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Review

Contemporary view and clinical implications of thyroid autoimmunity interactions in female fertility, reproduction and pregnancy

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Abstract

Thyroid autoimmunity (TAI) is known to influence female reproductive function and has been identified in 13–19% of infertile women, particularly in those with recurrent miscarriage, polycystic ovary syndrome (PCOS), diminished ovarian reserve, reduced embryo quality, or unexplained infertility. This review examines the relationship between TAI, including subclinical and overt hypothyroidism, as well as postpartum thyroiditis (PT), and female reproductive health, emphasizing the role of TAI in female subfertility. This narrative literature review draws on key medical databases to analyze recent and available evidence-based studies exploring the influence of TAI on ovarian function, fertility and pregnancy. TAI, even in its asymptomatic or subclinical forms, may impair fertility through direct ovarian mechanisms and immune-mediated pathways. Thyroid antibodies are associated with unexplained infertility and idiopathic low ovarian reserve that might be linked to one another. PT presents an additional challenge when pregnancy is followed by thyroid dysfunction, particularly in TPOAb-positive women. TAI should be considered in the diagnostic evaluation of subfertile women, especially those with unexplained subfertility or pregnancy loss/termination. Monitoring and individualized LT-4 therapy may improve reproductive outcomes and reduce pregnancy complications. Further research is needed to clarify the immune mechanisms linking TAI and reproductive failure.

Keywords: thyroid autoimmunity, subclinical hypothyroidism, female infertility, thyroid peroxidase antibodies (TPOAb), reduced ovarian reserve, unexplained infertility, postpartum thyroiditis, thyroid dysfunction in pregnancy

Introduction

This bibliographic review focuses on thyroid autoimmunity (TAI), with a particular emphasis on autoimmune thyroiditis (AT), also known as Hashimoto's thyroiditis (HT), as the primary subject of analysis. AT refers to chronic thyroid inflammation that was first documented over a hundred years ago. Currently, AT is acknowledged as the most widespread autoimmune condition [1], the most frequently occurring endocrine disorder [2], and the primary global cause of hypothyroidism [3]. Notably, up to 30% of individuals with

TAI are expected to develop hypothyroidism [4]. This disease shows a strong gender bias, being 4 to 10 times more common in women than in men [5].

In women of reproductive age, the prevalence of subclinical hypothyroidism (SH) ranges from 4 to 10%, compared to 2 to 4% for clinical hypothyroidism [6]. Also, TPOAb are present in 8–14% of this population [7], placing them at elevated risk for developing hypothyroidism compared to antibody-negative individuals.

Recent studies have reported that the prevalence of TAI among infertile women ranges from 13% to 19% [8]. Furthermore, secondary analysis from two multicenter randomized controlled studies indicated that 8.6% of infertile women had detectable levels of TPOAb [9].

Moreover, women with thyroid antibody positivity have been shown to experience higher rates of unexplained subfertility, recurrent pregnancy loss, PCOS, lower antral follicle counts, diminished ovarian reserve, and compromised embryo quality [9–19].

The etiopathogenesis of TAI remains only partially clarified, despite a long history of investigation. Nevertheless, hypothyroid TAI is acknowledged as an important negative influence on women's reproductive health. Even when asymptomatic or subclinical, TAI may persist undetected for years, leading to immune dysfunction and a breakdown in systemic and local immune tolerance, which may in turn impair implantation success [20–24].

This review focuses on the complex interplay between hormonal, immunological, and reproductive pathways in women affected by TAI, highlighting the specific challenges this condition poses for subfertile and pregnant women. A better understanding of these interconnections may help assess the necessity of routine screening and contribute to improved fertility outcomes, thereby enhancing maternal and fetal health.

This work aims to examine how TAI affects female reproductive health, with a specific focus on its role in subfertility and pregnancy complications. It also seeks to identify potential novel areas that can link TAI and female fertility, which can be considered for future research.

Material and methods

Study design

Although not conducted as a formal systematic review, this work was guided by selected principles of the PRISMA reporting guidelines [25]. The following databases were searched for the last 5 years: MEDLINE (PubMed), Embase, Scopus, Lilacs, Web of Science, Clinical Trials, and SciELO. The keywords used were: thyroid autoimmunity OR autoimmune thyroiditis OR thyroid autoimmune dysfunction, Hashimoto disease, subfertility AND thyroid autoimmunity, female reproductive health AND thyroid autoimmunity, pregnancy risks AND thyroid autoimmunity, ovarian reserve AND thyroid autoimmunity, as well as similar terms. Articles were selected based on titles and abstracts.

Data collection

Inclusion criteria were as follows: 1) original research articles, reviews, and meta-analyses; 2) studies involving women of reproductive age with TAI in the context of fertility or subfertility and pregnancy risks; 3) availability of full text. This review did not address long-term maternal and fetal outcomes associated with TAI during pregnancy. In addition, studies lacking a specific focus on the clinical or biological interaction between TAI and female fertility were excluded. There were no limitations on publication date or language.

Statistical analysis

As this is a narrative review, we did not carry out formal bias assessments or statistical synthesis. Still, we ensured transparency and reproducibility in the selection and analysis of the literature.

Results

TAI is a major cause of hypothyroidism, involving an erroneous immune response against thyroid tissue that progressively impairs its function. While early-stage AT is often clinically silent, its progression can contribute to notable endocrine and metabolic dysregulation. Accurate identification of these phases plays a critical role in diagnosis and clinical decision-making, particularly in managing reproductive health in women. TAI typically progresses from a euthyroid phase to subclinical and overt hypothyroidism, sometimes preceded by a transient thyrotoxic phase, and may eventually result in thyroid atrophy.

