmenopausal osteoporosis) and bazedoxifene (postmenopausal osteoporosis)¹³⁰. SERMs exert their effects through the ER α subunit activating factors AF1 and AF2 in a differential way, which means that they can affect both lymphopoiesis and bone health^{131–133}. This dual role is important not only for thymic T cell development and bone marrow B cell lymphopoiesis but also for bone integrity^{131–133}. Relevant to rheumatic diseases, SERMs might directly influence inflammation by modulating T cell and B cell precursors and autoantibody production¹³⁴.

A new therapeutic approach is to use SERMs in combination with oestrogens, known as tissue-selective oestrogen complex (TSEC). TSEC can treat menopausal symptoms and protect against osteoporosis in a similar way to oestrogen-only therapy, but also reduces the negative effects of oestrogens on the endometrium because the SERM has blocking effects there¹³⁵. In ovariectomized mice, TSEC inhibited thymic T cell development and bone marrow B cell lymphopoiesis but spared reproductive organs¹³⁶. These results suggest clinically relevant roles for TSEC in inflammatory settings such as rheumatic diseases. In fact, a TSEC of oestrogens plus bazedoxifene suppressed collagen-induced arthritis, protected bone from degradation and reduced autoantibody production in ovariectomized mice¹³⁷. Although this research is at an early stage in understanding the combined effects of TSEC on immune function, the intelligent combination of a SERM plus oestrogen could lead to important new drugs.

Androgen therapy. Androgens have shown the most promising inhibitory influence on immune responses of all the sex steroids in both preclinical and clinical studies, and so have been therapeutic candidates of interest for autoimmune rheumatic diseases for more than

three decades. However, given their clear suppressive effects on immune responses and inflammation, there have been remarkably few studies in rheumatic diseases, and those that have been performed were mostly small, which has led to a general loss of statistical power. As we know that many patients with rheumatic diseases have secondary inflammation-related hypogonadism¹³⁸, it is more than astonishing that androgen substitution treatment, at least in men with autoimmune rheumatic diseases, is not carried out more often.

Endocrinologists define hypogonadism using several criteria, such as clinical history, examination and serum testosterone concentrations¹³⁹. Development of hypogonadism in adult life is characterized by a loss of androgen-dependent functions such as a reduction in muscle mass (cachexia), a shift in body composition towards more adipose tissue (cachectic obesity), decreased sexual function with diminished libido, depressed mood (sickness behaviour), loss of 'mental energy' (sickness behaviour), osteoporosis and several other possible symptoms¹³⁹. Total testosterone concentrations of <8 nmol/l highly support a diagnosis of male hypogonadism, whereas concentrations >12 nmol/l are considered normal. Patients who fall into the 'grey zone' between 8 and 12 nmol/l require further evaluation and assessment of free or non-sex steroid-binding globulin-bound (bioavailable) testosterone. A trial period of testosterone treatment might be required for those in the grey zone¹³⁹. Although much experience exists for the use of androgens as anti-inflammatory therapy in men with hypogonadism¹⁹, rheumatologists are reluctant to use androgens and the necessary conversations with endocrinologists are lacking.

Small studies in the 1990s showed favourable results for androgen replacement therapy in men and postmenopausal women with RA^{140,141}, and no discrepant findings have subsequently been reported. For comparison, one extended case report showed beneficial results of testosterone replacement therapy in men with psoriasis¹⁴². By contrast, use of dehydroepiandrosterone was not beneficial in women with pSS¹⁴³, and testosterone seems to be ineffective (or even to have negative effects) in patients with SLE^{144–146}, whereas when danazol or dehydroepiandrosterone were used as androgenic compounds in SLE, modest beneficial effects were observed^{147,148}. The reason for the discrepant findings with testosterone and other androgens in SLE is not known, but might depend on the way in which different types of androgens are converted into other sex steroids in immune or stromal cells. For example, conversion of precursor hormones to B cell-stimulating oestrogens instead of conversion to immunosuppressive androgens would stimulate disease in patients with SLE. Looking at all studies carried out so far in rheumatic diseases, future RCTs in large cohorts might be promising for men with RA, PsA or SSx.

