

Thyroid Autoimmunity and Infertility

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Abstract

Autoimmune thyroid disease (AITD) is one of the most common endocrinopathies and is more prevalent in women. The circulating thyroid antibodies and the hypothyroidism that often follows AITD have effects on many tissues. The endometrium and ovaries are not spared, and therefore this common morbidity might have an impact on fertility. Despite challenging data interpretation and contradictory results, a general takeaway from published studies is that there is a higher incidence of elevated levels of thyroid-stimulating hormone (TSH) and the presence of thyroid antibodies among infertile women. While a single specific and direct pathophysiological mechanism through which autoimmune thyroid disease causes infertility has not been identified, there are multiple gynecological comorbidities that might perpetuate infertility (endometriosis, premature ovarian failure, polycystic ovaries) and defective immunological functions (a shift to a proinflammatory Th1 response, increased levels of natural killer cells, cross-reactivity of antigens, etc.) that are affecting fertility. There is insufficient evidence suggesting that levothyroxine (LT4) treatment can help women suffering from AITD conceive and carry out a pregnancy.

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Introduction

The thyroid hormone plays an essential role in the growth, differentiation and development of virtually all tissues. It also impacts numerous metabolic pathways, making it a significant factor in maintaining metabolic homeostasis. The two forms of thyroid hormone, triiodothyronine (T₃), which is more potent, and thyroxine (T₄), which is more abundant, can have effects on many different cellular components (1). However, they mostly regulate the transcription of target genes by binding to their specific intranuclear receptors, found in several different isoforms (1, 2). Thyroid hormones also

affect the female reproductive system, which is why dysfunction of the thyroid gland can subsequently lead to disturbances of the menstrual cycle and fertility issues (2).

Thyroid dysfunction, which leads to changes in circulating thyroid hormone levels, manifests itself as either hyperthyroidism or hypothyroidism. Hypothyroidism is the more prevalent variant and is linked to thyroid autoimmunity. Autoimmune thyroid disease (AITD) is the most prevalent cause of hypothyroidism in women of reproductive age (3, 4). Elevated levels of thyroid autoantibodies, such as thyroid peroxidase autoantibodies (TPO-

Ab) and thyroglobulin autoantibodies (TG-Ab) induce chronic inflammation in the thyroid gland, which leads to the loss of functional tissue. Hypothyroidism can manifest itself with typical signs and symptoms such as fatigue, constipation, depression, thinning hair, cold intolerance, bradycardia, hoarseness, etc. It can also be subclinical (SCH), which is classically defined as an increase in thyroid-stimulating hormone (TSH) concentrations over the upper limit of normal range (4.5 – 5.0 mIU/L) with normal fT4 levels (5).

Infertility is defined as an inability to conceive after at least 12 months of continuous intercourse without the use of contraception. Its current prevalence among couples ranges between 10 – 15% and has not changed significantly over the past few decades (6 - 8). Because of the effects thyroid hormone has on the ovaries (e.g., maturation of oocytes) and endometrial tissue, it is believed that AITD might play a role in the pathogenesis of infertility. Therefore, this review aims to interpret data collected on this subject thus far and summarize published studies to assess the association between AITD and infertility.

Pathophysiological links between autoimmune thyroid disease and infertility

Since AITD is the most common endocrine disorder in women of reproductive age, its effects on fertility have been investigated extensively and in detail. Nevertheless, a clear pathophysiological link connecting the two morbidities has not been identified and available data suggesting the prevalence of women with both AITD and infertility varies from study to study. Furthermore, interpretation of data from published studies on this subject matter is challenging due to several reasons, mostly relating to study designs and their flaws – retrospective studies providing incomplete information, small sample sizes, measurements of different thyroid antibodies, different populations investigated (heterogeneity of ethnicities and geographical locations), etc. Variations in SCH definitions and TSH ranges

additionally contribute to the complexity of data interpretation.

