Sexual disparities in the incidence and course of SLE and RA

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Abstract  Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) disproportionately affect females compared to males, with female to male prevalence ratios of 7–9:1 for SLE and 2–3:1 for RA. Interestingly, epidemiologic studies indicate that men that develop SLE may have more morbidity than women, but the same is not true for RA. Given the sex and age bias of SLE and RA, sex hormones may influence the pathogenesis of these diseases. However, the ways in which, and to what degree, sex hormones affect disease incidence and severity remain unclear and is the topic of ongoing research. Recent findings have implicated interactions between sex hormones, the immune system, genetic factors, and epigenetic modifications in influencing SLE and RA disease activity. This article reviews current hypotheses regarding the potential impact of sex hormones and genetics on disease pathogenesis, incidence, and severity of SLE and RA.

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1. Introduction

Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) are chronic autoimmune diseases of incompletely understood etiologies, both of which disproportionately affect females compared to males. Female to male prevalence ratios are 7–9:1 for SLE and 2–3:1 for RA. Interestingly, however, epidemiologic studies indicate that men that develop SLE may have more morbidity than women, but the same is not true for RA. The peak age of incidence is younger in SLE (15–40 years) than in RA (45–55 years). Given the sex and age bias of SLE and RA, sex hormones may be involved in the pathogenesis of these related diseases. However, the ways in which, and to what degree, sex hormones affect disease incidence and severity remain unclear and is the topic of ongoing research. Recent findings have implicated interactions between sex hormones, the immune system, genetic factors — including the presence of a second X chromosome in women — and epigenetic modifications in influencing SLE and RA incidence and disease activity. This article will review current hypotheses regarding the potential impact of sex hormones and genetics on disease pathogenesis, incidence, and severity of SLE and RA.

1.1. Immunologic abnormalities in SLE and RA

Although both SLE and RA are immune-mediated disorders, they have been thought to originate from disparate arms of the immune response. In the case of SLE, the humoral immune response, resulting from CD4+ T helper 2 (Th2) activity that leads to B cell activation and antibody production, is abnormally increased and dysregulated [1]. In RA, by contrast, CD4+ T helper 1 (Th1) activity is dysregulated, leading to an increase in the cell-mediated immune response particularly among synovial macrophages [2,3]. Deviating from this traditional line of thought, recent studies have suggested that SLE and RA may share similar underlying immunologic mechanisms, such as dysregulated B and T cell interactions, overproduction of inflammatory cytokines, and involvement of CD4+ T helper 17 (Th17) cells [4–6].

2. Effects of sex hormones on immunologic abnormalities in SLE and RA

Sex hormones, including estrogen, progesterone, androgen and prolactin, have numerous well-studied effects upon immune function, as summarized in Table 1. Alterations in hormone levels or hormone-mediated activities could thus potentially affect disease susceptibility or activity [4,5,7–10]. For example, estrogen receptors are present on a variety of immune system cells, including B and T cells [9]. Estrogen has been found to stimulate the Th2/humoral immune response, diminish the cell-mediated immune response, and increase Th1 production of interferon (IFN)-gamma and interleukin (IL)-10 (cytokines observed in high levels in RA) [3,8,11]. Murine studies have revealed further immunoregulatory effects of estrogen including decreased production of B cell precursors, impaired B cell tolerance, and increased activation and survival of autoreactive B cells, all of which are important in the pathogenesis of SLE in humans [7,12]. Additionally, estrogens decrease the proliferation Th17 cells, which are thought to be important in RA pathogenesis [9,13].

Progesterone, like estrogen, also stimulates a switch from a Th1 to a Th2-predominant immune response [8,11]. Hughes has proposed that progesterone-induced changes during pregnancy, including suppression of Th1 or Th17 responses and induction of regulatory T cells, could account for the often observed decrease in RA disease activity during pregnancy [5]. Several studies indicate that testosterone also interacts with the immune system by suppressing both cellular and humoral responses [3,11]. Prolactin regulates the maturation of precursor T cells to CD4+ T cells, decreases apoptosis of B cells (thereby allowing autoreactive B cells to propagate), and increases immunoglobulin production [12]. Prolactin levels have been reported to be elevated in 15–33% of both males and females with SLE, although it is not clear if this is a cause or consequence of SLE [14].

