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# The Influence of Female Health Issues on the Development of Autoimmune Thyroid Disease

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**Abstract**

Autoimmune diseases, including autoimmune thyroid diseases (AITD), affect women more often than men. AITD, namely Hashimoto's thyroiditis (HT) and Graves' disease, are the most common autoimmune endocrine diseases in women of reproductive age. Over the last few decades, patients with an AITD have been younger and autoantibodies were less frequent despite typical histological changes of AID. The female predominance is thought to be due to hormonal, genetic, and environmental factors that regulate the innate and adaptive immune system. Estrogens induce type 2 cytokines, stimulating mainly CD4+ cells and antibody production, whereas androgens induce type 1 cytokines, stimulating CD8+ cells. The genetic background of gene activation and deactivation is considered a crucial mechanism in the development of AITD.

**Keywords:** Hashimoto's thyroiditis; Autoimmune endocrine diseases; Estrogens

## Introduction

Autoimmune diseases (AID) are caused by an inappropriate autoantibody production and immune complex formation against auto-antigens [1]. This phenomenon can be seen predominantly in women, who represent 4/5$^{th}$ of all AID-affected patients worldwide. Moreover, female gender appears to be a major risk factor for polyautoimmunity. This large difference in the incidence rate between men and women suggests a strong influence of sex hormones on the innate and adaptive immune system, not to mention genetic, lifestyle factors and environmental influences. The strong link between steroidal hormones and their impact on the immune system has been extensively investigated. However, not all results from in vitro studies or mouse models can be transferred to humans. For example, a study in rodents suggested that female animals rejected allografts faster than male animals [2], results that could not be proven in humans.

However, these data already suggest a link between the immune system and hormonal factors. Estrogen is known to stimulate the production of Th2-lymphcytes and, therefore, the neoformation of antibodies by type 2 cytokines, whereas androgen stimulates Th1-cells and reduces T-helper cells by producing Th1 cytokines [2]. Physiological cycles in hormone levels during menses, menopause, pregnancy, or hormonal substitution therapy can, therefore, either improve or cause an exacerbation of an AID [3]. Thus, sex hormones are also believed to play a major role in the development of autoimmune thyroid diseases (AITD).

In this review, we outline the influence of gender specific hormones on the development of AIDs, especially on AITD, and give an overview of genetic aberrations and environmental factors, which are believed to influence the neoformation of an AID.

## The Role of Sex Hormones on the Immune System and their Influence on Autoimmune Diseases

Approximately 5% of the world's population develop an AID, and nearly 80% are women [4]. This female predominance can reach a female to male ratio as high as 9:1 in common autoimmune diseases such as AITD, systemic lupus erythematosus (SLE), and Sjogren's Syndrom (SS) [5-7], and a ratio of 3:1 in multiple sclerosis (MS) and rheumatoid arthritis (RA) [8]. On the other hand, no female preponderance in patients with type-1 diabetes can be observed.

In iodine-replete areas of the world, the incidence of an AITD is higher than in iodine-deficient areas. Hashimoto's thyroiditis (HT) most commonly affects women between 45 and 65 years of age, with a female to male ratio of 10:1 [9,10]. The prevalence rate of spontaneous hypothyroidism ranges between 1-2%. A lower prevalence is seen in areas of iodine deficiency [11]. GD is 10 times more common in females compared to males, with an annual prevalence between 0.5-2% in iodine-replete regions [9]. Nevertheless, studies show slightly higher prevalence in iodine-deficient areas [11,12]. The frequency of thyroid dysfunction also varies significantly, depending on the ethnic group, showing a 10-fold lower incidence in black populations than in Caucasians [9].

The above-mentioned gender differences clearly seem to suggest the strong influence of sex hormones on the immune system, and studies have explored this issue to explain the influence on autoimmune diseases and the differences in the immune systems between genders [13]. Monitoring of patients with an autoimmune disease revealed that changes in hormone levels led to an improvement of symptoms or to an exacerbation of the disease, triggered by the innate and adaptive immune system [14]. This was due either to physiological hormonal changes during puberty, menses, menopause, and pregnancy, or to systemic hormonal therapy [3].