The role of thyroid hormones

There is a clear connection between the thyroid gland and its hormones and the female reproductive system. Thyroid hormone receptors are expressed in the ovary and the endometrium. Furthermore, following egg fertilization, the thyroid hormone plays a role in the process of implantation and placentation (9). Generally, the proposed pathophysiological mechanisms contributing to infertility in women with AITD are either thyroid-dependent or thyroid-independent. Multiple studies have been conducted that aimed to establish the incidence of AITD in infertile women, as well as to connect AITD with certain morbidities affecting the female reproductive system. When observing the data collected and conclusions reached in each of those studies, it can be said that there is a significantly increased incidence of AITD in infertile women compared to controls (10 – 14). In a Danish study (10), conducted on 11,254 women, the conclusion reached was that higher TSH levels and higher TPO-Ab levels affect fertility. A study by Poppe et al. (11) demonstrated significantly higher levels of TSH in infertile subjects compared to controls (1.3 vs 1.1 mIU/L), however, TSH levels above or below the normal range were not more prevalent in infertile subjects (with fT4 levels within the normal range), indicating that women suffering from AITD might be affected by fertility issues even though they might seemingly be in a euthyroid state. In addition, women with AITD who are able to conceive are not without risk during pregnancy – a recent study among 10,990 patients, part of the FASTER (First and Second Trimester Evaluation of Risk) trial, shined a light on the connection between thyroid autoimmunity and pregnancy risks. It showed that there was an increased risk for preterm premature rupture of membranes when both TPO-Abs and TG-Abs were present in both the first and second trimester (15). On the other hand, there have been studies with different results and outcomes. A study by Abalovich et al. (16) observed a higher prevalence of SCH, but not

AITD, in 244 subjects consulting on infertility, providing an example of contradictory data making the interpretation difficult, as mentioned earlier. Another example is a study by Plowden et al. (17), part of the EAGeR (Effects of Aspirin in Gestation and Reproduction) trial. They found that there was no difference in the delay of pregnancy in women with TSH of at least 2.5 mIU/L or women with thyroid autoantibodies, compared with those with TSH under 2.5 mIU/L or without autoantibodies.

Couples undergoing ART (assisted reproductive technologies) treatments are a group of interest in this context. In a systematic review and meta-analysis of articles describing ART outcomes in the context of AITD, Busnelli et al. (18) concluded that AITD does not impact the outcome of ART treatments (IVF, ICSI) in terms of the number of oocytes retrieved and the likelihood of fertilization, implantation and clinical pregnancy. However, a wider implication similar to the one in the FASTER trial was made, that the presence of thyroid autoantibodies might have harmful effects on the course of the pregnancy, with an increased risk of miscarriage and decreased chance of live birth.

Poppe et al. also showed that elevated levels of TPO-Abs were higher in infertile subjects, while the highest prevalence of positive antibodies among all subgroups of infertility was observed with endometriosis (11). It is a benign condition also linked to altered immune conditions, where endometrial tissue appears outside of the uterus, most commonly in the pelvis, inducing a chronic inflammation (19). Endometriosis in the context of AITD has been investigated, but the results have been contradictory. While the study by Kim et al. and two other studies (16, 20) reported a higher prevalence of endometriosis in women with AITD versus controls, a study by Petta et al. (21) showed that the prevalence of AITD was similar in a group of subjects with endometriosis and in a control group. A more recent study identified anti-laminin-111 autoantibodies as having a potentially major role in the pathogenesis of endometriosis-associated infertility (22). Outside of the endometrium, research has been conducted that showed that the source of fertility issues

among women with AITD might be the ovary. Monteleone et al. (23) hypothesized that the critical source of female infertility due to AITD was in the ovarian follicle itself. Their study showed that TG-Abs and TPO-Abs were measurable in all samples of follicular fluid and serum drawn from subjects with AITD, while they were absent in controls. Furthermore, all subjects with AITD were in a euthyroid state, which suggested that the absence of progression of thyroid hormone status towards hypothyroidism due to AITD does not exclude issues with fertility. Expanding on that theory, Kelkar, et al. (24) demonstrated that human anti-zona pellucida antigens reacted to murine thyroid tissue, therefore suggesting their similarity in antigens, which suggests, in turn, that zona pellucida may be affected by thyroid autoantibodies. A very common ovarian disorder that may be connected to AITD is polycystic ovary syndrome (PCOS). Thought to be one of the most common endocrinopathies in women (6.5 - 8 %), it is a complex disease that is multifactorial in its etiology (genetics, obesity, sedentary lifestyle, intrauterine androgen exposure, etc.) It is characterized by hyperandrogenism, increased LH-to-FSH ratio, poor glucose tolerance and hyperinsulinemia and over long-term, it can cause infertility and carries an increased risk for cardiovascular diseases, malignancies, type 2 diabetes mellitus and psychiatric disorders (25). A threefold higher prevalence of AITD in subjects with PCOS was demonstrated in a study on 175 subjects, compared to 168 controls, which was, according to the authors of the study, partly correlated with an increased estrogen-to-progesterone ratio (26). Further showing that the ovary is a key organ when investigating infertility in women with AITD, in a group of 244 subjects consulting on infertility, AITD prevalence reached statistical significance only in those with premature ovarian failure, which the authors believed to be the result of a shared autoimmune etiology between the two morbidities (16).