Progesterone-only therapy. Progesterone is deemed to be a strong immunosuppressive sex steroid but, to the best of our knowledge, no studies on progestins have been carried out in patients with pSS, RA, SSx, PsA or AS. In SLE, the use of progesterone has been described in just one study from the 1980s, which showed that this

treatment did not affect the number of disease flares¹⁴⁹. However, one open-label study looked at the introduction of progestin contraceptives in 187 women with SLE¹⁵⁰. The results of this longitudinal study showed that two progesterone-only drugs had statistically significant beneficial effects on the appearance of disease flares. The difference was remarkable; before progestin treatment the number of observed flares was 2.6 ± 3.3 per person-year and under treatment it was 0.3 ± 0.4 per person-year ($P < 0.0001$)¹⁵⁰. Given that different immunomodulatory effects have been described for progesterone (mainly suppressive) compared with oestrogens (immunostimulatory and immunoinhibitory), it is surprising that more studies have not been conducted looking at the effects of progestins on rheumatic diseases.

Inflammation affects gonad function

Hypogonadism and related changes in the hypothalamus that occur as a consequence of inflammation were described in experimental inflammation in rats in the 1980s^{151,152}. In these experiments, the authors injected pro-inflammatory cytokines into rats and observed inhibited reproductive functions¹⁵². The first studies on hypoandrogenism in humans with rheumatic diseases also date back to the 1980s^{153–155} and have been summarized elsewhere^{156,157}.

In 2000, the phenomenon of androgen-to-oestrogen conversion was shown in macrophages from healthy volunteers¹⁵⁸. This study was followed by the description of sex steroid conversion in synovial cells from patients with RA (macrophages and fibroblasts), which demonstrated the increased activity of aromatase in synovial tissue from patients with rheumatic diseases for the first time²². Studies on urinary excretion of sex steroids also indirectly show aromatase activation^{159,160}. The concept of cytokine-modulated steroidogenesis was summarized for the first time in a review in 2002 (REF.¹⁶¹). After this period, it became clear why androgen concentrations are often low, whereas oestrogens remain normal in patients with chronic inflammatory rheumatic diseases, and in the middle of the 2000s, cytokine-neutralizing therapy was found to partly restore androgens in patients with RA¹⁶². From 2010 onwards, the phenomenon of male hypogonadism was described as a positively selected phenomenon for short-lived inflammatory conditions such as infections¹⁶³. Given that androgens have many anti-inflammatory effects, reduction of these sex steroids stimulates the immune system during short-lived infections. However, in the context of a long-lasting autoimmune disease, the positively selected principle is maladaptive and disease-propagating¹⁶⁴, leading to cachectic obesity and chronic inflammation.

Thanks to these findings on hypoandrogenism and rheumatic diseases from the past two decades, gonadal and sexual evaluation of patients with rheumatic diseases has been put on the agenda. Several aspects of gonad function have been investigated in different chronic rheumatic diseases, including ovarian reserve, fertility and menstrual problems in women, and erectile dysfunction, sperm quality and semen abnormalities in men. Of these aspects, the ovarian reserve has been studied the most by investigating anti-Müllerian

hormone (AMH), a secreted ligand of the transforming growth factor- β family that has a role in early ovarian follicle development. In the context of preservation of ovarian function in women with SLE who have undergone haematopoietic stem cell transplantation, AMH was introduced as a prognostic and diagnostic marker¹⁶⁵. Since 2009, AMH has been studied in SLE (for forecasting cyclophosphamide adverse effects)¹⁶⁵, RA¹⁶⁶, granulomatosis with polyangiitis¹⁶⁷, Behçet disease¹⁶⁸, dermatomyositis¹⁶⁹, spondyloarthritis¹⁷⁰, polymyositis¹⁷¹ and other diseases. Whether AMH is only relevant during genotoxic therapy or if it can be used as a general marker of infertility is unclear. Nevertheless, patients with rheumatic diseases have decreased serum concentrations of this hormone independently of gonadotoxic therapy, and this phenomenon has been linked to reduced ovarian reserve^{168–170}.