Steroid hormones have effects on the innate and adaptive immune system by binding to intracellular receptors, initiating the translocation of the formed complex to the cells' nucleus where it acts as a transcriptional complex [15,16].

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Estrogens function by forming a complex with estrogen receptors (ER), called ER-α and ER-β [17-19]. These receptors can be found not only on many different human organs, but also on immune cells, inducing or inhibiting different effects, depending on which receptor is stimulated. Estrogens stimulate the immune system to produce and activate T-helper cells 2 (Th2) as an adaptive response, and this leads to a higher production of antibodies by increased stimulation of B-cell lymphocytes due to the inhibition of B-cell apoptosis, such as activation and expansion of cells in the spleen [20,21]. The number of B2-lymphocytes depends strongly on estrogen levels, whereas B1-lymphocytes of the innate immune system remain unaffected. This can be observed after menopause, where the absolute number of B2-lymphocytes is lower than during the fertile period, whereas higher B2-lymphocyte levels can be observed during systemic hormonal therapy [22].

Other effects, such as the involution of the thymus, a reduction in the number of immature T-lymphocytes, and stimulation of various cytokines, have been attributed to the role of estrogens on the immune system [2]. Not surprisingly, those effects are accelerated during puberty and pregnancy where estrogen levels are known to be even higher.

Androgens, however, favor the stimulation of T-killer cells (CD8+) and T-helper 1 lymphocytes (Th1) [3,23]. Androgen receptors are also found on B-lymphocytes [24]. However, T- and B-cells also carry prolactin receptors, which demonstrate a stimulating effect on the immune system [3]. This hormonal preference toward either CD4+ or CD8+ cells explains the different CD4+ to CD8+ distribution between females and males [25]. The higher CD4+ cell count in women induces a stronger hormonal and cellular immune response and also precipitates higher antibody levels in females, and thus, could be a possible explanation for the female predominance of autoimmune diseases [2]. Studies on rodents, for example, have proven that female animals reject allografts faster than male animals [26].

For that reason, steroid hormones influence the progression of an autoimmune disease, by either improving the symptom load or causing exacerbation of the disease. This also depends on the Th1/Th2 balance, regulated by estrogens and androgens. When estrogen levels are high, a decrease of type 1 cytokines and an increase of type 2 cytokines can be observed. This process is characteristic of type 1 autoimmune diseases. A shift from a Th1 to a Th2 balance can also be observed in pregnant women with rheumatoid arthritis or multiple sclerosis, which in both cases leads to an improvement of the symptom load due to complex pregnancy-related alterations in immunological and hormonal levels in body fluids [3].

Type 2 autoimmune diseases improve when type 2 cytokines are low and type 1 cytokines are elevated. This can be seen in patients with decreased estrogen levels, for example, during the postpartum period or during therapy with aromatize inhibitors [2]. AITD belong to this group of autoimmune diseases.

## Autoimmune Thyroid Diseases and the Influence of Hormones

AITD is an acronym used to describe the pathophysiological process of auto-reactive immune cells, which can either cause thyroid gland hyperfunction or hypofunction.

Hashimoto thyroiditis (HT) is the most frequent autoimmune endocrine condition. It is characterized by the presence of lymphocytic infiltration of the thyroid gland and the presence of oncocytic changes in the follicular thyroid epithelium [27]. Projections estimate that it affects up to 10% of the general population, with an increasing incidence over the last few decades [28,29]. Notably, affected patients are now younger, the incidence in males has increased, and thyroid auto-antibodies have become less frequently positive [28]. In general, HT is associated with the presence of anti-thyroid antibodies—anti-thyroid peroxidase (anti-TPO), anti-thyroglobulin (anti-Tg), and/or TSH binding inhibitory immunoglobulin's (TBII)—which react with the TSH receptor [30,31], but are not necessarily always detectable. However, the amount of TPO-antigens is associated with disease activity [29]. By monitoring 790 euthyroid patients with at least one close relative with an AITD, Diez and Iglesias were able to show that TSH is a valuable parameter for predicting the spontaneous conversion to hypothyroidism [32].

