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Review Article

Biochemistry Section

Exploring the Diagnostic and Therapeutic Significance of Thyroid Hormones in Female Infertility: A Comprehensive Narrative Review

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ABSTRACT

Thyroid Hormones (TH) are essential for the healthy functioning of the female reproductive system because they regulate ovarian, uterine, and placental tissue metabolism and development. Therefore, hypo-and hyperthyroidism may result in infertility in women. Previous studies have been conducted on women with thyroid dysfunction, including prospective and retrospective studies, in-vitro and in-vivo tests for hypo-and hyperthyroidism using ovarian, uterine, and placental cell culture, and experimental animal models. In order to better understand the physiology of the reproductive system and to develop more effective therapy methods for reproductive dysfunctions that result from thyroid dysfunctions, these studies sought to shed light on the mechanisms by which TH affect reproduction. This comprehensive narrative review investigates the diagnostic and therapeutic implications of TH in female infertility. By scrutinising existing literature, the study aims to elucidate the intricate relationship between thyroid function and reproductive health in women. Such insights are crucial for enhancing diagnostic accuracy and formulating effective therapeutic interventions to address thyroid-related factors influencing female infertility.

Keywords: Female reproductive system, Hypothyroidism, Thyroid gland, Thyroid infertility

INTRODUCTION

Clinical and Subclinical Hypothyroidism (SH) is prevalent in 0.3% and 4.3% of women of reproductive age and during pregnancy, respectively [1]. Humans require Thyroid Hormones (THs) for healthy reproduction. L-thyroxine (3,5,3',5'-tetraiodothyronine, T4) and L-triiodothyronine (3,5,3'-triiodothyronine, T3) influence the growth and metabolism of ovarian, uterine, and placental tissues directly through unique nuclear receptors [1]. Through many interactions with other hormones and growth factors including oestrogen, Prolactin (PRL), and Insulin-like Growth Factor (IGF), they also have an indirect influence by affecting the release of Gonadotrophin-Releasing Hormone (GnRH) in the hypothalamic-pituitary-gonadal axis [2]. Infertility can result from variations in TH levels in the blood, such as hypo- and hyperthyroidism in women [3].

Thyroid disorders are widespread over time and can arise at any age [4]. One of the most prevalent endocrinopathies is hypothyroidism [5,6]. The most frequent cause of hypothyroidism is autoimmune thyroiditis, in which the body's own antibodies react against critical thyroid proteins like Thyroperoxidase (TPO) and/or Thyroglobulin (Tg), leading to gland destruction and loss of function [7]. In humans, hypothyroidism has been linked to problems with reproduction, including delayed puberty [8], ovarian cysts, irregular menstrual cycles, infertility, an increase in spontaneous abortions, and preterm births of infants with low birth weight and congenital anomalies [9].

A recent study has also revealed that these gestational changes are brought on by impaired placental development, which results in decreased proliferation and increased apoptosis of trophoblastic cells, impaired intrauterine migration, which is connected to altered endocrine, immune, and angiogenic profiles at the maternal-foetal interface [10]. A 1.3% of women of reproductive age experience hyperthyroidism, which is typically brought on by Graves' disease, a rise in antibodies against the Thyroid-stimulating Hormone (TSH) receptor [11]. There are currently little and occasionally conflicting data showing a connection between hyperthyroidism and infertility [12], but study suggest that 5.8% and 2.1% of women with hyperthyroidism, respectively, develop primary and secondary infertility [13]. Although it occurs less frequently than hypothyroidism, hyperthyroidism is associated with monthly irregularity, increased follicular atresia, and ovarian cysts [14]. Because thyroid dysfunction is associated with a number of morphological, physiological, and behavioural abnormalities, including reproductive illnesses in women, the objective of this review was to describe the role of THs in ovarian, uterine, and placental morphophysiology.

Similar studies have explored the link between thyroid dysfunction and reproductive issues, emphasising its impact on women's health [1,3]. However, a literature gap exists regarding a comprehensive review specifically focusing on the role of THs in ovarian, uterine, and placental morphophysiology. This study aims to bridge this gap by providing an in-depth analysis of THs' influence on these reproductive organs, consolidating existing knowledge and identifying areas requiring further investigation. The novelty lies in offering a synthesised perspective, facilitating a deeper understanding of the intricate connections between THs and female reproductive health, ultimately guiding future research and clinical approaches.

Effect of Thyroid Hormones (TH) on the Uterus and Uterine Tube

Thyroid Hormones (TH) act on intracellular receptors to control how sensitive the uterus and uterine tube are to oestrogen [15]. While deiodinases expression decreases throughout the secretory phase and is inversely correlated with progesterone levels, T3 and T4 receptor expression in the uterine epithelium peaks in the middle of the secretory phase [16]. Therefore, it is conceivable that variations in T3 and T4 serum levels have an impact on uterine and uterine tube morphophysiology by impairing the proper activation of their receptors during the estrous or menstrual cycle as well as by affecting plasma levels of sex steroids, which in turn affects the trophic action of these hormones on the genital tract [17].