Subclinical hypothyroid phase and fertility, reproduction and pregnancy issues

This phase is characterized by a mild increase in thyroid-stimulating hormone (TSH), accompanied by

normal free T3 and T4 levels, as the thyroid gland compensates for early functional decline. Symptoms, when present, are often mild and nonspecific, including fatigue, dry skin, or minimal weight gain.

Abalovich *et al*. studied the potential link between SH and unexplained subfertility in a study involving 40 women diagnosed with SH and 359 control participants. Their findings demonstrated a significant association between SH and unexplained subfertility. Notably, the study revealed elevated rates of SH among women diagnosed with premature ovarian failure (40.0%), tubal abnormalities (18.2%), and ovulatory dysfunction (15.4%), all of which were significantly higher than in the control group ($p<0.005$ for all comparisons) [26]. Despite the significant findings, the study did not provide insights into the pathogenesis underlying the observed association.

Bals-Pratsch *et al*. conducted one of the first studies aimed at uncovering hormonal interactions in women with TAI. However, its interpretive power was limited by the relatively small number of patients and controls included. The study did not identify any alterations in the pulsatile secretion of key hormones—prolactin, TSH, LH, and cortisol —between women with SH and those in the control group, suggesting preserved neuroendocrine rhythmicity. Additionally, even after treatment with levothyroxine (L-T4), the manner in which these hormones were released remained unchanged [27].

In the context of pregnancy, a major study assessing miscarriage risk in pregnancy found no significant difference between women with SH (n=240) and controls (n=10,518) (OR 0.69, 95% CI 0.10–5.0), reflecting a lack of association [28]. This conclusion was reinforced by a later investigation, which, despite being based on limited observational data, also failed to support any connection between SH and recurrent pregnancy loss [29].

In continuation, another meta-analysis demonstrated a significant association between SH and an elevated risk of preeclampsia when compared to women with normal thyroid function (OR 1.7, 95% CI 1.1–2.6) [30].

On the subject of levothyroxine treatment and pregnancy with SH, a meta-analysis of three high-quality RCTs suggested that L-T4 treatment could improve pregnancy success rates in women with SH undergoing assisted reproduction (ART), highlighting its potential role in fertility care [31]. While clinical pregnancy rates did not significantly improve (RR 1.75; 95% CI: 0.90–3.38), L-T4 treatment was associated with a higher delivery rate (RR 2.76; 95% CI: 1.20–6.44) [31]. Later, another meta-analysis, which included seven cohort studies and six randomized controlled trials involving women undergoing ART, yielded similar results. It was found that L-T4 treatment in cases of SH was associated with a 17% reduction in the risk of pregnancy loss (95% CI: 0.72–0.97). However, the results showed variability due to differences in the timing of treatment initiation and the TSH thresholds applied across studies [32].

On the other hand, two randomized controlled trials conducted in the United States enrolled 677 pregnant women diagnosed with SH (TSH≥4 mIU/L and normal free T4) and 526 women with hypothyroxinemia (free T4<0.86 ng/dL). Participants were randomly assigned to receive either L-T4 or a placebo, with treatment beginning at a median gestational age of 16.7 weeks. Treatment with LT-4 for SH had no significant impact on pregnancy outcomes, including rates of preterm delivery, gestational hypertension, preeclampsia, gestational diabetes, stillbirth, miscarriage, low birth weight, or neonatal respiratory distress syndrome [33, 34].

In continuation, another recent paper by authors suggests using a TSH threshold of >4.5 mIU/L to initiate LT-4 supplementation in women planning pregnancy. Once pregnant, free T4 may serve as a more reliable marker for monitoring thyroid function, which is a new perspective on the matter [35].

Interestingly, a recent study investigated predictors of thyroid function changes during pregnancy in women with TAI. Although the findings were focused on the euthyroid group of women, they may also be relevant to women with SH. The study identified maternal age, body mass index (BMI), parity and smoking as statistically significant risk factors for the development of thyroid dysfunction during gestation. However, due to the relatively small absolute risk differences observed, these variables are unlikely to meaningfully improve the efficiency of screening in this population. This is despite the fact that international guidelines continue to recommend targeted screening approaches for detecting gestational thyroid disorders, including SH [36].

Overt hypothyroid phase and fertility, reproduction and pregnancy issues

In the state of overt hypothyroidism, thyroid hormone production is markedly diminished, typically resulting in elevated serum TSH and decreased free T4 levels, with free T3 levels also potentially reduced. Clinically, this condition is characterized by symptoms such as significant fatigue, cold intolerance, hair thinning, constipation, depressive mood, and a general slowing of metabolic processes.

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The influence of hypothyroidism on fertility is multifactorial, involving both direct hormonal imbalances and indirect metabolic and/or systemic effects.

Thyroid hormones are believed to contribute directly to the regulation of ovarian function under normal physiological conditions. Notably, TSH receptors and thyroid hormone receptors (TR-α1 and TR-β1) are expressed in the ovarian surface epithelium as well as in oocytes within primordial, primary, and secondary follicles [37, 38]. Studies in animal models suggest that thyroid hormones work in collaboration with follicle-stimulating hormone (FSH) to enhance granulosa cell functions, including morphological differentiation, the formation of LH/hCG receptors, and the activation of 3β-hydroxysteroid dehydrogenase and aromatase [39]. As a result, thyroid dysfunction can interfere with these direct mechanisms and affect ovarian function (Figure 1).