Thyroid hormone - independent immunological mechanisms

Independently of the thyroid, multiple immunological mechanisms have been described as potential contributors to impaired fertility and fecundity in individuals with AITD. A dominant Th1 immune response promotes inflammation evoked through cell-mediated mechanisms, which is harmful for pregnancy. Th2 cell subsets, on the other hand, regulate and control the inflammation and tissue injury implemented by Th1 reactions, as well as protect against autoimmune damage (27). The regulatory mechanisms and balance of Th1 and Th2 cells are impaired in women with fertility and fecundity issues, with multiple studies confirming a distinct Th1 bias (28, 29), even in the endometrial tissue itself (30). A study by Kwak-Kim et al. (30) showed significantly higher Th1/Th2 ratios of TNF- α /IL-4 and TNF- α /IL-10 in both women with recurrent pregnancy losses and women with multiple implantation failures, while IFN- γ /IL-4, IFN- γ /IL-10 were additionally higher in women with recurrent pregnancy losses. Links between impaired T-cell immunity and thyroid autoimmunity have recently been made. TNF- α /IL-10 T-cell ratios were significantly increased in women with AITD (12), thus showing that thyroid antibodies can serve as markers for abnormal immunity, which is an important factor in impaired fertility. When observing abnormal B-cell function and its potential contribution to infertility in women with AITD, a clear connection between the presence of certain non-organ specific antibodies (NOSAs) and infertile women with AITD has not been proven yet. Kim et al. (12) reported that women with AITD did not have a higher prevalence of antiphospholipid antibodies (APAs), but did have a higher prevalence of NOSAs than women with no thyroid antibodies. One study suggested that NOSAs, in addition to TPO-Abs and TG-Abs, may serve as independent risk markers for repeated pregnancy loss in women with AITD, but no such statement was made for unexplained infertility (31). Aggravation of infertility in women with concurrent thyroid autoimmunity and other systemic autoimmune diseases has also been

described, specifically systemic lupus erythematosus (SLE) and Sjogren's disease (32, 33). In addition to effects T-cells and B-cells might have on the reproductive system, hyperactive and overproduced natural killer (NK) cells can also infiltrate the endometrial tissue and potentially alter the body's immune response, thus affecting fertility (34). TSH has been shown to have a stimulatory effect on NK cells (35) and studies have described increased levels and cytotoxicity of NK cells in AITD (12, 36 - 38). Therefore, NK cells are an additional potential contributor in the pathogenesis of infertility in women with AITD.

Autoimmune thyroid disease, infertility and nutritional deficiencies

Yet another contributor linked to both AITD and infertility is vitamin D deficiency. As an omnipresent protein, vitamin D plays a key role in the calcium and phosphate metabolism. It has also been identified as a beneficial factor in many morbidities, including autoimmune diseases, cardiovascular diseases and malignancies (39). Vitamin D deficiency (< 10 ng/ml), on the other hand, is, among other things, linked to both AITD and infertility. Kivity et al. (40) found that vitamin D deficiency was significantly more prevalent in subjects with AITD than in controls. Furthermore, vitamin D deficiency correlated to the presence of thyroid antibodies and abnormal thyroid function. In the context of fertility, vitamin D has been identified as mandatory for reproductive function in the murine model (41). Vitamin D deficient rats demonstrate, among other behavioral patterns and physiological changes affecting their reproductive systems, a diminished fertility capacity (42, 43). In humans, the vitamin D receptor (VDR) is expressed in the ovary, the endometrium and even the placenta. Furthermore, vitamin D is involved in better IVF outcomes, it plays a role in PCOS (deficiency is linked to obesity and metabolic morbidities) and it also affects the regularity of menstrual cycles and influences the production of sex hormones (44). With all that in mind, it is clear how vitamin D deficiency can contribute to both AITD and infertility.

