Thyroid Diseases and Female Infertility

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5.1 Introduction

Normal thyroid function is crucial for human reproduction. Thyroid diseases—hypothyroidism and hyperthyroidism—in women of reproductive age are associated with a broad spectrum of disorders, from menstrual irregularities and infertility to pregnancy loss. The effects of thyroid hormones on female reproduction have been extensively studied and are well documented; an important amount of evidence from animal and human studies is available, supporting the role of thyroid hormones on ovarian, endometrial, and placental physiology. Treatment of thyroid diseases can successfully restore menstrual function and fertility, reducing the likelihood of further procedures of assisted reproduction technology. Consistently negative association exists between thyroid autoimmunity without thyroid dysfunction and infertility and early miscarriage.

5.2 Epidemiology of Thyroid Diseases

Thyroid diseases are common endocrine disorders. Estimates of the prevalence of thyroid disorders are mainly from iodine replete areas—in the US National Health and Nutrition Examination Survey (NHANES III), the prevalence of hypothyroidism was 4.6% (0.3 overt and 4.3% subclinical) and the prevalence of hyperthyroidism 1.3% (0.5 overt and 0.7% subclinical) [1]. The incidence of thyroid disorders in

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adults in a community followed for 20 years (The Whickam Study) was for hypothyroidism in women 350/100,000/year and in men 60/100,000/year while for hyperthyroidism in women 80/100,000/year and in men 8/100,000/year. The most striking features of the epidemiological studies were the high prevalence of hypothyroidism, the marked female preponderance, and the increasing occurrence with advancing age [2]. Worldwide, the most common cause of hypothyroidism is iodine deficiency. In areas of adequate iodine intake, autoimmunity is the main cause of hypothyroidism. Autoimmune thyroid disease (AITD) refers to the interrelated conditions: Hashimoto thyroiditis (goitrous or atrophic), hyperthyroid Graves' disease, and postpartum thyroiditis.

In women of reproductive age, the prevalence of hypothyroidism is 2–4%. In this age group, AITD is the most frequent cause of hypothyroidism. In iodine replete areas, the incidence of autoimmune hypothyroidism in women was 498/100,000/year and in men 2/100,000/year while for autoimmune hyperthyroidism in women 99/100,000/year and in men 0.7/100,000/year [3]. The US NHANES III reported the presence of TPO-AB in 13% and Tg-Ab in 11.5% of the population. AITD is the most common autoimmune disorder, affecting 5–20% of women in the childbearing period. Although thyroid autoimmunity predisposes to development of hypothyroidism, the majority of women with AITD do not have thyroid dysfunction.

5.3 Physiological Effects of Thyroid Hormones on the Female Reproductive System: Molecular Basis and Mechanism of Action

Thyroid hormones play an important role in reproductive function both through direct effects on the female reproductive organs and indirectly by interacting with sex steroids and sex hormone-binding protein. Thyroid hormone synthesis and release into circulation are regulated in a negative feedback manner by the pituitary hormone thyroid-stimulating hormone (TSH); hypothyroidism results in increased TSH levels, and hyperthyroidism produces suppression of TSH levels. Thyroid hormones are produced by the follicular cells of the thyroid gland, from the precursor protein thyroglobulin; iodination of the tyrosine residues of thyroglobulin by thyroid peroxidase produces the thyroid hormones T4 (thyroxine or tetraiodothyronine) with four iodine atoms and T3 (triiodothyronine) with three iodine atoms per molecule. The predominant physiological thyroid production is the biologically inactive T4, with a smaller amount of bioactive T3—in a ratio 14/1 to 20/1 [4]. The circulating thyroid hormones are bound to transport proteins (thyroxine-binding globulin TBG, transthyretin TTR, and albumin), with only a small fraction (0.1%) being free and transferred across the membranes in target cells by an active transporting mechanisms involving monocarboxylate transporters (MCT), L-type amino acid transporters (LAT), and organic anion transporting polypeptides [5]. The prohormone T4 is converted to the active T3 form by iodothyronine deiodinases—three distinct enzymes (DIO1, DIO2, DIO3) with specific tissue expression. T3 acts through nuclear thyroid hormone receptors alpha (THRA) and beta (THRB),

expressed in a tissue-specific manner. Thyroid hormone receptors regulate gene expression by binding to hormone response elements [6].

