

GENDER-SPECIFIC IMMUNITY: THE IMPACT OF SEX HORMONES AND GENETICS ON AUTOIMMUNE DISEASE IN WOMEN’S HEALTH

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Introduction:

Historically, medical research prioritized male subjects, excluding women due to hormonal complexities (Decker, 2020). This exclusion skewed our understanding of autoimmune diseases (AIDs), many of which show a striking female predominance. For example, systemic lupus erythematosus (SLE) exhibits a female-to-male ratio of 9:1, while rheumatoid arthritis (RA) is approximately 3:1. These sex-based differences underscore the need to investigate biological, hormonal, and genetic mechanisms driving female-biased autoimmunity.

Objectives:

Investigate how sex hormones, vitamin D, and X chromosome-linked factors contribute to increased autoimmune risks in women.
Highlight disease-specific differences (e.g., SLE, RA, PsA) and their clinical manifestations.
Recommend personalized, gender-sensitive approaches to research and therapy.

Methods:

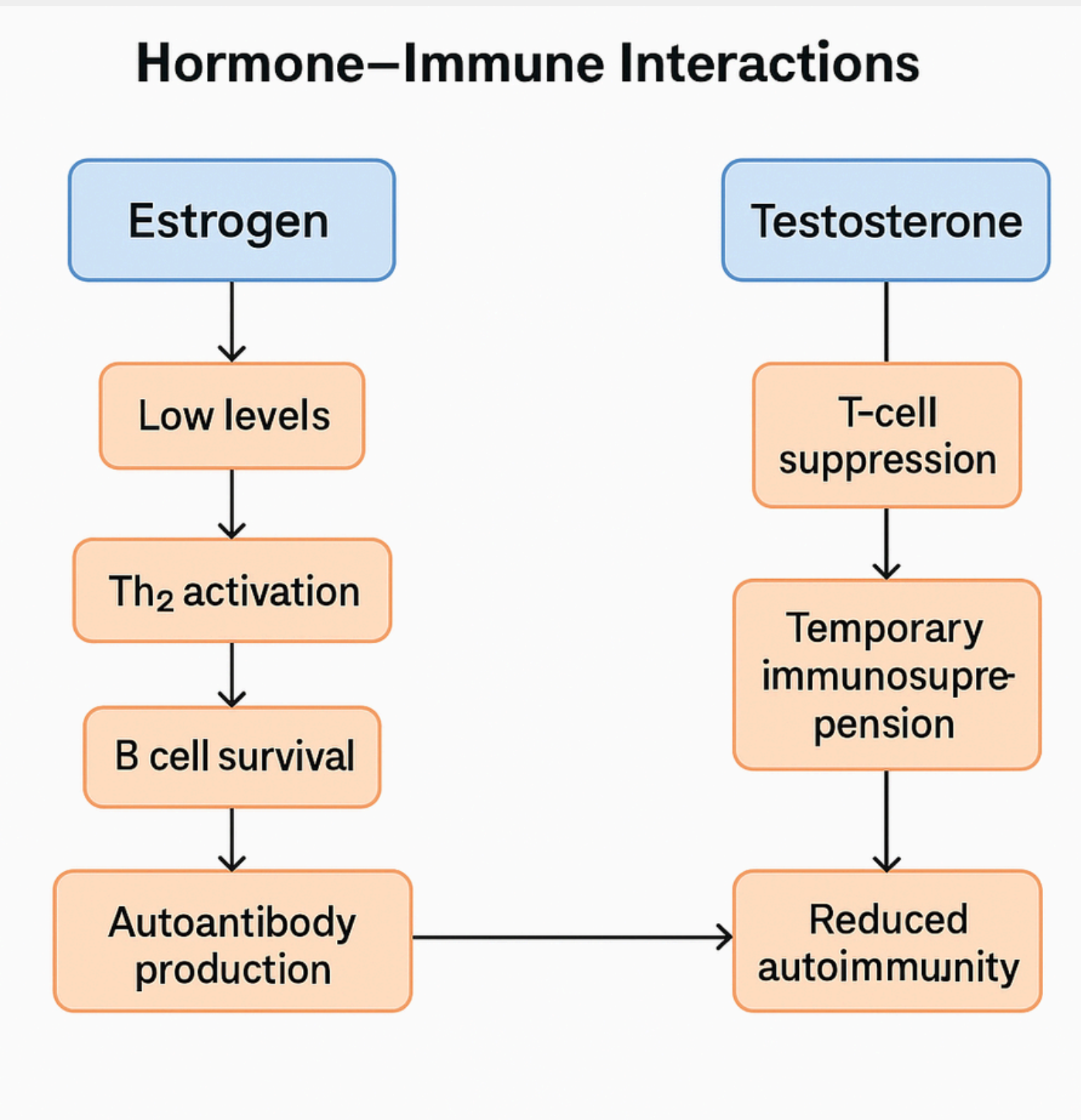
Systematic literature review (2018–2024) in Google Scholar and Science Direct.
Keywords: “gender,” “autoimmune diseases,” “sex hormones,” “vitamin D,” “Xist RNP”
Analysis included clinical studies, experimental models, and genomic data on sexual dimorphism in AIDs.