3. Sex disparities in SLE incidence and severity

3.1. Incidence of SLE among females compared with males

The commonly-cited female to male ratio of 9:1 characterizes incident cases of SLE during the childbearing years (Table 2). Prior to puberty this ratio has been shown to be lower, on the order of 2–6:1, and after menopause, it is on the order of 3–8:1 [15,16]. This pattern suggests that some factor associated with female reproduction may underlie the uptick in incidence among women during the reproductive years. Mohan has suggested that the skewed female prevalence of SLE may result from a lower threshold for SLE disease initiation in women. In this model, the same quantity of combined genetic and environmental factors may produce SLE in women much more frequently than it would in men [17] (fig. 1).

It is also possible that women and men have different environmental exposures during their lifetimes, due to occupational or culturally-determined factors. Several gender-specific (culturally constructed, rather than based on biological sex) environmental exposures have been proposed as potentially linked to the increased incidence of SLE among women. However, studies investigating hair dyes and lipstick use, for example, have not revealed any strong associations with SLE risk [18,19].
Sexual Disparities in the Incidence and Course of SLE and RA

Table 1  Sex influences on SLE and RA.

<table>
<thead>
<tr>
<th>X chromosome</th>
<th>Contains candidate risk genes for SLE (e.g. IRAK1, Foxp3, TLR7, MECP2, and gene for CD40 ligand)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex hormones</td>
<td>Possible impact of incomplete X inactivation and skewed X inactivation in SLE</td>
</tr>
<tr>
<td>Estrogen</td>
<td>Increased risk of SLE in patients with Klinefelter's syndrome (47,XXY)</td>
</tr>
<tr>
<td>Prolactin</td>
<td>Females with Turner syndrome (45,XO) rarely develop SLE</td>
</tr>
<tr>
<td>Androgens</td>
<td>X-linked miRNAs may be subject to skewing of inactivation</td>
</tr>
</tbody>
</table>

Exogenous estrogen use may have a triggering effect on the development of SLE in some, but not all, women. In a prospective cohort study of 238,308 female Nurses’ Health Study participants, age < =10 years at menarche, oral contraceptive use, and postmenopausal hormone use were each associated with higher relative risk of SLE among this population of mostly Caucasian women (relative risks of 2.1, 1.5, 1.9) [20]. The highest risk of developing SLE was observed during the first two years of oral contraceptive exposure. A case–control study employing data from the United Kingdom’s General Practice Research Database compared 786 women with a diagnosis of SLE to 7817 women without that diagnosis [21]. Recently prescribed estrogen-containing oral contraceptives were associated with 2.5-fold higher adjusted odds of developing SLE. There was also a strong dose–response relationship between oral contraceptive estrogen dose and development of SLE, which suggests that for some women, higher levels of estrogens have a triggering effect for the development of SLE. Breastfeeding of one’s infants, which is associated with increased prolactin levels, has not been found to be associated with SLE risk [20].

3.2. Sex differences in SLE severity

While SLE is more common in women than in men, male patients are thought to have more severe disease than females [16]. Several studies, including one from the U.S.-based Lupus in Minorities: Nature versus Nurture (LUMINA) group, have suggested an increased prevalence of renal involvement and progressive renal damage among males compared to females with SLE [22–24]. In contrast, a multinational cohort study of 1214 patients with SLE in Latin America found similar average disease activity index scores in both sexes [25].

Sex-based differences in SLE mortality are difficult to study given that men in the general population have a higher risk of mortality. Studies published in or before the 1990s reported that males with SLE had equal or better longevity compared to females with SLE [26–28]. In contrast, a retrospective analysis of 2614 patients (82% male) with SLE in the Veterans Affairs healthcare system found that males had more all-cause hospitalizations and higher all-cause mortality at one year compared to females [29]. This study did not control for co-morbidities such as cardiovascular disease and cancer, which are more common among male patients. Causes of death were similar among male and female SLE patients studied in Latin America and Taiwan [25,30].

Numerous studies have addressed the issue of hormonal influences on disease severity, most often focusing on estrogen. The randomized, placebo-controlled, multicenter Safety of Estrogens in Lupus Erythematosus, National Assessment (SELENA) trials investigated the effects of hormone replacement therapy and oral contraceptive use on disease activity. The hormone replacement therapy-SELENA trial included 351 postmenopausal women and showed that combined estrogen–progestin hormone replacement therapy over a 12 month period was significantly associated with a small increase in the relative risk for mild-to-moderate (relative risk 1.34), but not severe, flares [31]. Other studies that did not sub-stratify flares by severity found no increase in the rate of flares in patients taking hormone replacement therapy versus placebo [32–34]. The oral contraceptive-SELENA trial arm included 183 women with inactive or stable lupus, and found...
that rates of mild, moderate, and severe lupus flares were similar (relative risk 0.98, p = 0.86) in the oral contraceptive (triphasic combined estradiol/progestin pills) and placebo arms [35].