Hypothyroidism also exerts indirect effects by disrupting the hypothalamic-pituitary-ovarian axis, reducing SHBG production, and thereby elevating circulating levels of unbound testosterone and estradiol. Additionally, low thyroid function also slows the breakdown of certain hormones, such as androstenedione and estrone, which contributes to the hormonal imbalance. High levels of thyrotropin-releasing hormone (TRH), typical in hypothyroidism, can cause increased prolactin and a weaker or slower luteinizing hormone (LH) response when triggered by gonadotropin-releasing hormone (GnRH) (Figure 2). These hormonal disruptions do not just interfere with cycles- they directly undermine fertility. Nearly a quarter of women with hypothyroidism report menstrual irregularities, with oligomenorrhea being particularly common [40–42].

A study by N. Oki *et al.* provided evidence supporting the role of thyroid hormones, especially T3, in modulating both placental and endometrial function, which are essential for successful implantation and early embryonic development. Crucially, T3 enhances the ability of extravillous trophoblasts to penetrate the uterine lining by stimulating integrins and matrix metalloproteinases (MMPs), both of which are essential for stable placental implantation and the establishment of maternal-fetal interface function. Additionally, T3 enhances the endocrine activity of differentiated trophoblasts, thereby contributing to the hormonal environment necessary for maintaining early pregnancy. This underscores the clinical importance of maintaining optimal thyroid function to prevent potential reproductive impairments [43].

Even in mild hypothyroidism, where conception may still take place, the risk of miscarriage, stillbirth, or preterm birth is significantly elevated [44]. Restoring thyroid function through L-T4 administration

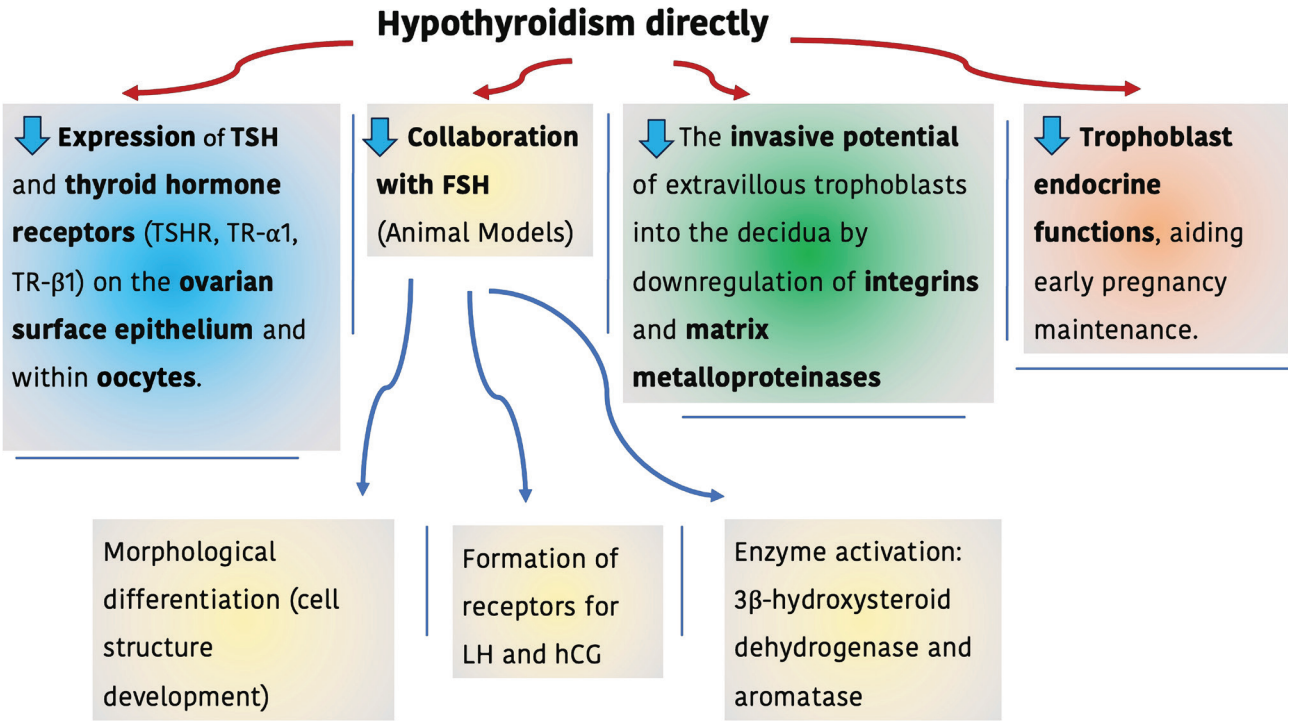

Figure 1: Direct effects of hypothyroidism. TSH – thyroid-stimulating hormone; TSHR – thyroid-stimulating hormone receptor; TR-α1 – thyroid hormone receptor Alpha-1; TR-β1 – thyroid hormone receptor Beta-1; FSH – follicle-stimulating hormone; LH – luteinizing hormone; hCG – human chorionic gonadotropin.