Hyperthyroidism

The illness known as Graves' disease, which is caused by an increase in antibodies against the TSH receptor, accounts for 1.3% of cases of hyperthyroidism in women of reproductive age [1].

In people, THs are known to affect the molecular pathways that control the menstrual/estrous cycle, sexual behaviour and

development, ovulation, maternal capacity, pregnancy maintenance, postnatal growth, and lactation [18]. These outcomes are a result of both the direct action of THs on the reproductive organs and their influence on the bioavailability of other hormones and growth factors, which are also necessary for the healthy operation of the female reproductive system [19]. Effect of hyperthyroidism is different in different age groups [Table/Fig-1] [20].

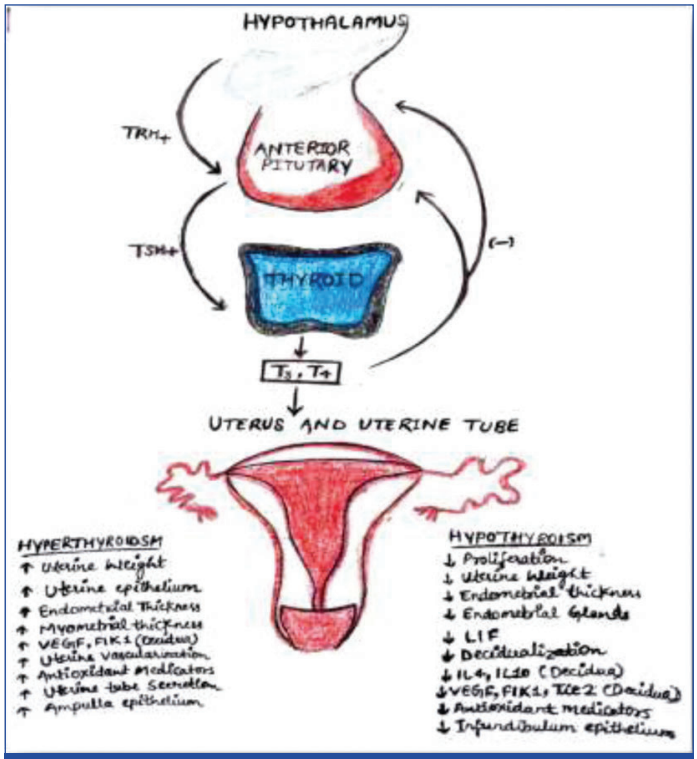
Age	Reproductive problems related to hyperthyroidism
At birth	Neonatal Graves' disease
Before puberty	Delayed onset of menses
At the age of menarche	No significant effect of hyperthyroidism
Reproductive age	Graves' disease; other causes are toxic goitre and thyroiditis

[Table/Fig-1]: Reproductive problems of hyperthyroidism with age [20].

Hyperthyroidism can cause infertility in women. TH regulates the metabolism and development of ovarian, uterine, and placental tissues. They are essential for the healthy operation of the female reproductive system. Higher synthesis of the protein Sex Hormone-binding Globulin (SHBG), which can result in irregular, lighter, or skipped periods, is one way that hyperthyroidism can affect menstruation. High blood levels of PRL, a hormone that can influence ovulation, fertility, and menstruation. Thyroid problems can occasionally even cause an early menopause. Problems with fertility include variations in the menstrual cycle, which are frequently associated with altered or hindered ovulation [1].

Hypothyroidism

Hypothyroidism lowers the uterine cells' sensitivity to oestrogen, which lowers the proliferative rate of epithelial and stromal cells, as well as the uterine muscle. The infundibulum's villus height, as well as the quantity and size of villus-lining cells in the uterine tube, are all impacted by TH deficiency, and as a result, the segment's epithelial height is significantly reduced [21]. The embryo's fertilisation, differentiation, feeding, and implantation can all be compromised by all of these alterations in the uterus and uterine tubes, which explains the embryonic loss and low implantation rate observed in hypothyroid patients [Table/Fig-2] [22].



[Table/Fig-2]: Effect of hypo-and hyperthyroidism on the morphophysiology of uterus and uterine tube. Low blood levels of THs are detected by the hypothalamus and the pituitary. Thyrotropin-releasing Hormone (TRH) is released by the hypothalamus, stimulating the pituitary to release Thyroid-stimulating Hormone (TSH) [1].