The role of thyroid hormone in reproduction and early pregnancy is supported by the evidence that almost all factors essential for thyroid hormone action, such as THRA and THRB, thyroid hormone transporters, and deiodinases, are expressed in the oocytes, cumulus cells, granulosa and stromal cells, endometrium, placenta, and early embryo, indicating the bioavailability of thyroid hormones in these tissues and their dynamic local regulation.

5.4 Effects on Ovarian Follicles

Thyroid hormones T3 and T4 are detected in the follicular fluid, with positive correlation between serum and follicular fluid levels [7]. Both thyroid hormone receptor isoforms THRA and THRB are expressed in human oocytes, with an increased expression during follicular growth—indicating a direct effect on folliculogenesis and ovulation [8]. The growth of rat preantral follicles is stimulated by thyroid hormones. T3 in combination with FSH enhances granulosa cell proliferation and inhibits granulosa cell apoptosis by the PI3K/Akt pathway [9]. Thyroid hormones play a role in the production of ovarian steroid hormones. T3 acts as a biological amplifier of the stimulatory action of FSH on granulosa cell function, also increasing LH receptors and progesterone secretion by the granulosa cells. T3 stimulates the proliferation of granulosa cells and hCG-induced c AMP in these cells [10]. Abnormal thyroid hormone levels may therefore produce alterations in ovulation

5.5 Effects on the Endometrium

Thyroid hormones have direct effects on the endometrium. Thyroid hormone receptors THRA and THRB are detected in the glandular endometrium, with variable expression during the phases of the menstrual cycle, increasing in the secretory phase and decreasing subsequently. Deiodinases DIO2 and DIO3 are present in the human endometrium throughout the menstrual cycle with lower expression in the mid-secretory phase and an inverse relationship with serum progesterone levels [11]. DIO2 activity in the stromal cells is regulated by progesterone; DIO2 produces intracellular T3 that may influence the uterine response to implantation [12].

5.6 Effects on Fertilization

Data of effects of thyroid hormones on fertilization and embryo quality derive from studies of assisted reproduction technologies ART. The positive effect of thyroid hormones on fertilization was evidenced by improvement of the number of high quality embryos and birth rate in women with subclinical hypothyroidism undergoing ART treated with L-thyroxine compared with non-treated women [13].

5.7 Effects on Implantation and Placentation

A potential endocrine, paracrine, and intracrine role of the thyroid hormones on embryo implantation and trophoblasts has been discussed. Thyroid hormone receptors THRA and THRB, TSH receptors, thyroid hormone transporters, and deiodinases are widely expressed in the fetomaternal unit during implantation and placentation. Thyroid hormones act either directly or by modulating the production and activity of various cell adhesion molecules and cytokines. Furthermore, the expression of genes involved in thyroid hormone production—thyroglobulin, thyroid peroxidase, and NIS sodium iodide symporter—in endometrial and syncytiotrophoblast cells could support a local production of thyroid hormones. It is unknown if the relatively low expression levels also mean that there is a functional effect, but we could speculate that alteration of factors that might regulate the uterine production of thyroid hormones could modify the local effects of thyroid hormones, even in the presence of normal systemic hormone levels [14]. Thyroid hormones stimulate the secretion of progesterone and human placental lactogen in trophoblast cells. Progesterone is responsible for the optimal endometrial lining and embryo implantation, as well as for the local immune tolerance preventing the rejection of the fetal allograft. Human placental lactogen is involved in fetal glucose supply by reducing maternal insulin sensitivity and increasing lipolysis, playing also a role in embryonic growth. T3 increases the expression of matrix metalloproteinases MMP-2 and MMP-3, fetal fibronectin, and integrin α5β1 in cultured early placental extravillous trophoblasts, suggesting a role in the invasive potential of trophoblasts. Also, thyroid hormones modulate the inflammatory cytokines involved in implantation—upregulating leukemia inhibitory factor (LIF) expression in endometrial cell cultures [15].

The placental tissue has all the equipment for transporting thyroid hormones—T3 membrane transporters are localized in the syncytiotrophoblast, in order to supply the thyroid hormones to the embryo. A highly sensitive regulation of thyroid hormones in the placenta is possible due to the expression of all three types of deiodinase.

Further studies are needed to better characterize the molecular mechanisms of thyroid hormones involved in female reproduction and the implications associated with thyroid dysfunction that could help resolve infertility in thyroid diseases.