Several case reports and small studies have evaluated the use of sex hormone therapy to modulate disease activity. A Cochrane review of seven randomized controlled trials of the impact of the androgen DHEA as treatment for SLE found that it had little clinical effect on disease activity in patients with mild or moderate SLE, but was associated with a modest, clinically significant increase in health-related quality of life measures [36]. A double-blind, placebo-controlled trial among 381 women with active SLE similarly found that prasterone, a generic formulation of DHEA, was associated with improved or stable disease over a 12 month period (p = 0.017) [37]. A double-blind, placebo-controlled trial of bromocriptine, a medication that inhibits prolactin secretion, showed an improved SLEDAI score but no difference in the total number of flares over 12 months [38].

3.3. Pregnancy and SLE

The data on pregnancy and SLE have evolved over the past decade. Whereas many older studies suggested an increased rate of SLE flare during pregnancy, some of these studies included women newly diagnosed with SLE during pregnancy, leading to an overestimation of flare rates [39–42]. Several recent prospective studies have demonstrated that women with inactive SLE at the time of conception tend not to flare during pregnancy, whereas those with active SLE, particularly lupus nephritis, are at increased risk for adverse maternal and fetal outcomes [43–45].

While experience with assisted reproductive therapies is limited in this population, in one small study three of seven women with SLE experienced a mild flare with either rash or arthritis during ovulation induction [46].

3.4. Genetic influences on sex disparities in SLE pathogenesis and severity

A recent genetic study has demonstrated that men with SLE carry a greater number of SLE-associated autosomal risk alleles than do women with SLE [47]. Earlier age at SLE onset has also been associated with a higher number of risk alleles compared to later age at onset [48]. These data also potentially suggest that hormonal, environmental factors and/or gene–environment interactions play proportionally greater roles in SLE pathogenesis among women and older adults than among men and younger people.

The presence of a second X chromosome in females may be important for SLE pathogenesis and could contribute to the differing incidence rates in females and males. During thymic development, one X chromosome in each XX cell is thought to be inactivated by epigenetic modification, such that each cell expresses genes from either the maternally- or paternally-derived X chromosome, but not both. Skewed X inactivation occurs when a disproportionate number of cells express either the maternal or the paternal X chromosome, and can lead to the survival of autoreactive T cells [49]. It is not clear that this is important for the development of SLE, however, as no evidence of skewed X inactivation was found in a study involving 46 women with SLE compared to 30 healthy controls [50].

The importance of incomplete X inactivation in the pathogenesis of SLE has been explored. Cells with incomplete X inactivation express gene products from both the maternal and paternal X chromosomes, thereby producing twice the normal amount of X-encoded proteins. The X chromosome encodes several genes of interest in SLE pathogenesis, including the gene for CD40 ligand (a T cell surface molecule that stimulates B cells), IRAK1 (encoding a protein kinase associated with interleukin-1 signaling), Foxp3 (encoding a transcription factor for regulatory T cells), TLR7 (encoding Toll-like receptor 7, which mediates the innate immune response), and MECP2 (encoding a protein that represses transcription from methylated promoters) [51–56]. All of these have been associated with increased risk for developing SLE, and any of these could be over expressed in women due to incomplete X inactivation.

Epigenetic modification of genes on the inactive X chromosome in females has been proposed as a possible mechanism for the increased female prevalence of SLE. Women, but not men, with active SLE had demethylation of the gene for and increased expression of CD40 ligand, which raises the possibility that demethylation of the inactive X chromosome may be related to disease activity [57]. Men have been reported to have a higher number of SLE risk alleles and more T cell DNA demethylation during SLE flares compared to women [58]. These results support the hypothesis that women may have a lower threshold to develop SLE disease activity.