There are numerous other microelements and vitamins that play a role in the physiology of thyroid function, so their deficiency, overload or perhaps impaired functionality might also play a role in the development of thyroid autoimmunity and be linked to infertility. These effects haven't been extensively researched, but we know that microelements such as magnesium, iodine, selenium and zinc, as well as other molecules such as riboflavin, vitamin C and coenzyme Q10 have been associated with different forms of thyroid disease. Magnesium deficiency is the basis of mitochondrial dysfunction which can explain changes associated with thyroid dysfunction (45). An iodine overload increases the risk for an immune reaction, which additionally increases with selenium (Se) deficiency (46). Se is a necessary trace mineral because of its anti-inflammatory and antioxidant properties. While a study by Moncayo et al. (47) did not show a correlation between Se deficiency and thyroid autoantibodies, there have been several studies that showed lower Se levels in patients with Hashimoto thyroiditis (48, 49). Se levels were significantly decreased in patients with subacute or silent thyroiditis (47). However, Se supplementation during pregnancy and postpartum reduces inflammation in the thyroid and lowers the risk of hypothyroidism (50), while it decreases autoantibody levels and improves the ultrasound structure of the thyroid in patients with Hashimoto's thyroiditis (51). Antioxidant enzymes also depend on the availability of copper and zinc. A study by Stolinska et al. (52) did not confirm, however, that zinc supplementation in patients with normal zinc levels can affect thyroid metabolism. While riboflavin, vitamin C and coenzyme Q10 have been researched in the context of thyroid dysfunction, there is insufficient data to show a link between deficiency, overload or dysfunction of those antioxidants with AITD, especially in correlation with infertility (53, 54).

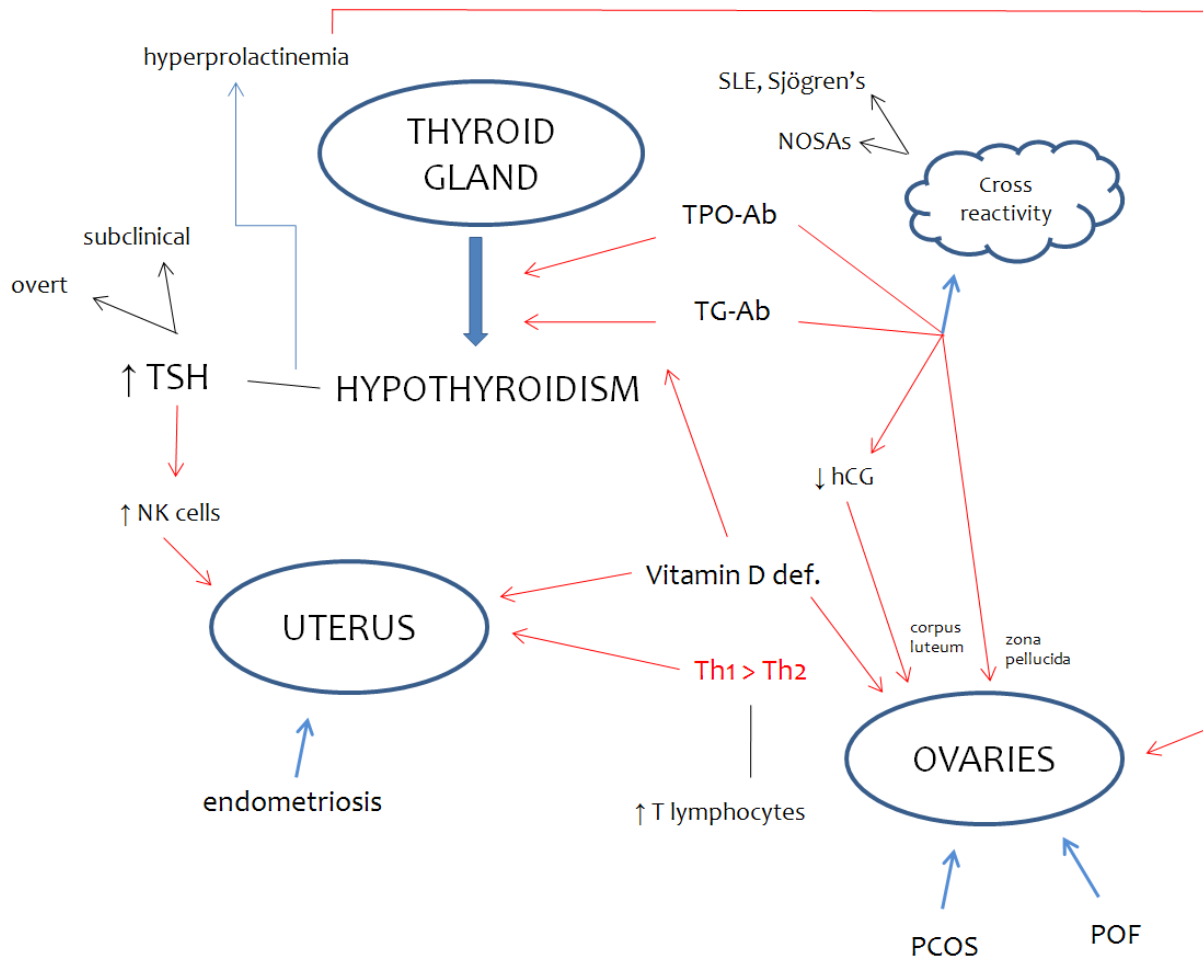
Hypothyroidism has also been associated with hyperprolactinemia - elevated levels of thyrotropin-releasing hormone (TRH) and TSH cause increased secretion of prolactin. Studies have shown that women of fertile age are most