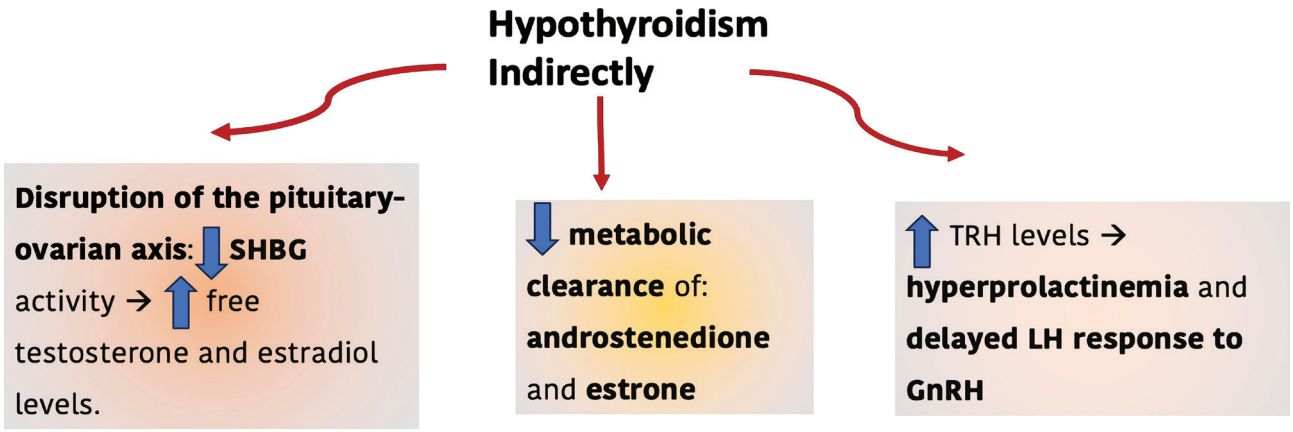

Figure 2: Indirect effects of hypothyroidism. SHBG – sex hormone-binding globulin; TRH – thyrotropin-releasing hormone; LH – luteinizing hormone; GnRH – gonadotropin-releasing hormone.

addresses several pathophysiological disruptions, notably by stabilizing menstrual rhythms, enhancing ovulatory capacity, and correcting the endocrine and metabolic consequences of hypothyroidism [45]. Achieving euthyroidism is particularly crucial in infertile women prior to initiating ART procedures.

In a study conducted by Negro *et al.*, several pregnancy outcomes associated with hypothyroidism were evaluated. The findings indicated no statistically significant associations between hypothyroidism and preeclampsia (OR 1.52, 95% CI 0.36–6.5), gestational diabetes mellitus (GDM) (OR 2.3, 95% CI 0.67–7.5), or preterm labor (OR 2.6, 95% CI 0.91–7.7). However, a notable association was found with placental abruption, where hypothyroid patients demonstrated an increased risk (OR 10.7, 95% CI 1.2–94). Importantly, women identified as hypothyroid during initial screening were started on LT-4, with dosage adjusted according to trimester-specific reference ranges [46].

Although the study by Negro *et al.* did not demonstrate significant associations with preeclampsia, the observed increased risk of placental abruption can often be the consequence of preeclampsia. Regarding this, the recent analysis of two large Danish pregnancy cohorts clarified that maternal hypothyroidism is linked to a heightened risk of preeclampsia, and the degree of thyroid dysfunction played a significant role. Conversely, TAI alone did not appear to be a risk factor for the condition, according to the results of this research [47].

Thyroid antibodies positivity and fertility, reproduction and pregnancy issues

Numerous studies have examined the relationship between TAI and infertility by assessing levels of TPOAb and TgAb.

Poppe and Glinoer's meta-analysis evaluated data from eight studies assessing the link between thyroid antibody-positive women and those with infertility. Only two of the eight studies demonstrated statistically significant differences between the two groups. Most studies exhibited considerable heterogeneity in case and control group selection, as well as in the specific thyroid antibodies assessed. Moreover, most studies were retrospective in design, introducing potential biases that may have affected the validity of the findings. Some studies concentrated solely on the relationship between TAI and specific infertility etiologies, thereby introducing bias due to the limited scope of their investigation. Nevertheless, when data from all included studies were aggregated, the calculated average relative risk revealed a strong and statistically significant association between the presence of antithyroid antibodies and infertility [48]. Altogether, the results suggest that in women with infertility, an immune system issue, though not yet fully understood, might be part of the problem.

Later, Van den Boogaard *et al.* analyzed four studies on thyroid antibodies and unexplained subfertility, involving 334 women with antibody-positive results and 1,679 controls. The odds of unexplained subfertility were significantly higher in the antibody-positive group (OR, 1.47; 95% CI, 1.06–2.02) [10]. Unlike the earlier analysis by Poppe and Glinoer, this study showed minimal heterogeneity, suggesting more consistent and reliable findings.

Interestingly, Romitti and colleagues reviewed data from 13 studies and found that women with PCOS had a significantly higher likelihood of developing TAI than women without PCOS, with an odds ratio of 3.27 [49].

Also, selenium deficiency was linked to indicators of AT, such as a higher rate of positive TPOAb (13.3% in selenium-deficient individuals *versus* 4.6% in those

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with optimal levels, P=0.031) and greater thyroid tissue irregularity seen on ultrasound (33.3% in the deficient group *vs*. 14.6% suboptimal and 17.3% optimal, P=0.042). Additionally, severe preeclampsia occurred more frequently among women who did not take selenium supplements, especially in twin pregnancies [50].