Pathophysiology of reproductive abnormalities in thyroid disorders—hormonal changes.

Both primary hypothyroidism and hyperthyroidism in women of reproductive age produce variable degrees of gonadal dysfunction leading to ovulation disturbances and menstrual cycle irregularities.

The hormonal changes in women with in hypo- and hyperthyroidism are summarized in Table 5.1.

Changes in SHBG (sex hormone-binding globulin) due to the stimulating effects of thyroid hormones on hepatic production of SHBG, altered estrogen

Table 5.1 Hormonal abnormalities in women with thyroid dysfunction

	Hypothyroidism	Hyperthyroidism
SHBG	Decreased	Increased
E2	Decreased Decreased metabolic Clearance rate	Increased D\decreased metabolic clearance rate
LH	Reduced response to GnRH	Increased Increased response to GnRH
FSH	Reduced response to GnRH	Increased Increased response to GnRH
PRL	Increased	Unmodified
Progesterone	Decreased/unmodified	Decreased/unmodified
Testosterone	Decreased	Increased
Δ4-androstenedione	Decreased	Increased
Testosterone to E2 conversion	Increased	Increased

and androgen metabolism, and modified response of gonadotropins to GnRH are frequently observed in hypo- and hyperthyroidism. By influencing peripheral estradiol metabolism, abnormal thyroid hormone has profound effects on regulation of the hypothalamic-pituitary-ovarian axis, inadequate ovulation, and corpus luteum formation, on the proliferation and maturation of endometrial tissue, and consequently on implantation and early development of the blastocyst. In hypothyroidism SHBG serum level is reduced leading to decreased level of total estradiol and increased level of free estradiol, while in hyperthyroidism increased SHBG leads to an increase of circulating total estradiol, with normal or reduced free estradiol. The metabolic clearing rate of estradiol is reduced in both hypo- and hyperthyroidism [16].

Alterations in steroid metabolism resolve with the restoration of the euthyroid state. Testosterone and androstenedione plasma levels increase, and the production rates of testosterone and androstenedione are significantly elevated in hyperthyroid women. The conversion ratio of androstenedione to estrone, as well as of testosterone to estradiol, is increased in hyperthyroid women. LH levels are significantly higher in hyperthyroid women than in normal women, with an exaggerated response to GnRH. FSH levels may be increased. Serum LH levels decrease to normal after a few weeks of treatment with antithyroid drugs. Hyperthyroxinemia increases the gonadotrophin response to GnRH, and baseline gonadotrophin concentrations are also frequently elevated [17]. Hypothyroid women, beside a blunted or delayed LH response to GnRH and an abnormal pulsatile release of LH, can also present hyperprolactinemia due to increased hypothalamic TRH that stimulates both TSH and PRL secretion and explain the high frequency of ovulatory dysfunction and infertility in women with hypothyroidism. Galactorrhea may also occur; all these hormonal modifications usually disappear after restoration of normal thyroid hormone levels; thyroxine administration in hypothyroid women increases the chance of spontaneous pregnancy [18].

5.8 Menstrual Abnormalities in Thyroid Dysfunction

Changes in menstrual cycle length and blood flow are common in women with altered thyroid function; approximately three times higher than in the normal population, oligomenorrhea and menorrhagia are the most common menstrual abnormalities. Amenorrhea was already reported by von Basedow in 1840. Since then, amenorrhea has been frequently described, as well as a number of other changes, including oligomenorrhea, hypomenorrhea, polymenorrhea, menorrhagia, and anovulation.

There is a striking difference between earlier and recent studies reporting the prevalence of menstrual irregularities in hypo- and hyperthyroid women, with earlier studies showing a higher prevalence. This can be explained by the delayed diagnosis of hypothyroidism in earlier studies, with a more severe clinical picture. The prevalence of menstrual abnormalities in hyperthyroidism was described in earlier studies up to 60%, while the recent studies found irregular cycles in approximately only 20% [19].

Similar patterns are observed for hypothyroidism in women of reproductive age—early studies showing up to 80% prevalence of menstrual disorders [20] and recent studies about 20%. Menorrhagia and polymenorrhea are frequently described in hypothyroid women, probably due to estrogen breakthrough bleeding secondary to anovulation and defects in hemostasis factors associated with hypothyroidism (decreased levels of factors VII, VIII, IX, and XI) [21].

