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Mini Review

Sex Differences in Autoimmune Diseases: Why Females Are More Affected Than Males

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Abstract: For a long time, medicine neglected disparities in health problems between the sexes, confining women's conditions mainly to the reproductive sphere. Today, increasing attention is being paid to both sex- and gender-related differences, culminating in the establishment of dedicated research centers such as the Reference Center for Gender Medicine at the Italian National Institute of Health (Istituto Superiore di Sanità). One of the most striking manifestations of these differences is the significantly higher prevalence of most autoimmune diseases among females compared to males. This mini-review of recent reports highlights some of the known mechanisms for such difference.

Keywords: autoimmunity; sex bias; X chromosome.

1. Introduction

Autoimmune diseases constitute a heterogeneous group of over one hundred distinct disorders that may affect a single organ (e.g., autoimmune thyroiditis, autoimmune hepatitis and encephalitis, type 1 diabetes, pemphigo), an entire system (e.g., multiple sclerosis, rheumatoid arthritis, myasthenia gravis, celiac disease, some vasculitides, myositis), or multiple organs simultaneously or progressively (e.g., systemic lupus erythematosus, Sjogren's syndrome, systemic sclerosis). It is estimated that about 5% of the population suffers from an autoimmune condition, and about 75% of them are females. These conditions share a common pathogenetic mechanism: the immune system, whose role is to defend the body from foreign agents, erroneously recognizes self-tissues as foreign and attacks them, causing progressive tissue destruction [1].

This process involves both adaptive immune cells (T and B lymphocytes) and innate immune cells (neutrophils, monocytes, NK cells), leading to chronic inflammation, cellular damage, and eventual loss of organ function. The paradoxical nature of autoimmunity—recognized only in the mid-20th century—has become a central focus of modern immunology.

The fundamental issue is immune tolerance: why the surveillance system that detects foreign substances remains inactive (i.e., tolerant) toward the organism's own molecules. This extends as well to maternal tolerance during pregnancy (the fetus carries paternal antigens), and toward the microbiota, in particular the intestinal one which contributes to pathogen defense, response to therapeutic drugs, and cancer resistance.

Epidemiologically, a constant and yet not fully explained finding is the greater prevalence of autoimmune diseases in women, with female-to-male ratios reaching as high as 9:1 for conditions such as systemic lupus erythematosus, Hashimoto's thyroiditis, Sjögren's syndrome, and lower but still strongly biased (3:1) in rheumatoid arthritis, multiple sclerosis and other demyelinating diseases [2]. A few exceptions—such as certain

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neurological disorders and type 1 diabetes—show less pronounced sex imbalance. Sexual dimorphism extends not only to disease incidence but also to clinical manifestations, symptom severity, age of onset, and therapeutic response [3].

Biological sex is primarily determined by chromosomal composition, with XX individuals classified as female and XY individuals as male. Less common chromosomal configurations, including XXY, XYY, and XO karyotypes, have also been associated with altered susceptibility to immune-mediated disorders, highlighting the important contribution of sex chromosomes to immune regulation. Increased X chromosome dosage has been linked to several autoimmune diseases, including systemic lupus erythematosus, Sjögren's syndrome, and scleroderma, supporting the hypothesis that X-linked genetic mechanisms contribute directly to immune dysregulation and disease susceptibility [2].

Many other hypotheses for the sex bias have been advanced, among them abnormal X chromosome inactivation [4], differences in environmental exposures such as cosmetic chemicals or sunlight [5,6], and the microbiome [7,8] (see also the paragraph below). Although some or all these factors may play a role for the observed sex imbalance in autoimmunity, no convincing explanation has been offered and supported by data [6]. An evolutionary based hypothesis has been put forward recently [9], postulating that evolution imposed a higher B cell activation and higher antibody production in females, in order to protect the offspring, and this could explain the higher frequency and levels of autoantibodies—an indicator as well as cause of autoimmune diseases—in the female sex. All this remains purely speculative.