In a groundbreaking study, Monteleone *et al*. provided the first evidence of antithyroid antibodies (TgAb and TPOAb) within the follicular fluid of women with TAI undergoing oocyte retrieval. The analysis revealed strong positive correlations between serum and follicular fluid antibody levels (R=0.95 for TgAb and R=0.99 for TPOAb; P<0.05), with follicular fluid concentrations approximately 50% lower than those in serum [51]. Importantly, all women maintained a euthyroid status during the study.

While Monteleone *et al*. proposed that antithyroid antibodies may pass through the perifollicular vascular network and exert antibody-mediated cytotoxic effects on developing follicles, this remains a hypothesis without direct evidence. Given the lack of known thyroid-specific antigens in ovarian tissue, it is plausible that these antibodies act more as bystanders within the follicular fluid. Nonetheless, systemic immune dysregulation associated with TAI may still influence oocyte quality through indirect pathways such as inflammatory mediators or oxidative stress.

Vissenberg *et al*. attempted to clarify the pathophysiological role of antithyroid antibodies in reproduction, summarizing mechanisms by which TPOAb may negatively affect folliculogenesis, spermatogenesis, fertilization rates, embryo quality, and pregnancy outcomes. These effects are thought to result from immune-mediated inflammation and disrupted cytokine signaling. However, the supporting evidence remains limited, relying mostly on small human studies and animal models, making these mechanisms hypothetical rather than confirmed [52].

In one meta-analysis, a significantly higher prevalence of TPOAb positivity was reported among women with diminished ovarian reserve or premature ovarian insufficiency (POI) (OR: 2.26, 95% CI: 1.31–3.92, p=0.004). Interestingly, TgAb positivity did not show a similar trend [53]. By analyzing data from 30 studies, the authors concluded that reproductive-aged women with Hashimoto's thyroiditis, regardless of whether they were hypothyroid or euthyroid, tended to have lower levels of anti-Müllerian hormone (AMH) and a reduced antral follicle count (AFC), suggesting a negative impact of TAI on ovarian reserve. However, an important limitation of this meta-analysis was the absence of a dedicated subgroup analysis for euthyroid women, which left open questions.

This gap was later addressed in a large retrospective study by Li Z., which included 4,302 euthyroid women. The findings demonstrated that TAI was associated with an increased risk of POI only in those with TSH levels exceeding 2.5 µIU/ml. No such association was observed in women with TSH levels at or below this threshold [54]. These results suggest that even in the absence of overt thyroid dysfunction, a subtle elevation in TSH may act as a mediator between TAI and compromised ovarian function.

One particular study included in the Li F. meta-analysis conducted by Chen *et al*. provides additional nuance to this discussion [53, 55]. Among 1,044 infertile women, no direct association was found between AMH levels and TSH, TPOAb, or TgAb when looking at the entire cohort. However, after excluding individuals with known causes of diminished ovarian reserve, the researchers observed a significantly higher rate of TPOAb positivity in women with idiopathic low reserve [55]. This finding suggests that, in the absence of other explanatory factors, TAI, specifically TPOAb positivity, may play a contributory role in otherwise unexplained cases of reduced ovarian function and will be further discussed in the following section [56].

Another review indicated that TAI serves as a marker of generalized immune dysregulation, affecting critical reproductive stages, including fertilization, implantation, and pregnancy maintenance (Figure 3). The described mechanisms involved both thyroid-specific and non-organ-specific antibodies, contributing to impaired oocyte quality and implantation, as well as dysregulated activation of T cells and natural killer (NK) cells [57]. The analysis of the included studies revealed that thyroid antibodies may contribute to a localized pro-inflammatory environment, disrupting both the ovarian follicular ambient and endometrial receptivity. Additionally, non-organ-specific antibodies, such as antiphospholipid antibodies, can further compromise implantation by interfering with essential vascular and cellular mechanisms required for successful early pregnancy [57]. In the context of antiphospholipid antibodies, two other studies have shown that women with TAI more frequently present with these types of antibodies, which have been implicated in compromised implantation outcomes [24, 58].

Under normal conditions, maternal immune tolerance is maintained through a shift toward T helper 2 (Th2) cytokine dominance, enhanced immunosuppressive activity of regulatory T cells (Tregs), which play a