5.9 Fertility in Women with Thyroid Dysfunction

Few studies about fertility in women with hyperthyroidism are available, mainly uncontrolled and cohort studies, making difficult to assess the impact of hyperthyroidism on female infertility. The prevalence of infertility in hyperthyroid women was estimated 2–5% [22]. Most hyperthyroid women remain ovulatory according to results of endometrial biopsies [20]. What we can affirm is that women of reproductive age and increased thyroid hormone levels should be treated appropriately restoring euthyroidism, avoiding radioiodine especially if pregnancy or ART procedure is planned.

Studies that examined the incidence of infertility in hypothyroid women are also scarce, most of them uncontrolled, retrospective, cross-sectional, or in selected hypothyroid patients (therefore biased) attending infertility clinics. Ideally, this should be studied prospectively and with an age-matched control group. The estimated prevalence of overt hypothyroidism in infertile women from different available studies was 2–6% [23, 24].

Subclinical hypothyroidism (SCH) is a challenging aspect for female infertility. The classic definition of SCH is a TSH level greater than the upper limit of normal range (4.5–5.0 mIU/L) with normal free thyroxine (FT4) levels. Controversies persist in the appropriate upper limit for serum TSH in women attempting pregnancy and the decision to treat, some authors proposing a value of 2.5 mIU/L and the

initiation of therapy with L-thyroxine. TSH upper reference values in pregnancy have already been modified because human chorionic gonadotropin (hCG) can bind to the TSH receptor and influence TSH values: 2.5 mIU/L is the recommended in the first trimester, 3 mIU/L in the second, and 3.5 mIU/L in the third. Studies investigating the association between SCH and female infertility are based on different upper serum TSH cutoffs, and the data are limited and highly variable due to study design, poorly controlled, prospective, or retrospective, selection criteria, and type of infertility studied. Overall, the prevalence of SCH in women with infertility ranged from 1 to 4%, reporting also as high as 30% [25], while some authors suggested that the prevalence of SCH is similar in infertile women and the general female population [26]. The main trend in these studies is that SCH is higher in women with ovulatory dysfunction than in other causes of infertility.

5.10 Autoimmune Thyroid Disease AITD and Female Infertility

The immunological markers of AITD are the circulating serum antibodies TPO-Ab (thyroid peroxidase antibodies), Tg-Ab (thyroglobulin antibodies), and TSHR-Ab (TSH-receptor antibodies). The last 10 years brought considerable progress in understanding the multifactorial etiology of autoimmune thyroid disease (AITD)—a combination between genetic susceptibility (HLA-DR alleles, CTLA-4 polymorphism) and environmental factors (iodine intake, radiation, smoking, selenium and vitamin D deficit, drugs, toxins, microorganisms). AITD can be associated with other organ-specific and non-organ-specific autoimmune diseases (autoimmune polyglandular syndromes I, II, and III), suggesting a shared immunogenetic background [27].

AITD has a strong female preponderance, 5–10 times higher than in men. This can be explained, at least in part, by a combination of genetic factors, estrogen-related effects, chromosome X abnormalities, and fetal microchimerism. Autoimmunity is abnormally high in practically all X-linked disorders. The X chromosome contains the largest number of immune-related genes of the human genome, and the long arm (Xq) controls functional ovarian reserve and autoimmunity. The FMR1 gene (fragile X mental retardation 1-ovarian function) is involved in ovarian recruitment and reserve, and its mapping at Xq27.3 occupies the crossroads between ovarian function and autoimmunity. X chromosome might constitute the common trait of the susceptibility to autoimmune diseases [28].

Many studies have investigated the relationship between AITD and female infertility. However, the interpretation of the data is rather difficult because of the heterogeneity of the sample size or geographic origins with variable iodine intake, uncontrolled retrospective design of many studies, difference in assays used to measure thyroid antibodies, selection biases, and causes of infertility. Overall, the majority of the studies showed an increased prevalence of AITD among women with infertility; the relative risk of AITD for female infertility ranges from 1.2 to 3.8 [25], while only a few studies did not show any difference in AITD prevalence in infertile women compared with fertile controls [26].