In this short narrative review we shall examine only sex differences—biologically determined by chromosomal dosage—and not gender differences—due to social or psychological reasons and someone's own concept of their gender—which may not correspond to the sex assigned at birth [10]. Moreover, we shall focus our attention to the development of autoimmune diseases, and not to the presence of autoimmune phenomena such as autoantibodies. Antibodies against self-antigens are present not only in autoimmune diseases, where they offer an important clue to diagnosis and also pathogenesis, but they can be also found in cancer, during massive tissue damage and even in healthy subjects (so called natural autoantibodies) [11]. Given such limits, we shall explore the recent literature about this subject.

2. Immune System Differences

This sex imbalance arises from multiple factors—genetic, hormonal, and environmental (epigenetic)—along with intrinsic differences in immune system functioning between the sexes [3]. Several distinctions are accentuated during specific life stages (e.g., pregnancy) and evolve with aging. During pregnancy, potentially harmful immune responses are attenuated to protect the semi-allogenic fetus bearing paternal antigens; hormonal changes drastically reshape the immune milieu.

In the prospective *InCHIANTI* study [12], a significant sexual dimorphism in circulating neutrophil counts and in the neutrophil-to-lymphocyte ratio, an indicator of immune system aging, was reported. This may be explained by a relatively stronger adaptive immunity in females, which is needed for infectious disease control, but predisposes to damaging inflammatory conditions and autoimmunity.

The female immune system appears more reactive, especially in its adaptive component (T and B lymphocytes). Consequently, immune responses—both humoral (antibody-mediated) and cellular—are stronger in females. This enhanced reactivity is influenced by biological factors (e.g., immune response and regulatory genes on the X chromosome), epigenetic mechanisms, sex hormones, and gender-related psychosocial influences. Gender is a social construct, including behaviours and roles which may differ from biological sex and varies from society to society and can change over time. Gender belongs to the social factors affecting health outcomes and intersecting with sex, but will not be discussed in our mini-review, except in a short paragraph.

Lymphocytes play a central role in both immune defense and autoimmunity progression. T cells can deviate toward autoreactivity when tolerance mechanisms fail (notably through reduced function of regulatory T cells, or Tregs), while unrestrained autoreactive B cells produce autoantibodies directed against self-tissues, leading to cellular damage. Autoantibodies thus serve as diagnostic markers and tools for disease monitoring.

Women display higher numbers of $CD4^+$ T helper cells and B cells, which underlie stronger immune reactions to infections and vaccines but may compromise tolerance maintenance. Conversely, Treg cells are more prevalent among males—a key difference emerging after puberty. These cells, whose discovery earned the Nobel Prize in Physiology or Medicine in 2025, maintain immune homeostasis and tolerance [13].

Such sex-specific immunological architecture is profoundly shaped by hormones: estrogens are generally pro-inflammatory, while testosterone exerts immunosuppressive effects. Several studies have explored changes during the menstrual cycle and under hormonal suppression, confirming the hormonal modulation of immunity.

3. The Role of Sex Chromosomes

Genetically, the X chromosome is crucial, carrying numerous genes involved in immune regulation. Women possess two X chromosomes, but one undergoes partial inactivation. This inactivation, however, is incomplete, often resulting in heightened immune gene expression and a tendency toward autoimmunity [14].

With aging, the fidelity of X chromosome inactivation (XCI) progressively declines, leading to increased escape of selected X-linked immune genes from transcriptional silencing and consequently to enhanced gene dosage in female immune cells [15,16]. Conversely, age-related mosaic loss of the Y chromosome (LOY), one of the most common somatic genetic alterations in aging men, has been associated with immune dysregulation, chronic inflammation, and increased susceptibility to several age-related disorders, including autoimmune diseases [16].

Several immune-related genes located on the X chromosome contribute to this sex-biased immune regulation. Among them, FOXP3, which encodes the master transcription factor required for the development and function of regulatory T cells (Tregs), plays a pivotal role in maintaining peripheral immune tolerance. Altered FOXP3 expression or function may impair Treg-mediated immunosuppression, thereby facilitating the breakdown of self-tolerance and the development of autoimmune responses. In addition, other X-linked immune genes, including TLR7 and CD40L, may escape XCI in female immune cells, resulting in enhanced innate immune activation, increased type I interferon production, and augmented B-cell responses, all of which are characteristic features of several autoimmune diseases, particularly systemic lupus erythematosus [15–17]. Although these mechanisms provide a compelling biological framework for female-biased autoimmunity, their relative contribution likely varies among diseases and remains an active area of investigation.