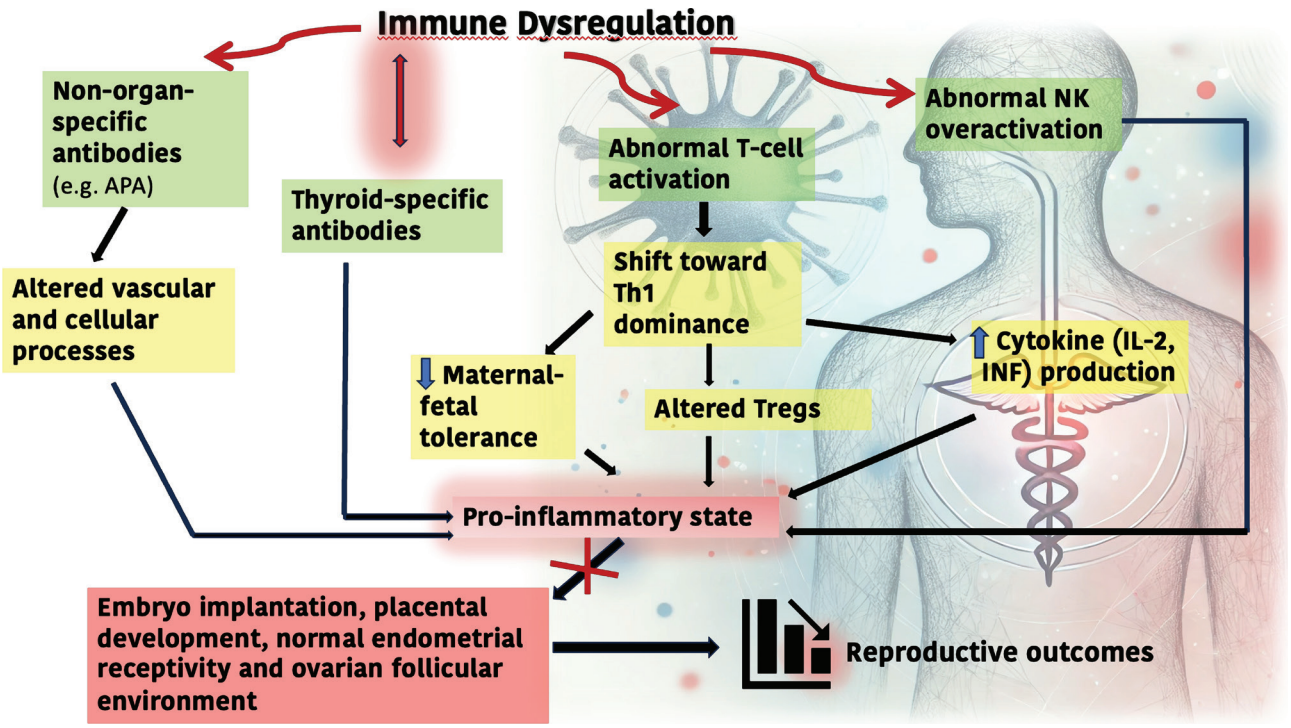

Figure 3: Immune dysregulation in TAI. APA – antiphospholipid antibodies; Th1– type 1 helper T cells; NK– natural killer cells; Tregs – regulatory T cells; IL-2 – interleukin-2; INF – interferon.

crucial role in supporting maternal-fetal tolerance, and tuned immune communication at the maternal-fetal boundary [59].

In contrast, women with antithyroid antibodies often exhibit a Th1-biased immune response and impaired Treg function, resulting in a pro-inflammatory state that can interfere with implantation and placental development. Increased NK cell activity, common in TAI, also disrupts trophoblast invasion and endometrial receptivity, negatively affecting fertility outcomes [57].

An alternative perspective, noted in several studies, is that thyroid antibody titers typically decline during pregnancy, only to rebound postpartum to levels statistically comparable to those observed before pregnancy [60–63]. Moreover, in women with recurrent miscarriage, those who tested positive for thyroid antibodies were found to have an increased number of Treg cells in the endometrium. This implies that Tregs may contribute to immune tolerance by suppressing TAI via linked immune regulation, thereby modulating immune responses and preventing excessive inflammation during pregnancy [11, 56]. Zhu *et al.* further emphasize the need for further studies to better understand TAI-related infertility and to improve current diagnostic and treatment methods [57].

Continuing in the context of pregnancy, eight studies investigated the presence of thyroid antibodies in women with recurrent miscarriage, analyzing data from 447 antibody-positive patients and 1,880 controls. The pooled analysis demonstrated a significantly higher prevalence of thyroid antibodies in affected women, with an odds ratio of 2.26 (95% CI 1.46–3.5) [10].

As mentioned in the context of the SH study, Joris *et al.* also revealed that the presence of thyroid antibodies during pregnancy significantly increased the likelihood of developing overt hypothyroidism. The risk was minimal (0.1%) in women without antibodies but rose progressively with antibody positivity- 2.4% for TgAb alone, 3.8% for TPOAb alone, and 7.0% for those positive for both ($p<0.001$) [36]. Authors also linked thyroid antibody positivity to an increased risk of developing SH during pregnancy. The incidence of SH was 2.2% among antibody-negative women, compared to 8.1% with isolated TgAb, 14.2% with isolated TPOAb, and 20.0% when both antibodies were present ($p<0.001$). Similarly, the need for treatment followed a comparable trend: 0.2% in antibody-negative cases, 2.2% with TgAb alone, 3.0% with TPOAb alone, and 5.1% with both antibodies ($p<0.001$). Additionally, twin pregnancies were associated with a markedly higher risk of overt hyperthyroidism (5.6% *vs.* 0.7%; $p<0.001$) [36]. These findings support the recommendation for close monitoring of pregnant women with thyroid autoantibodies, as they are at significantly higher risk for hypothyroid transition and may require timely intervention.

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Postpartum thyroiditis in the context of fertility

In certain instances, TAI can present with temporary hyperthyroid phases resulting from thyroid cell destruction and subsequent hormone release, leading to suppressed TSH levels. This transient period, referred to as the thyrotoxic phase, is characterized by clinical symptoms of hyperthyroidism such as palpitations, nervousness, heat intolerance, and unintentional weight loss. These symptoms can look similar to Graves' disease, but they are generally milder. Graves' is more likely when exophthalmos is present, along with a higher FT3:FT4 ratio and positive TSH receptor antibodies, which are beyond the scope of this review.