Two studies have suggested a dose-effect of the X chromosome, evidenced by a 10-fold increased prevalence of genotype 47,XXY (Klinefelter’s syndrome) compared to 46,XY in men with SLE [59,60]. However, these studies did not measure hormone levels or products of X-encoded genes. In the cohort from Dillon’s study, seven Klinefelter’s syndrome men had significantly fewer severe manifestations of SLE than normal karyotype men with SLE [59]. These findings are interesting when viewed through the lens of Mohan’s hypothesis that females (or perhaps any individual with two X chromosomes) have a lower threshold to develop SLE, yet men (or perhaps any individual with only one X chromosome) have more severe disease when they develop SLE. Potential explanations for this observed difference include a protective effect of the second X chromosome in terms of disease severity, or an increased estrogen-to-androgen ratio.

4. Sex disparities in RA incidence and severity

4.1. Incidence of RA among females compared with males

RA affects females twice as often as males and has a peak incidence at age 45–55, which coincides with the perimenopausal years and suggests a possible association between estrogen deficiency and disease onset [61,62] (Table 3). Data concerning estrogen exposure and RA risk are varied, however. One case–control study found that current oral contraceptive use may protect against RA development, but no effect was apparent for prior oral contraceptive use [63]. Among women followed since the 1970s in the Nurses’ Health Study cohort, there was no clear association between age of menarche,
parity, regularity of menses, or oral contraceptive pill use and RA risk [64]. Several studies have indicated that the relative risk for developing RA is 1.8 to 2.0-fold among nulliparous compared to parous women, and that currently pregnant women may have a reduced risk of developing RA during the pregnancy [65,66]. An increased risk of developing RA after a woman's first pregnancy has also been reported [66]. In the Women’s Health Initiative, a randomized controlled trial of postmenopausal hormone use, there was no significant difference in RA incidence between those who did or did not receive hormones [67]. However, overall RA incidence was lower than expected for the population, suggesting incomplete case ascertainment.

After age 45, the incidence rate of RA among men increases rapidly and approaches that of age-matched women. This trend suggests that decreased levels of androgens in both men and women are associated with RA onset. Below age 45, men may be protected against RA due to their higher levels of androgens [11]. Among women, however, data from the Nurses’ Health Study revealed no difference in androgen levels prior to the onset of RA in 449 female patients compared to healthy, age-matched controls [68]. However, overall RA incidence was lower than expected for the population, suggesting incomplete case ascertainment.

Breastfeeding for longer than 24 months was associated with a protective effect against RA risk (relative risk 0.5) [64]. The mechanism for this is unknown, but may involve long-term suppression of prolactin secretion with prolonged breastfeeding [64]. Finally, environmental exposures such as smoking differentially affect the risk for development of RA in men and women. In men, tobacco use has been associated with a higher relative risk of RA, in particular seropositive RA. This may be because men are heavier smokers, or due to interactions with other environmental exposures linked to RA risk, such as silica and solvents [70–72].

4.2. Sex differences in RA severity

Multiple studies have found that men and women have similar disease severity at the time of diagnosis, but that men are more likely to achieve remission early in the course of RA [73–75]. Several studies have demonstrated that men have a better response to RA therapy and are more likely to go into remission compared to women [73,74,76,77]. One observational study of 2129 patients in the DANBIO Registry compared sex-based differences in treatment response to anti-TNF therapy. Among patients diagnosed with RA for two years or less, treatment response occurred more quickly in

![Figure 1: Interaction of sex, genetic load, and environmental exposures in the development of SLE. Reprinted, with permission, from [17]. Genetic and environmental factors both contribute to autoimmunity. Both environmental factors and susceptibility genes may together dictate an individual's propensity to surpass the threshold for disease development. As portrayed in this model, one would predict that an individual with a high genetic load (e.g., '3') would develop disease in almost any environment. On the other hand, an individual with a minimal load of autoimmunity susceptibility genes (e.g., '1') is unlikely to develop disease in most environments. One would predict that most individuals who develop autoimmunity may have an intermediate genetic load and an 'intermediate' load of environmental insults, as illustrated by individual #2. Finally, 'short-term' environmental insults may exacerbate specific component lupus phenotypes transiently, and these phenotypes may subside once the insult is removed, as exemplified by individual '1a'. A good example of such a scenario would be drug-induced lupus. The disease susceptibility threshold is likely to be significantly lower in females (right) compared to males (left), owing possibly to hormonal differences.