Recent evidence further suggests that XIST ribonucleoprotein complexes, which are uniquely associated with the inactive X chromosome, may themselves constitute female-specific autoantigenic structures, providing an additional mechanistic link between X chromosome biology and female-biased autoimmunity [17].

Notably, most experimental autoimmune studies historically used male animals, limiting the translational understanding of sex dimorphism in autoimmunity and underscoring the urgent need for balanced experimental designs.

4. miRNA and Sex-Biased Immunity

MicroRNAs (miRNAs) are short non-coding RNA molecules that regulate gene expression at the post-transcriptional level and play a crucial role in immune homeostasis. Growing evidence suggests that sex-specific differences in miRNA expression contribute significantly to the sexual dimorphism observed in autoimmune diseases. Notably, the X chromosome contains one of the highest densities of miRNA genes in the human genome, raising the possibility that sex chromosome composition may influence immune regulation beyond the effects of protein-coding genes [15,18].

Several X-linked miRNAs participate in pathways controlling lymphocyte activation, cytokine production, immune tolerance, and inflammatory responses. In females, incomplete X chromosome inactivation may result in increased expression of selected miRNAs, thereby amplifying immune reactivity. This mechanism has been proposed as a contributing factor to the stronger adaptive immune responses observed in women and to their increased susceptibility to autoimmune disorders [15,16].

Among the best-characterized examples, miR-223 regulates granulocyte differentiation and inflammatory responses and has been implicated in rheumatoid arthritis and systemic lupus erythematosus. miR-106a influences regulatory T-cell function and immune tolerance, whereas miR-18b has been associated with the modulation of cytokine signaling pathways involved in autoimmunity. Dysregulated expression of these and other miRNAs has been reported in several autoimmune diseases, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome [18].

MiRNAs also participate in the regulation of regulatory T cells, B-cell differentiation, and interferon signaling pathways, all of which are central to autoimmune disease pathogenesis. In particular, type I interferon signatures, a hallmark of systemic lupus erythematosus, appear to be influenced by sex-dependent epigenetic and post-transcriptional mechanisms involving miRNA networks [16].

In addition to genetic regulation, miRNA expression is modulated by sex hormones, creating a complex interaction between chromosomal, endocrine, and epigenetic factors. This integrated network may contribute to the maintenance of immune tolerance under physiological conditions and, conversely, to its breakdown in genetically susceptible individuals. Therefore, miRNAs are increasingly recognized as important mediators linking sex chromosomes to immune function and autoimmune disease susceptibility, representing promising biomarkers and potential therapeutic targets for precision medicine approaches [18].

5. Microbiota and Sex Immune Differences

In recent years, the gut microbiota has emerged as a critical regulator of immune system development, maturation, and function. Increasing evidence suggests that sex-specific differences in microbial composition may contribute to the marked female predominance observed in many autoimmune diseases. Rather than acting as an isolated factor, the microbiota appears to participate in a complex bidirectional interaction with sex hormones and the immune system, forming a microbiota–hormone–immune axis that influences immune homeostasis throughout life.

Sex hormones significantly shape microbial diversity and composition. Experimental studies have demonstrated that puberty is associated with the emergence of sex-specific microbial profiles, while pregnancy and menopause are accompanied by substantial alterations in gut microbial communities. Conversely, the microbiota itself can influence systemic hormone levels through the activity of bacterial enzymes involved in steroid metabolism, collectively referred to as the estrobolome. Through these mechanisms, microbial communities contribute to the regulation of circulating estrogens and other sex hormones, thereby indirectly modulating immune responses [19].

A growing body of evidence indicates that microbial metabolites play a pivotal role in maintaining immune tolerance. Among these, short-chain fatty acids (SCFAs**)**, including acetate, propionate, and butyrate, promote the differentiation and function of regulatory T cells (Tregs), which are essential for preventing excessive immune activation and autoimmunity. Alterations in microbial composition may therefore shift the balance between pro-inflammatory and regulatory pathways, favoring chronic inflammation and loss of self-tolerance.