This condition is usually the first sign, seen in lab tests, that the immune system has started attacking the thyroid. In our previous study, we emphasized the importance of anticipation of this phase in conditions such as postpartum thyroiditis (PT), particularly when preparing for ART treatment [64]. PT is an autoimmune condition commonly linked to the presence of TPOAb. PT can present in three clinical patterns: isolated transient hyperthyroidism, observed in approximately 32% of cases; isolated transient hypothyroidism, affecting about 43% of patients and a biphasic course involving initial hyperthyroidism followed by hypothyroidism and subsequent recovery, which represents the classic form of the disorder, seen in 25% of cases. Among pregnant women who test positive for TPOAb early in gestation, the risk of developing PPT ranges between 30% and 52% [65]. The hyperthyroid phase generally manifests between one and six months after childbirth and lasts approximately one to two months [66]. Interestingly, the risk of PT in women with TAI predating pregnancy is higher among women with preserved thyroid functional capacity [67].

Even though it is called postpartum thyroid dysfunction, it can happen not just after childbirth but also after a miscarriage or medical abortion during 5 to 20 weeks of pregnancy [65, 68]. Thus, it is important to consider the patient's history of TPOAb positivity when seeking pregnancy within a year after indicated circumstances, as it increases the probability of PT and can negatively influence ongoing pregnancy outcomes [69].

Being aware of the nuances of this transitional period allows healthcare professionals to better anticipate and manage the risk of developing hypothyroidism after spontaneous pregnancies or especially after ART procedures.

Discussion

The evidence regarding SH and its impact on fertility and pregnancy outcomes remains conflicting, reflecting both the heterogeneity of study populations and variability in TSH thresholds used to define SH. Moreover, in the study by Velkeniers *et al.*, who identified a significant increase in delivery rates after LT-4 treatment in women with SH, the upper limit of TSH to define SH differed. The TSH level often went over 4 mIU/L [31, 70].

To account for physiological alterations during pregnancy, the American Association of Clinical Endocrinologists and the American Thyroid Association have recommended trimester-specific upper reference limits for TSH: 2.5 mIU/L in the first trimester, 3.0 mIU/L in the second trimester, and 3.5 mIU/L in the third trimester [70]. Due to the stimulatory effect of hCG on TSH receptors, serum TSH concentrations may shift during pregnancy, necessitating the use of pregnancy-specific reference ranges [71].

This suggests that not all the cases of increased delivery rates following L-T4 treatment in the study by Velkeniers B involved women with true SH [31]. Based on the established trimester-specific TSH reference ranges, some of these cases might have already met the criteria for overt hypothyroidism.

At the same time, in managing subfertile couples before conception, clinicians should remain mindful of both the potential value and the limitations of current evidence regarding routine screening for TAI. According to the European Thyroid Association guidelines, routine TAI testing in subfertile women may help identify those at an increased risk of fertilization failure [72, 73]. In contrast, the 2024 guidelines from the American Society for Reproductive Medicine recommend assessing TSH and T4 levels only in women who exhibit symptoms of hypothyroidism, such as irregular menstrual cycles, rather than universally screening all subfertile patients (evidence level: B; recommendation strength: moderate) [74]. Supporting a more selective approach, Hamad *et al.* argued that the financial costs of routine TAI screening may outweigh its clinical benefits for many patients [75]. Although the question remains unresolved, the potential benefit that preconception TAI screening can add to the prognosis and management of hypothyroid transition in these women can sometimes be crucial.

Treatment with L-T4 has consistently been shown to reverse many of the adverse reproductive effects of hypothyroidism and is critical to ensure optimized

thyroid function prior to pregnancy [45]. Treating hypothyroidism around the time of pregnancy involves distinct clinical challenges. International practice guidelines recommend having the LT4 dosage adjusted prior to conception to ensure that TSH levels are below 2.5 mIU/L. Once pregnancy is confirmed, it is important to increase the LT4 dose by approximately 30% as early as possible. In practical terms, this can be achieved by taking an extra daily dose twice a week [76]. However, for clinicians, this recommendation can be particularly challenging in real-world practice. When pregnancy does not occur immediately, which is common even among healthy couples with an average monthly conception rate of around 30%, preemptively increasing LT4 may result in iatrogenic hyperthyroidism. Thus, physicians must carefully balance the potential benefits of early dose escalation against the risks of overtreatment. Individualized decision-making becomes essential, weighing the possible harm and benefit to both the patient and the anticipated pregnancy.

In continuation of this statement, one study aimed to determine how many women actually achieve this target TSH level in real-world settings and to assess whether TSH levels exceeding this threshold are associated with negative outcomes for the mother or fetus. They revealed that most women with hypothyroidism fail to reach the recommended TSH targets before conception and in early pregnancy. However, having a TSH level above 2.5 mU/L during this period was not linked to negative outcomes for the mother or fetus [41].

In contrast, for euthyroid women with TAI and TSH levels slightly above 2.5 mU/L, the necessity of hormonal support remains controversial.

In this context, the study by Gietka-Czernel *et al.* provides a nuanced perspective [77]. While recognizing the potential benefits of low-dose LT-4 (25–50 µg/day), particularly in women at high risk for pregnancy complications or those undergoing ART, the authors caution against universal treatment in all pregnant women with TSH levels just above 2.5 mIU/L. Given the absence of clear harm from slightly elevated TSH levels and the lack of consistent benefit from treatment in these cases, routine prescribing of L-T4 remains premature [77]. Moreover, unnecessary medication burden adds psychological stress or perception of illness in otherwise healthy women [78, 79]. This reflects the current shift in the field toward more individualized, risk-based approaches, which balance potential benefits with concerns about overtreatment.