AITD is especially prevalent among women with polycystic ovary syndrome (PCOS) and endometriosis. A strong association between thyroid autoimmunity and PCOS—two of the most common endocrine diseases in women—has been described; the prevalence of AITD in PCOS patients is 2.2–3.5 times higher than in controls [29–33]. Women with PCOS and AITD showed a higher risk of clomiphene citrate resistance (OR of 7.7) compared to controls; elevated TPO-Ab levels were associated with poor treatment response in infertile PCOS women [34].

AITD and PCOS frequently occur together. A shared immunogenetic background has been incriminated; lower levels of TGFβ were found in AITD as well as in PCOS women. *FBN3* gene polymorphism seems to be the most plausible candidate due to their influence on TGFβ activity-key regulator of immune tolerance by stimulating regulatory T cells (Tregs) which are known to inhibit excessive immune response [35]. Vitamin D deficiency is often seen in autoimmune disease and PCOS. Sex hormone imbalances with high estradiol to progesterone ratio due to anovulatory cycles in PCOS women could trigger an exacerbate immune response. The role of sex hormones in the pathogenesis of autoimmunity has been studied; estradiol decreases the activity of T suppressor cells, increases the activity of B cells, and increases the secretion of Th2 cytokine IL6 and the formation of antibodies; progesterone decreases the synthesis of IL6 and the peripheral antibody production [36].

A positive association between AITD and endometriosis has also been described in various studies; the relative risk of AITD was 2–3.5 in women with endometriosis as a cause of infertility [24]. The prevalence of endometriosis reaches 25–44% among women with AITD versus 9–14% among controls [26]. Other study could not confirm the association [37]. Endometriosis is associated with immunological changes: autoantibodies to endometrial antigens, complement deposits, decline in the concentration of natural killer cells, and cytotoxic effects on autologous endometrium [38].

AITD with normal thyroid function is associated with greater ART failure and miscarriage after controlled ovarian hyperstimulation (COH). It is important to mention the major impact of COH on thyroid function. The marked increase in serum estradiol and TBG levels with a decrease of free T4 levels—changes that occur more rapid and pronounced after COH—can produce a significant burden on the thyroid, especially in women with AITD, leading to more severe thyroid dysfunction than observed with spontaneous pregnancy. During the first weeks of pregnancy after COH in women with AITD, the TSH values are higher, and FT4 values are lower compared with women without AITD [39].

A first study that described the negative impact of AITD on ART outcomes showed lower pregnancy rates per cycle in women with thyroid antibodies (10.8%) compared with controls (25%), with no differences in the numbers of oocytes retrieved, fertilization rate, or number of transferred embryos [40]. Studies that followed showed controversial results but overall indicate a significant increased risk of miscarriage in euthyroid women with thyroid autoimmunity following ART. Most of the studies reported no difference in clinical pregnancy and delivery rates [41–43], while another study showed lower oocyte fertilization and percentage of grade

A embryos in AITD than in women with negative thyroid antibodies [44]. A recent meta-analysis of the impact of thyroid autoimmunity on ART outcomes involving 12 cohort studies of women showed higher miscarriage rates and lower live birth rate in thyroid antibody-positive women than in women without antibodies. The number of oocytes retrieved and rates of fertilization and implantation did not differ between antibody-positive and antibody-negative women, and clinical pregnancy rates were similar [45]. A randomized study of L-thyroxine therapy impact in women with AITD undergoing ART and throughout pregnancy [46] revealed that therapy in TPO-Ab-positive women did not affect the pregnancy and delivery rate. The study also evidenced a twofold increase in the risk of miscarriage in AITP patients compared with controls; miscarriage rate was reduced to 33% in treated TPO-Ab-positive women, compared with 52% in untreated controls. Recently, a prospective cohort study of women with a history of miscarriage showed that TSH levels greater than 2.5 mIU/L or positive thyroid antibodies were not associated with impaired fecundity, pregnancy loss, or live birth rates [47].