Several autoimmune diseases characterized by a marked female predominance, including systemic lupus erythematosus, rheumatoid arthritis, multiple sclerosis, and Sjögren's syndrome, have been associated with microbial dysbiosis. Although causality remains difficult to establish, animal models provide compelling evidence that sex-dependent microbial communities can influence disease susceptibility. In some experimental settings, transfer of microbiota from male animals has been shown to confer partial protection against autoimmune disease development in females, suggesting a direct contribution of microbial factors to sex-biased immune responses.

The interaction between microbiota and immunity also appears to involve innate immune signaling pathways, including toll-like receptors, type I interferon responses, and cytokine networks that are already known to differ between females and males. These observations support the hypothesis that microbiota-related mechanisms may amplify pre-existing genetic and hormonal determinants of immune dimorphism rather than acting independently.

Taken together, current evidence supports the concept that the microbiota represents an additional layer of regulation contributing to sex differences in autoimmunity. Future studies integrating microbiomics, endocrinology, epigenetics, and systems immunology will be essential to clarify how microbial communities interact with host biological sex to influence autoimmune disease susceptibility and progression.

6. Sex Hormones and Immune Regulation

Sex hormones—estrogens, progesterone, prolactin, and androgens—profoundly influence immune function [3,20]. Rather than exerting uniformly pro-inflammatory effects, estrogens display context-dependent and concentration-dependent immunomodulatory properties. Depending on hormonal levels, receptor signaling (ERα and ERβ), target cell type, and the physiological or inflammatory milieu, estrogens may either enhance or suppress immune responses.

At physiological concentrations, estrogens generally promote B-cell survival, antibody production, and humoral immunity while modulating T-cell differentiation and cytokine production. However, during specific physiological conditions such as pregnancy, elevated estrogen levels favor immune tolerance by promoting regulatory T-cell expansion and shifting immune responses toward less inflammatory phenotypes. These dynamic effects help explain why autoimmune disease activity may fluctuate across different hormonal states, including puberty, pregnancy, and menopause.

In contrast, androgens, particularly testosterone, are generally associated with anti-inflammatory and immunosuppressive effects. They reduce B-cell maturation, inhibit pro-inflammatory cytokine production, and promote immune regulatory pathways, potentially contributing to the lower incidence of many autoimmune diseases observed in males. Nevertheless, recent evidence suggests that the interaction between sex hormones and immunity is considerably more complex than previously appreciated, involving extensive crosstalk with sex chromosomes, epigenetic regulation, and tissue-specific immune microenvironments [16,21].

7. Genetic Polymorphisms

Autoimmunity can develop in genetically predisposed individuals, when modifying factors from the environment act as triggers. Genetic polymorphisms are heritable alterations in the DNA sequence. As such they

are major contributors to phenotypic variation, and also to disease susceptibility, being able to exert their effects on gene expression and function. Identification of genetic polymorphisms in autoimmune diseases provides clues to the pathogenetic mechanisms involved. Autoimmune diseases with strong genetic associations are mainly represented by systemic lupus, rheumatoid arthritis, multiple sclerosis and type 1 diabetes [22].

Beyond conferring disease susceptibility, genetic polymorphisms may also contribute to sex differences in autoimmune diseases. Current evidence suggests that the biological effects of genetic variants may differ between females and males because of their interaction with sex chromosomes, sex hormones, and epigenetic regulatory mechanisms. In particular, polymorphisms affecting immune-related pathways—including type I interferon signaling, antigen presentation, and lymphocyte activation—may have different functional consequences depending on the hormonal and genetic background of the individual, thereby contributing to the female predominance observed in many autoimmune diseases [16,23]. Although the precise mechanisms remain incompletely understood, these findings support the concept that genetic susceptibility should be interpreted within a broader framework integrating sex-specific biological regulation.

8. Epigenetic and Environmental Factors

Beyond chromosomal and hormonal influences, epigenetic and environmental factors further shape sex differences in autoimmunity [24]. Mechanisms such as DNA methylation and microRNA regulation significantly affect immune cell function and are responsive to both intrinsic and external stimuli.