Graves' disease is characterized by an over-stimulation of the TSH receptor by thyroid-stimulating immunoglobulin's (TSI) [29]. Symptoms of hyperthyroidism include palpitations, anxiety, sleeping disorders, hyperplasia, weight loss, and hyperhidrosis. In patients with a newly diagnosed GD, a change in Th1/Th2 balance can be observed, resulting in a shift towards higher Th2 cytokine production [33].

In a prospective study, Effraimidis et al. [34] reported that, in cases where a transition from euthyroidism to an AITD occurred, significantly more hypothyroid events during the post-partum period and more hyperthyroid cases during pregnancy were observed, which further underlines the effect of hormones on the immune system [30,34]. Moreover, these authors showed that the progression from normal thyroid function to an overt autoimmune hypothyroidism is a process that occurs over several years, whereas the progression from euthyroidism to autoimmune hyperthyroidism develops within a median duration of four months from the first symptoms until diagnosis [30,35]. Based on the extent of TSH and antibody abnormalities, the annual progression rate from subclinical to a manifest hypothyroidism can differ: (i) women with positive TPO-antibodies have a conversion rate of around 2% per year; (ii) women with elevated TSH have a conversion rate of about 3%; and (iii) women with positive TPO-antibodies and elevated TSH have a conversion rate of about 4% [36]. The clinical conversion rate of subclinical hyperthyroidism to overt hyperthyroidism reportedly varies between 1 – 5% per year [37–39]. In addition, studies by Amino et al. have shown higher rates of hyperthyroid AITD in the postpartum period [40].

Notably, the hypothyroid cases already had higher TSH and antibody levels, such as a lower FT4 at baseline, whereas only the prevalence of TPO-antibodies and Tg-antibodies were elevated in the hyperthyroid group, with normal TSH and FT4 at baseline [30].

There are controversial opinions about the effect of oral estrogen therapy on thyroid function, but few studies exist that describe a protective effect of hormonal substitution therapy on the development of hyperthyroidism [41,42]. In patients with HT, antibody levels did not differ from baseline in women who received oral estrogen therapy [43].

Nevertheless, substitution therapy with dehydroepiandrosterone (DHEA) has been proven to have positive effects on patients with polyautoimmunity [44]. Women with HT and premature ovarian failure (POF) notably had decreased levels of DHEA before treatment. Supplementation of DHEA over a time period of three months showed a significant decrease in TPO- and Tg-Ab of >30% in about 60% of patients [44].

## Other Hypotheses for the Development of Autoimmune Thyroid Disease

### Genetic factors

It is a well-accepted concept to view autoimmune thyroid

dysfunction as a complex disease, taking genetic and social factors into consideration. HLA-DR3, HLA-DQA1, CD40, CTLA4, and PTPN22 are a group of immune modulated genes associated with AITD; the polymorphism CTLA4 is associated with Hashimoto's disease and HLA-DR3 and DQA1, HLA-C, CTLA-4, CD40, PTPN22 and arginine at position 74 of the DRβ1 chain are associated with the highest risk to develop GD [29,45-47]. On the other hand, HLA-DRB1 has a protective effect on the development of hyperthyroidism [48]. Other disease-related alleles were associated with the thyroid genes, including TSHR and TG [45].

Nevertheless, the differences in prevalence and severity between genders cannot be simply explained by these mechanisms, indicating a possible influence of gonosomes.

### Changes in X chromosome activity and dosage

Studies have shown that the silenced Barr body in females is still partially active, and up to 15% of all genes on the X-chromosome can therefore be expressed by both chromosomes [49]. In some cases, skewed DNA or mutations can influence the activation of the second X-chromosome, a phenomenon which has been described more commonly in patients with an autoimmune disease, compared to controls [50,51]. This suggests that additional X-chromosome inactivation leads to silencing of a gene that protects against autoimmunity [52,53].

Observations of patients with inherent X-monosomy have reported an increased incidence of autoimmune disorders. Also, studies in patients with AITD, systemic sclerosis, and elderly patients have shown higher rates of X monosomy in peripheral T- and B-cells [3]. It is a matter of some controversy whether this X-chromosome monosomy causes a haploinsufficiency due to increased X-chromosome inactivation, and therefore, T-cells are not exposed to antigens, which are normally encoded by alleles on both X-chromosomes [54].