Interestingly, findings from Chen *et al.* raise further questions regarding the relationship between TAI and ovarian reserve, as TPOAb positivity was significantly more frequent in women with idiopathic low ovarian reserve [55]. This suggests a potential link between idiopathic diminished ovarian reserve and unexplained infertility. Women with unexplained infertility may sometimes present with normal ovarian reserve markers (*e.g.*, AMH, FSH, antral follicle count), yet still exhibit suboptimal ovarian function mistakenly related to unexplained subfertility. In this context, TAI may serve as an underlying, often overlooked contributor. The higher prevalence of TAI in women with unexplained subfertility, as demonstrated by Van den Boogaard *et al.* [10], supports the hypothesis that these two seemingly unexplained conditions might share a common autoimmune basis. The statistically significant results across studies may, in fact, reflect varying manifestations of a single underlying pathology driven by the presence of thyroid antibodies (Figure 4). Further research is warranted to test this hypothesis and clarify its clinical implications.

Finally, although PT traditionally refers to thyroid dysfunction occurring after delivery, it is increasingly recognized that similar autoimmune thyroid responses can also follow miscarriage and medical abortion. This wider spectrum of clinical onset emphasizes the importance of considering thyroid status not only during pregnancy but also in the periconceptional period, particularly in women with known TPOAb positivity.

From a fertility perspective, the biphasic pattern of PT- an initial hyperthyroid phase followed by hypothyroidism- is particularly relevant. It can interfere with menstrual regularity, ovulation, and endometrial receptivity. Therefore, identifying women at risk for PT is crucial before initiating ART cycles or planning conception. The reported incidence of PT in TPOAb-positive women (30–52%) supports the need for proactive thyroid monitoring in this population, especially in the months following delivery, miscarriage, or elective abortion [65, 68].

Conclusions

In conclusion, SH has been linked to unexplained subfertility and a higher risk of pregnancy complications, including preeclampsia. However, evidence supporting the benefits of L-T4 treatment remains inconsistent. The use of pregnancy-specific TSH thresholds is essential due to gestational physiological changes, yet differences in these thresholds pose challenges for comparing study outcomes. Although certain risk

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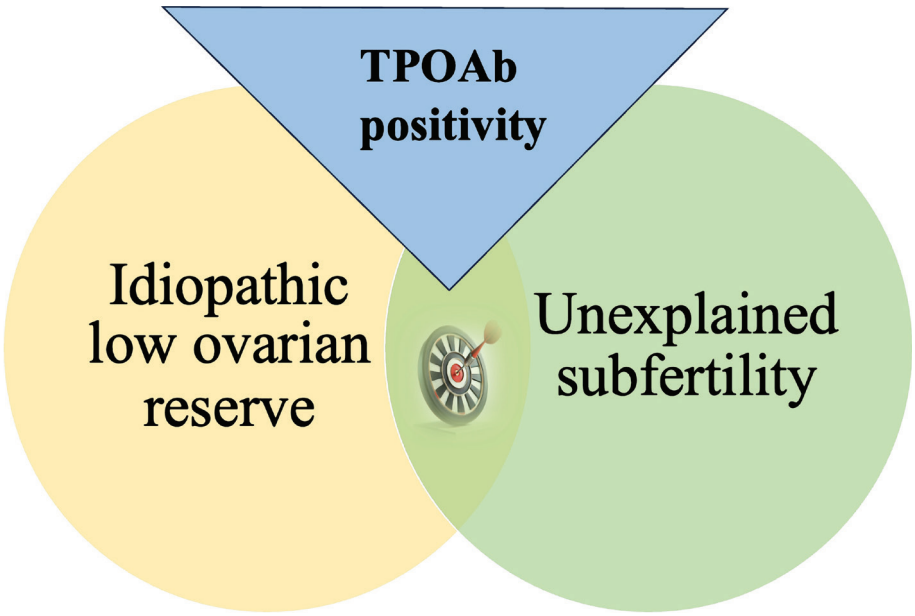

Figure 4: Possible connection between idiopathic low ovarian reserve and unexplained infertility. TPOAb – thyroid peroxidase antibodies.

factors for thyroid dysfunction progression during pregnancy show statistical significance, their limited absolute impact reduces their clinical utility in improving screening strategies.

The impact of hypothyroidism on the interplay between thyroid hormones and the pituitary-ovarian axis, as well as its involvement in promoting trophoblast invasion and placental attachment, highlights its critical role in fertility and early pregnancy. Overt hypothyroidism has been linked to complications such as preeclampsia and increased risks of placental abruption, underscoring the importance of careful thyroid function monitoring during pregnancy.

The presence of thyroid antibodies is associated with subfertility in cases of unexplained subfertility and idiopathic low ovarian reserve. These antibodies are believed to impair ovarian follicular health, oocyte quality, and endometrial receptivity through immune-mediated mechanisms involving pro-inflammatory states, T-cell imbalance, and natural killer (NK) cell overactivation. This review also suggests thyroid antibody positivity as a possible shared underlying cause between idiopathic low ovarian reserve and unexplained infertility. Moreover, TAI increases the risk of recurrent miscarriage and pregnancy-related complications, including hypothyroidism.

Taken together, these findings support the importance of early thyroid evaluation in women planning pregnancy, especially those with known thyroid dysfunction or subfertility. While L-T4 remains the cornerstone of management in overt hypothyroidism, its use in borderline or mildly elevated TSH levels should be guided by broader clinical context, including thyroid antibody status, symptomatology, and reproductive history.

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Conflict of interest

The authors declare no conflict of interest.

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