The pathophysiological mechanisms associating AITD and female infertility remain hypothetical until today; there are no clear data that indicate a causal relationship between thyroid antibodies and reproduction failure. The current knowledge on thyroid antibodies and their impact on female fertility are extrapolated mainly from studies in ART settings, examining oocyte retrieval, fertilization rates, embryo quality, miscarriage, and pregnancy rates. Serum thyroid antibodies can pass the blood-follicle barrier; TPO-Ab and Tg-Ab have been identified in the follicular fluid and correlate with serum levels; this could negatively influence the quality of the maturating oocyte, as lower fertilization rates, grade A embryos, and pregnancy rates were observed in AITD women undergoing ART compared with controls [44]. Antithyroid antibodies may react with antigens in the zona pellucida altering its functional role. Human anti-zona pellucida antibodies recognize antigens within murine thyroid tissue; zona pellucida and thyroid tissue seem to share similar antigens [48]. From a practical point of view, intracytoplasmic sperm injection ICSI (which requires no interaction between the sperm cell and the zona pellucida) could be the preferred assisted reproductive method in infertile women with thyroid autoimmunity; this finding must be confirmed through randomized controlled studies.

Evidence for the influence of TPO-Ab on embryo quality is inconsistent among studies, showing either no differences in oocytes retrieved, fertilization rate, and embryo grades between AITD women and controls [40, 49] or a lower fertilization, implantation, and pregnancy rate following ART in women with antithyroid antibody than in controls [50].

No studies are available on the direct effect of thyroid antibodies on the endometrium. TPO and Tg are expressed in the endometrium, and it can be only hypothesized that the endometrium is a potential target for the action of TPO-Ab and Tg-Ab. It is also worth mentioning that TPO-Ab diffuse through the placental barrier, with good evidence of this during the third trimester, without excluding a transfer at earlier pregnancy stages and speculating an interaction at the maternal-fetal interface [51].

Three main hypotheses have been proposed for the association between AITD and infertility, a combination of TSH-dependent and TSH-independent mechanisms. A subtle thyroid hormone deficit due to chronic lymphocytic thyroiditis produced by thyroid antibodies could be incriminated. Although in euthyroid range, TSH levels in AITD infertile women are slightly increased compared to controls. A second hypothesis is that TPO-Ab and Tg-Ab reflect a general autoimmune imbalance (both humoral and innate immunity) that could be responsible for the rejection of the embryo. A third hypothesis is the age factor—the prevalence of AITD increases with age and older women have a higher risk of infertility and miscarriage, but this has not been confirmed in recent meta-analyses [52].

5.11 Recommendations and Guidelines for Women with Infertility and Thyroid Diseases/AITD

Women with infertility—especially with PCOS and endometriosis—should be screened for AITD and thyroid dysfunction, because of the increased prevalence of AITD in this category of patients. Treatment of thyroid diseases and restoration of euthyroidism can improve fertility.

Universal screening of healthy women for thyroid dysfunction and thyroid antibodies before pregnancy is not recommended. TPO-Ab and Tg-Ab measurement should be considered when evaluating women with infertility and particularly miscarriage (spontaneous or recurrent). Selected thyroid screening in women seeking pregnancy is recommended for women over 35 years, infertility, history of miscarriage, history of autoimmune disease, family history of AITD, clinical signs of thyroid dysfunction or goiter, and living in areas of iodine deficiency.

The Endocrine Society, the American Thyroid Association (ATA), and the American Association of Clinical Endocrinologists (AACE) have elaborated guidelines on treating subtle, subclinical thyroid dysfunctions in women of childbearing age. L-thyroxine therapy should be initiated in women who are pregnant or planning a pregnancy, including ART, if TPO-Ab positive and TSH greater than 2.5 mIU/L. Therapy should be considered in women planning a pregnancy including ART or in the first trimester of pregnancy if the TSH level is between 2.5 mIU/L and the upper reference range. Treatment with L-thyroxine should be considered in women with normal serum TSH levels when they are pregnant or planning a pregnancy, including ART, if they have or have had positive levels of serum TPO-Ab, particularly when there is a history of miscarriage or past history of hypothyroidism. The upper limit of TSH of 2.5 mIU/L is therefore proposed as a cutoff before ART, independent of thyroid antibody status. Serum TSH levels should be maintained below 2.5 mIU/L before starting the COH procedure, and monitor thyroid function tests closely thereafter [53, 54].

The American Society for Reproductive Medicine recommends that if TSH levels prior to pregnancy are between 2.5 and 4 mIU/L, either monitor levels and treat when TSH >4 mIU/L or treat with levothyroxine to maintain TSH <2.5 mIU/L. Due to the inconsistent data of the impact of subclinical hypothyroidism on fertility outcomes, L-thyroxine therapy for TSH levels greater than 2.5 mIU/L remains controversial [55].

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