commonly affected by hyperprolactinemia as well as its presence in SCH, showing yet another consequence of this silent morbidity (55, 56). It can also impair fertility, since elevated prolactin levels and the pulsatile GnRH secretion may lead to a delayed LH response and affect corpus luteum function (56 - 58).

Finally, thyroid antibodies could also inhibit the activity of human chorionic gonadotropin (hCG) on the corpus luteum due to cross-reactivity that has been observed between hCG and TSH. The corpus luteum plays a key role in supporting and maintaining a pregnancy in the first trimester through progesterone and estrogen secretion and is largely dependable on hCG. This pathophysiological mechanism doesn't cause infertility per se, but it may impair fecundity, since TSH receptor blocking antibodies could also block luteinizing hormone (LH) and hCG receptors, causing a decrease in steroid hormone production, resulting in spontaneous miscarriages (59).

The American Thyroid Association published Guidelines for the Diagnosis and Management of Thyroid Disease During Pregnancy and the Postpartum in 2017. They stated that evaluation of serum TSH concentration is recommended for all women seeking care for infertility. Additionally, they recommended levothyroxine (LT4) treatment for infertile women with overt hypothyroidism who desire pregnancy. However, no such recommendation was made for women suffering from AITD and euthyroid women due to insufficient evidence to determine whether or not LT4 therapy actually improves fertility in such cases. The only case where administration of low-dose LT4 was to be considered was in infertile women suffering from SCH, but were thyroid antibody-negative (60). There are several examples of conflicting data and evidence that is insufficiently strong to suggest LT4 therapy improves the chances of achieving pregnancy. Negro et al. (61) investigated the effects of LT4 treatment in TPO-Ab positive women undergoing assisted reproduction technologies (ART) and found that the pregnancy rate was not affected by treatment with LT4. In the study by Abalovich et

Figure 1. Clinical entities and pathophysiological mechanisms linking female infertility with AITD. (TSH – thyroid-stimulating hormone; SLE – systemic lupus erythematosus; NOSAs – non-organ specific antibodies; hCG – human chorionic gonadotropin; NK – natural killer; PCOS – polycystic ovary syndrome; POF – premature ovarian failure)



al (16), however, LT₄ was prescribed to 34 subjects with SCH and after 6 months of follow-up, 44.1% achieved pregnancy.

Conclusion

AITD and infertility are two morbidities that have separately been widely investigated and detailed pathophysiological mechanisms for both entities have been described. However, there is a wide variety of overlapping factors that make it difficult to distinguish how and if AITD and infertility are interconnected. All the factors described in this review (abnormal lymphocyte production, a Th1 immune response bias, vitamin D deficiency, etc.) (Figure 1.) could be contributing to infertility as well as AITD to some extent, but the possibility remains that one or a

few of them might have a more significant impact on the pathogenesis. Conflicting data and different study designs make shedding light on the interconnectedness of these morbidities difficult. There is even no consensus on the exact organ of origin of infertility caused by thyroid autoimmunity, with the uterus and the ovary both potentially playing roles and being targeted by the thyroid antibodies.

Based on the findings of the studies, there is still an insufficient amount of evidence that would suggest levothyroxine treatment is a viable treatment option for infertile women suffering from AITD. Recommendations from 2015 have only been made for infertile women suffering from SCH, but who are thyroid antibody-negative. Even in those cases, however, LT₄ treatment should simply be "considered". That is

why it is crucial to continue researching these two entities to potentially increase the chances for women to conceive and carry out a healthy pregnancy.

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