Important environmental contributors include psychological stress, diet, obesity, vitamin status (especially vitamins A and D), viral infections, chemical exposures, and smoking [9]. Many of these act more strongly in females or are mediated through psychosocial and gender-related pressures—reflecting historically embedded social roles.

Diagnostic delays are also more frequent in women, partly due to the slow and subtle progression of symptoms and the tendency to attribute early signs to psychological conditions. These disparities highlight the interplay between biology and cultural context in shaping disease trajectories.

9. Gender Medicine and Autoimmunity

Awareness of sex- and gender-based differences has revolutionized biomedical research, giving rise to the field of gender medicine. Women face a higher psychosocial burden—balancing occupational stress, family care, and gendered expectations—all of which modulate immune and neuroendocrine function. Studies in Sex and Gender Medicine have made steady progress, culminating in the establishment of dedicated research centers such as the Reference Center for Gender Medicine at the Italian National Institute of Health (Istituto Superiore di Sanità). Disparities in health care access and delivery are present in all countries, both developed and underdeveloped ones. However, sex biased diseases represent a unique scenario where hormonal, genetic and sex-driven factors are pivotal for imbalanced male:female ratio of affected patients. One of the most striking manifestations of these differences is the significantly higher prevalence of most autoimmune diseases among females compared to males.

Autoimmune symptoms in women are often overlooked or misinterpreted, delaying diagnosis and treatment. Gender medicine thus aims to correct these clinical and cultural imbalances, integrating biological and psychosocial insights into more equitable healthcare strategies.

A developing area of inquiry involves transgender individuals undergoing hormone therapy [25].

Current evidence suggests that gender-affirming hormone therapy may influence immune function through complex endocrine–immune interactions. However, available data remain limited and heterogeneous, and do not yet support definitive conclusions regarding its impact on autoimmune disease susceptibility. Recent prospective studies indicate that hormone therapy may exert context-dependent immunomodulatory effects rather than simply increasing autoimmune risk, highlighting the need for larger longitudinal studies to better characterize immune outcomes throughout gender transition [26].

10. Conclusions and Take-Away Messages

Women live with an immune system that is persistently primed for defense—a benefit in combating pathogens and conferring passive immunity to offspring via placental transfer and breastfeeding, but also a liability regarding self-reactivity.

Historically, clinical research generalized male-derived data to both sexes, masking crucial biological dimorphisms. Today, sex-disaggregated medicine recognizes sex differences as key to accurate pathophysiology, early diagnosis, and precision therapies.

The discrepancy in autoimmune disease prevalence stems not from a single cause but from the intricate interplay of genetic, hormonal, immunological, and environmental factors. As noted by many authors, there is no single factor able to explain the differential burden of autoimmune diseases (but not all- for instance type 1 diabetes) [27]—instead, there are multiple concurring mechanisms [28]. The definition of autoimmune disease is not entirely secure and many diseases considered autoimmune may not meet commonly cited definitions [11,29]. Nonetheless, there are perhaps 80–120 human illnesses that are designated as autoimmune, and a large majority of these affect women more often than men. Naturally, this bias toward the female sex has led to study of sex steroid hormones in autoimmune disease, which is wrought with problems. Chronic disease, including inflammatory disease, affects sex hormones. Therefore, studies should address the very early phases of diseases, and perhaps cohorts of at risk subjects, since the onset of the disease may precede clinical diagnosis by several years.

Women's immune systems are both stronger and more self-reactive—a duality that reflects the evolutionary balance between protection and vulnerability. The recent recognition that sex chromosomes exert distinct, cell-autonomous effects on health, aging, and disease [30] through different mechanism—escape from X chromosome inactivation, X reactivation X-skew, and unique X or Y linked genes—indicates further roles in autoimmunity: atypical memory B cell expansion and type 1 interferon production, which promote autoantibodies production and disease activity [31], with a role for XIST ribonucleoprotein complexes which become targets for autoantibodies.

Many questions remain unresolved, but evidence increasingly confirms that biology governs sexual dimorphism in autoimmunity expression. Continued interdisciplinary research—combining genetics, epigenetics, endocrinology, and environmental health—is crucial for translating these insights into personalized and equitable medical practice.

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Conflicts of Interest

The authors declare no conflict of interest.

Use of AI and AI-Assisted Technologies

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