Results:

Sexual Dimorphism in Immunity:

Heightened Immune Reactivity in Women:

- Women exhibit higher numbers of circulating CD4+ T cells (helper T cells) compared to men, with studies showing counts approximately 1.2–1.5 times higher.
- B cells are also more numerous and active in females, contributing to enhanced antibody production.
- These immune cells are influenced by estrogen, which enhances survival and proliferation of autoreactive lymphocytes, contributing to autoimmune disease susceptibility.



Amplified Th2 Responses:

Estrogen skews the immune system towards a Th2-dominant response, increasing production of cytokines like IL-4, IL-5, and IL-10. This shift favors humoral immunity (antibody production) over cellular immunity (cytotoxic T cells), predisposing to autoimmune diseases such as SLE and Sjögren’s syndrome.

Increased Expression of Pro-Inflammatory Cytokines:

Women show higher expression of IL-6, TNF- α , and IFN- α , which drive inflammation and tissue damage in autoimmune diseases. For example, IL-6 levels in female SLE patients can be 2–3 times higher than in healthy controls, correlating with disease activity index. Estrogen upregulates TLR7 expression, promoting type I interferon production, a hallmark of SLE pathogenesis.

Influence of Sex Hormones on Antigen Presentation:

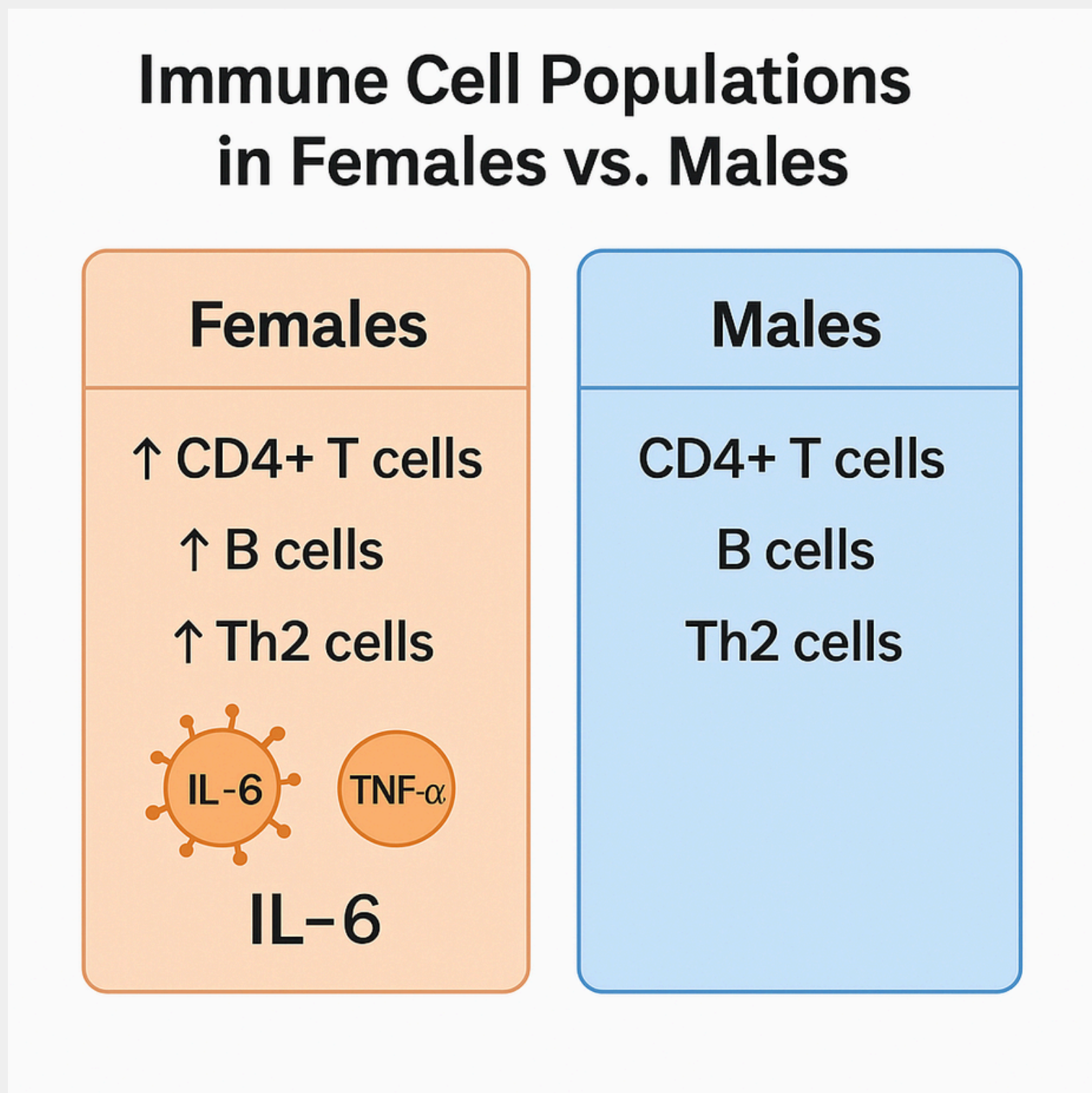
Dendritic cells (DCs) from women show increased MHC-II expression and costimulatory molecule upregulation (CD80/CD86), enhancing T-cell activation. Estrogen stimulates DC maturation, increasing antigen presentation and perpetuating autoimmunity.