On the other hand, it has been observed that patients with karyotype 47XXY (Klinefelter syndrome) have a strong predilection for developing systemic lupus erythematosus (SLE) [55]. This seems to indicate that it is not only an over-inactivation of X-chromosomes, but also an over-activation of genes that causes autoimmune diseases [51]. This hypothesis was underlined by Scotfield et al. [56], who discovered that men with SLE had a 14-fold higher risk of underlying Klinefelter syndrome, compared to 46XY controls.

There is also evidence that genetic factors alone seem insufficient to induce AITD. This was proven by monozygotic twin studies, in which a concordance rate of 100% would be expected, which was not the case. In fact, genetic factors are estimated to account for approximately 70% of those who develop an AITD [57,58]. The other 30% could be attributable to environmental factors, such as infections, stress, smoking, and iodine intake [30]. With regard to hyperthyroidism, it is more commonly seen in regions with less iodine intake [11]. In iodine-replete areas, AITD-predominantly hypothyroidism-can be observed significantly more often, with an annual prevalence rate of 1 – 2% for HT and around 0.5 – 2% for GD [9,11,30].

### Microchimerism

The increasing incidence of Hashimoto's thyroiditis with parity led to the hypothesis that fetal microchimerism might play a role in the development of AITD. Microchimerism is defined as the presence of genetically distinct hematopoetic stem cells in another individual. Thus, fetal microchimerism describes the occurrence of fetal cells persisting in the maternal circulation [51]. It is plausible that the innate and adaptive immune system target these foreign cells, and therefore, induce the production of autoantibodies and trigger the pathogenesis of an autoimmune disease [3]. A study by Artlett et al. on the pathogenesis of SLE discovered that 46% of women with SLE in his study group had traces of Y-chromosomes in their circulation, significantly more than unaffected women, which were the result of prior pregnancies in which the fetus was male [59]. Interestingly, Y-chromosomes were also detected in nulliparous women. However, this could be explained by other possible sources of transmission, ranging from unrecognized pregnancy in which the fetus was male, an unrecognized male twin, a transfer from an older male sibling through the maternal circulation to the female twin, or even sexual intercourse [3,60].

There is also some evidence that the persistence of fetal cells in maternal blood and tissue contributes to the worsening or even development of autoimmune thyroid diseases. Renne et al. analyzed thyroid specimens of women with an AITD who had at least one forgone pregnancy in which the fetus was male, and found Y-chromosome cells in over 80% of women [61]. Based on this study, Greer reported that the number of parities correlated with the level of TPO-antibodies, implying a role of microchimerism in AITD [62].

### Influence of lifestyle factors

As studies have shown, the influence of lifestyle factors on AITD should not be ignored. Smoking habits over a longer time period have been proven to cause hyper functioning of the thyroid gland. However, if patients reported a history of excessive smoking, discontinuation can promote the production of TPO- and Tg-antibodies and the development of hypothyroidism [30,63].

According to some studies, stress evoked by traumatic life events also has an influence on the genesis of AITDs, especially linked to GD [64,65]. Nevertheless, production of autoantibodies in association with stress has not been proven [30].

There have been theories that hypothesized that dietary factors could also induce autoimmune diseases. Bhatia et al. have proven in *ad libitum*-fed mouse models that diets can profoundly influence the development of thyroiditis and also affect the severity of an AITD [66]. Certain dietary modifications could, therefore, lead to a decrease in severity, as well as facilitate therapy and alleviate symptoms.

Selenium (Se) is another possibility to influence the progression of an AITD. Supplementation in physiological levels of sodium selenite has shown to have an effect on thyroid echogenicity, antibody levels, and thyroid size. TPO-Ab and Tg-Ab can be significantly reduced by Se supplementation after a time period of 12 months, but TSH and FT4 levels are not modified by Se-therapy [67]. In children with HT, a daily dose of 50 μm of selenomethionine over three months led to a thyroid volume reduction of >30% in 35% of patients [68].