The study of fertility and fecundity goes back into the 1990s, when authors reported reduced fecundity in women with RA before the onset of disease¹⁷². Several studies have also reported reduced fertility in individuals with different rheumatic diseases independently of gonadotoxic therapies (reviewed elsewhere^{173–175}). A 2015 study in women with RA concluded that time to pregnancy is longer as patients get older or if they are nulliparous, and if they have high disease activity, use NSAIDs or use >7.5 mg prednisone daily, and that preconception treatment strategies should aim to suppress disease activity as much as possible¹⁷⁶. Similarly, men with rheumatic diseases often have sexual function and fertility problems such as erectile dysfunction and sperm abnormalities, which have been studied in SSc, AS, gout, SLE, Behçet disease, dermatomyositis and other diseases^{177–185}. The results of a systematic review revealed that TNF inhibitor therapy has a positive effect on sperm quality and showed that this therapy does not interfere with fertility in men¹⁸⁶. Although several factors can lead to sexual problems and reduced fertility, disease activity independent of gonadotoxic therapy is the main disturbing factor. Interestingly, these dysfunctions are still not perceived as a naturally occurring phenomenon that is part of sickness behaviour and the general energy redistribution programmes that serve an acutely activated immune system, as occurs during an infection^{163,187}. In long-term autoimmunity, sexual problems and reduced fertility are a maladaptive process.

Conclusions

Overall, oestrogens can be thought of as stimulators of the immune response (mostly (auto)antibody generation in rheumatic diseases via B cells and some non-B cell innate pathways) that might also have anti-inflammatory functions (such as those related to M1 macrophages and T cells) (FIG. 1). Clinical studies of oestrogen receptor

agonists failed in patients with RA, but were efficient in mouse models of arthritis, suggesting that the translation of oestrogen studies in animals into humans is not straightforward. We think that oestrogens might still be useful as part of the treatment of certain autoimmune rheumatic diseases, but only for those diseases that are not B cell-mediated (so would not be suitable for SLE, for example). The stratification of patients with rheumatic diseases according to the prevailing mediator of disease and subsequent treatment with oestrogen has yet to be trialled, but the results could prove interesting. TSEC, which combines SERMs with oestrogens, might be another promising pathway.

By contrast, androgens and progesterone mainly exert immunosuppressive and anti-inflammatory activities in autoimmune rheumatic diseases, which suggests that they might be favourable therapeutics (FIG. 1). Indeed, serum androgen concentrations are often low in patients with rheumatic diseases (except for AS, which is currently unexplained). HRT with androgens could have beneficial effects for many general problems related to hypogonadism, such as cachexia and obesity, as well as having anti-inflammatory effects by targeting PTPN1 and JAK–STAT signalling pathways. The use of androgens as HRT might be promising for men with RA, SSc or PsA, but their role in women has yet to be clarified. To this end, collaboration with endocrinologists will help rheumatologists to understand how to best use androgen therapy in women and men. Similarly evident is the anti-inflammatory role of progestins, which are beneficial in women with SLE who use progestin-only therapy as oral or device contraceptives. Rheumatologists have so far been reluctant to actively test androgens as substitution therapy for patients with hypogonadism or progestins as an anti-inflammatory treatment approach. The discovery of the modulation of PTPN1 by androgens suggests that similar intracellular targets might also be discovered for progesterone. Thus, the development of targeted therapies could help to prevent the possible broad therapeutic effects of pure androgen or progestin drugs.

Finally, it is becoming evident that microbiota have sex-related differences, both in animal models and in humans (the microgenderome). These sex-related differences often lead to sex-dependent changes in local gastrointestinal inflammation, systemic immunity and, possibly, in susceptibility to rheumatic diseases. Whether manipulation of the microbiota sex hormone-mediated epigenetic modulation can be favourably used remains an open question. We feel that there is a great potential for new research in this area, but that the technologies required to unravel such interactions will need careful development.

Published online: 02 October 2020

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Acknowledgements

M.C. and R.H.S. are members of the EULAR Study Group on Neuroendocrine Immunology of Rheumatic Diseases (NEIRD).

Author contributions

R.H.S. researched data for this article and wrote the draft. M.C. contributed substantially to discussions of content. Both authors wrote and reviewed or edited the manuscript before submission.

Competing interests

The authors declare no competing interests.

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A search for articles published between 2006 and 2020 was performed in PubMed, Embase and the Cochrane library using the following search terms alone and in combination: “oestrogens”, “androgens”, “progesterone”, “steroid hormone”, “immun*”, “inflam*”, “rheum*”, “SLE”, “vasculitis”, “autoimmun*” and “systemic sclerosis”.

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