Impact on Regulatory T Cells (Tregs):

While high estrogen levels during pregnancy expand Treg populations, at lower levels (follicular phase), Treg activity is reduced, compromising self-tolerance. This fluctuation may explain flare-ups of autoimmune diseases during menstrual cycles and postpartum periods.

Sex Hormones and Immune Regulation:

Estrogens (17 β -estradiol) promote Th2 polarization and regulatory T-cell expansion during pregnancy, but at lower levels, they enhance B-cell activation, increasing autoantibody production. At levels >100 pg/mL (mid-luteal phase), E2 enhances regulatory pathways; at <50 pg/mL (follicular phase), it favors pro-inflammatory responses. Testosterone exerts immunosuppressive effects by: Inhibiting T-cell proliferation (~30% decrease observed in experimental models). Reducing NK cell activity and immunoglobulin production.



Vitamin D and Autoimmune Diseases:

Acts via Vitamin D Receptor (VDR) present in immune cells (T cells, B cells, macrophages, dendritic cells). Modulates over 1000 genes, influencing both innate and adaptive immunity. Low vitamin D levels (<20 ng/mL) correlate with increased AID risk in women (Vasilea, 2016). Women’s mean serum 25(OH)D levels ~18 ng/mL vs. men’s ~22 ng/mL in European cohorts. Vitamin D reduces B-cell hyperactivity and downregulates aromatase, indirectly lowering estrogen synthesis.

Sex Chromosomes and Xist Ribonucleoproteins:

15% of X-linked genes escape inactivation—leading to enhanced immune gene expression (Ortona et al., 2016). Xist RNP complex (Xist lncRNA + proteins) initiates X chromosome inactivation but also exhibits immunogenicity. Dou et al. (2024) demonstrated that forced Xist expression in male mice induced SLE-like autoimmunity, with multi-organ damage (kidney, liver, lungs). Y chromosome genes (e.g., SRY, UTY) in males may suppress autoimmunity via regulatory pathways.

Disease-Specific Highlights:

Disease	Female-to-Male Ratio	Key Features	Therapeutic Implications
SLE	9:1	- Estrogen promotes autoreactive B cells and plasma cell survival - Testosterone deficiency worsens disease severity	- VDR agonists reduce IL-12 and Th1 infiltration - Potential therapy target
Psoriatic Arthritis (PsA)	1.5:1 (approx.)	- Women more likely to develop polyarticular, chronic pain-dominant disease - Men have more severe axial disease - Women have higher TNFi dropout rates (~30% vs. 20% in men)	- Consider hormonal influence on immunogenicity - Tailor therapy to gender-specific immune profiles
Rheumatoid Arthritis (RA)	3:1	- Higher incidence in women - Vitamin D supplementation (>50 ng/mL) may reduce disease activity scores (DAS28) by ~20% - High estrogen and low testosterone linked to severe disease	- Combine Vit D supplementation with standard therapy - Monitor sex hormone levels for disease management

Recommendations:

Incorporate sex as a biological variable in all stages of research. Develop VDR agonists and hormone modulators tailored to female immune profiles. Enhance clinical trial participation by women; consider hormone phases (follicular, luteal) in trial design. Promote personalized medicine incorporating sex, genetics, and environment.

Conclusions:

Sex hormones, X chromosome gene escape, and vitamin D deficiency collectively increase AID risk in women. Gender-specific medicine is essential for drug development and clinical trial design, ensuring equitable and effective treatments.

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