## Effects of Steroid Hormones on Other Common Autoimmune Diseases

### Rheumatoid arthritis

In patients with rheumatoid arthritis (RA), higher estrogen levels in the synovial fluid, as well as low androgen levels, are associated with disease exacerbation [69,70]. This is consistent with the observation that tumor necrosis factor alpha (TNF-α) blocks the conversion from androgens to estrogens in the synovial fluid by inhibiting aromatase [71]. Studies have also proven that men with RA have lower testosterone levels, confirming that androgens act as anti-inflammatory

hormones [70]. Interestingly, the disease activity in patients with RA improves during pregnancy and may worsen in the postpartum period or after menopause [3]. This could be explained by hormonal and immunological alterations during pregnancy, such as a change in the predominant Th1 response to a Th2 response, the influence of progesterone [72,73] and the decrease of pro-inflammatory cytokines, TNF-α and interleukin-12 by increased levels of cortisol, estrogens and vitamin D [3]. Furthermore, the shift from a Th1 to a Th2 response can be evaluated by elevated production of immunoglobulin and autoantibodies by stimulation of B-cells [3].

### Multiple sclerosis and systemic lupus erythematosus

Patients with multiple sclerosis (MS) also experience disease improvement during pregnancy. Conversely, elevated levels of estrogen and decreased levels of testosterone in men are associated with more severe damage to the brain tissue [74], again confirming the anti-inflammatory effect of androgens.

However, systemic lupus erythematosus (SLE) tends to worsen during pregnancy and improve after menopause [75,76]. Estrogens and prolactin act as important stimulators of the immune system by stimulating B-lymphocytes, and thus, the production of autoantibodies [3]. Orbach et al. [77] have reported that 22-33% of patients with SLE also have hyperprolactinemia, which leads to increased rates of kidney involvement in lupus patients [77,78]. Diminished hypoandrogenism in women can also induce SLE due to the lack of anti-inflammatory effects of androgens [79]. Likewise, men with low testosterone levels or elevated estrogen levels are more likely to have SLE [76]. Furthermore, a paper from Zandman-Goddard et al. reported that testosterone also has a suppressing function on anti-double-strained DNA (dsDNA) antibodies [76].

### Influence of pregnancy on autoimmune diseases

Pregnancies appear not to have an adverse effect on patients with Sjörgen syndrome (SS) or systemic sclerosis (SSc) [3]. Studies in rodents have shown that specific mouse models for SS, which included gonadectomy, had a worse outcome of the disease [80]. Interestingly, oral substitution of ethinylestradiol (EE) did not change the outcome in the mouse models. Therefore, Verheul et al. suggested that the protective role of androgens in patients with SS appears to be of more importance than normal estrogen itself [80]. Around 90% of patients with SS are women, which led Quintero et al. to summarize the published data about the difference in SS between genders [3]. This revealed that women are more likely to present with Raynaud's and also to produce more anti-Ro antibodies (an antibody, which, when positive in pregnant women with SLE, indicates the possibility of passing the disease to the child), and men carry a higher risk of lymphoma and a higher risk of neurological involvement during disease exacerbation [3,81]. Therefore, the risk of neonatal SLE is higher in patients with SS [82].

Studies that have focused on the hormonal influence on systemic sclerosis (SSc) presented interesting results, concluding that high prolactin and low dihydroepiandrosterone (DHEA) levels was concomitant with an increased severity of SSc and that estrogens induce a dysfunction of fibroblasts *in vitro* [83].

## Conclusion

The distribution of AITD between men and women shows a strong predilection, of approximately 80%, for the female gender. Over the past few decades, the incidence of AITD in young people has increased and the positive detection of autoantibodies has declined. This distribution is best explained by the hormonal differences between genders. Estrogens stimulate the production of type 2 cytokines, T-helper cells, and B-cells, and therefore, antibody production, and have an influence on the Th1:Th2-ratio whereas androgens induce CD8+ cells and proves to have a protective and anti-inflammatory effect.

Autoimmune diseases are correctly defined as multifactorial diseases, considering genetic factors and life styles. Both autosomes and gonosomes influence the extent of symptoms and the severity of autoimmune disorders. Inactivation or over-expression of specific alleles could lead to a silencing or activation of genes and directly influence auto-immunity. Lifestyle factors, such as smoking habits, iodine intake, and multiple pregnancies, must be considered as factors that may trigger AITDs and polyautoimmunity.

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