<table>
<thead>
<tr>
<th>Table 2</th>
<th>Incidence rates of SLE by sex, per 100,000 adults.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hochberg et al., 1985 (U.S.) [89]</td>
<td>3.9 (white women) vs. 0.4 (white men)</td>
</tr>
<tr>
<td>McCarty et al., 1995 (U.S.) [90]</td>
<td>11.4 (AA^a women) vs. 2.5 (AA men)</td>
</tr>
<tr>
<td>Naleway, et al., 2005 (U.S.) [91]</td>
<td>3.5 (white women) vs. 0.4 (white men)</td>
</tr>
<tr>
<td>Feldman, et al., 2012 (U.S.) [92]</td>
<td>9.2 (AA women) vs. 0.7 (AA men)</td>
</tr>
<tr>
<td></td>
<td>8.2 (women) vs. 1.9 (men)</td>
</tr>
<tr>
<td></td>
<td>30.5 (low SES^b women) vs. 4.9 (low SES men)</td>
</tr>
</tbody>
</table>

^a AA = African-American.  
^b SES = socioeconomic status.
ment and men were significantly more likely to have a good response to therapy over 48 months [78]. Possible explanations for these differences include variations in pathogenesis of early RA in men and women; differences in drug metabolism or in vivo activity; or differences in pain perception and reporting, which affect disease activity scores.

On the other hand, the multinational QUEST-RA cohort included a one-time assessment of 6004 patients and found that RA disease activity, as measured by Disease Activity Score for 28 joints (DAS28) and Health Assessment Questionnaire (HAQ) scores, was not significantly different for men and women. However, men in this cohort were significantly more likely than women to be in remission at the time of study enrollment based on the DAS28 score [79]. A recent observational study of 1912 patients with RA receiving biologic therapies found that women and men had similar DAS28 scores, although women reported subjectively worse symptoms [80].

Since synovial macrophages and lymphocytes express androgen and estrogen receptors and may metabolize gonadal hormones, variations in systemic estrogen and androgen levels might also influence RA disease activity. However, several placebo-controlled trials of hormone replacement therapy in postmenopausal women with RA have not shown statistically significant differences in disease activity [81–83]. Given that low levels of androgens could potentially be associated with increased disease activity, testosterone therapy has also been studied [69]. A double-blind, placebo-controlled study of testosterone therapy for postmenopausal women with RA showed a slight disease-modifying effect that was not statistically significant [84]. In contrast, androgen replacement therapy has shown positive effects in male RA patients, particularly as adjuvant treatment [3].

### 4.3. Pregnancy and RA

Data from retrospective studies has suggested that many women with RA experience a remission during pregnancy. A prospective study of 140 pregnant women with RA found a small improvement in functional status during pregnancy, although only 16% were in complete remission. This study also found that women’s functional status did not change significantly by six months postpartum, in contrast to the common notion that RA flares in the postpartum period [85]. One theory for the improvement during pregnancy is that the immune system switches from a Th1- to Th2-predominant response to develop tolerance for embryonic cells expressing paternal MHC complexes, thereby decreasing RA activity [11,86].

### 4.4. Genetic influences on sex disparities in RA pathogenesis and severity

There is limited information on genetic influences on sex disparities in RA. In contrast to SLE, RA has been described very rarely in patients with Klinefelter’s syndrome, suggesting that the extra X chromosome does not confer an added risk for RA. One study found an association between RA and single nucleotide polymorphisms of the X-encoded genes TIMP1 (which inhibits matrix metalloproteinases and prevents cartilage degradation) and ILR9 (which is involved in interleukin-9 signaling and in early T cell development) [87]. Additionally, the ILR9 polymorphism was significantly more common among males with RA, compared to females with RA. To date, no studies have focused on epigenetic modification of the inactivated X chromosome as related to RA susceptibility. A recent population-based cohort study of patients with SLE or RA and their parents found no association between maternal or paternal history of disease and patient sex, suggesting that transmission of the X chromosome from mother vs. father is unlikely to account for sex differences in disease prevalence [88].

### 5. Conclusions

Sex differences in SLE and RA incidence and severity result from a complex interaction of hormonal, genetic, and epigenetic factors. Both diseases affect women more frequently than men, yet striking differences in the peak age of incidence and the degree of sex-based disparity are seen. Men seem to have a more severe course of SLE compared to women, whereas men may be less severely affected than women with RA. The study of how epigenetic modifications are involved in the pathogenesis and activity of these related diseases will hopefully allow us to understand how genetic, hormonal and environmental risk factors interact in the development of SLE and RA in men and women.

### Conflict of interest statement

Sara Tedeschi, MD has nothing to disclose. Bonnie Bermas, MD is a consultant for UCB Pharmaceuticals < $5000/year. Karen Costenbader, MD, MPH has nothing to disclose.

### References