Hypothyroidism, defined as an abnormally increased TSH concentration in women of reproductive age, affects 2 to 4% of the population [23]. Age and dietary iodine consumption are two factors that can have an impact on the prevalence of iodine insufficiency [24]. The majority of patients have thyroid peroxidase antibodies, making Auto-Immune Thyroid Disease (AITD) the most common cause of hypothyroidism in women of reproductive age [24]. Some of the less common causes of hypothyroidism are post 131-I (radioactive activity), post-thyroiditis, and drug-induced hypothyroidism [24].

Numerous reproductive problems, including irregular menstruation, infertility, and improper sexual development, are associated with hypothyroidism [25].

Changes in the menstrual cycle have been connected to hypothyroidism since 1950 [25]. In earlier research, menorrhagia (increased blood flow), which affected 60% of overtly hypothyroid women, was the most prevalent symptoms [26]. Effect of hypothyroidism in different age groups is summarised in [Table/Fig-3] [25].

Age group	Reproductive problems related to hypothyroidism
First 10 years	Delayed sexual maturation
Early puberty	Galactorrhoea, delay in pubic hair growth and occasionally associated with juvenile hypothyroidism
Adult women	Ovulatory issues like menorrhagia, galactorrhoea and hirsutism, change in cycle length also blood flow is frequent

[Table/Fig-3]: Reproductive problems related to hypothyroidism with age [25].

Increased blood TSH in the presence of normal free thyroxine (fT4) concentrations is known as SH. Recent studies have shown that individual variations in off T4 are narrower than variations in the population's reference range. These results imply that an abnormal fT4 in a patient with elevated serum TSH may be reflected by a normal fT4 (within the population reference range) [27]. SH has been more prevalent since the introduction of third-generation serum TSH testing. SH shares the same aetiology as overt hypothyroidism and thyroid antibodies are one factor that can influence whether SH develops into overt hypothyroidism [28].

The relationship between SH and infertility has been the subject of numerous studies. The bulk of studies are retrospective and uncontrolled in nature. In 1981, TRH tests were administered to 185 infertile women between the ages of 25 and 34. Women who had a subclinically high TSH response to TRH (20 mU/mL) were deemed infertile. SH was discovered in 20 women (20/185), or 11% of the entire population. There was no mention of the causes of infertility. The authors claim that SH is a contributing cause to infertility. When 50 mg of LT 4 was administered to eleven of the twenty women, their mid-progesterone output was stabilised, leading to two pregnancies [17]. Corpus luteum deficiency in female infertility was related to SH or whether this changed with LT4 for reproductive purposes [29].

Screening and Treatment of Thyroid Abnormalities in Female Infertility

In comparison to other well accepted preventative therapies, general population screening for moderate thyroid impairment is more cost-effective. The three possible benefits-progression to overt hypothyroidism, serum cholesterol levels in those with hypercholesterolaemia, and treatment of potentially undiscovered TH deficiency symptoms- are the basis for screening anyone over 35 [30]. Menstrual cycle, Luteinizing Hormone (LH) pulsatility, and hyperprolactinaemia are surrogate endpoints that thyroid dysfunction medicine affects [31]. Small intervention study in India has shown positive effect on the rate of spontaneous conception, but the findings are dubious because there were no controls [32]. A previous study found that among a case group of infertile women, the frequency of overt and subclinical thyroid dysfunction was comparable to that of a control female population with normal fertility [17]. There is compelling evidence connecting AITD to female infertility, especially endometriosis. A shared immunopathogenic

mechanism is the cause of this connection. In addition to the potential harm AITD may do to fertility, a study has shown that AITD raises the chance of hypothyroidism during pregnancy (with possible harmful consequences on both the mother and the foetus), and that this risk can be decreased by early LT4 treatment. Additionally, research on the association between AITD and miscarriage demonstrates that women with AITD had a two to five times greater likelihood of experiencing an early miscarriage [2]. In patients with a low thyroid reserve, the Assisted Reproductive Technology (ART) approach may aggravate thyroid dysfunction [33]. Contrarily, AITD does not seem to have an impact on the rate of conception following ART, with the exception of people who initially had SH [34]. The potential to reverse infertility and avoid expensive ART procedures, the progression to overt thyroid dysfunction during pregnancy, with detrimental effects on mother and child, the increased risk of miscarriage, and postpartum thyroiditis and depression are all advantages of screening for and treating thyroid failure in infertile women [35]. Thyroid abnormalities screening in infertility is a potentially cost-effective method due to all of these aspects.

Treatment is recommended in cases of overt thyroid malfunction or SH. It's unclear if isolated AITD needs to be treated. When AITD and euthyroidism are present, a close follow-up is recommended, and these patients should be regarded as miscarriers. Weak evidence supports LT4 therapy; more research with appropriate randomised controlled prospective studies is needed to elucidate the effect on fertility and pregnancy outcome [20].

Markers of Ovarian Reserve, Peripheral TH Metabolism, and Potential "Local" Crosstalk

There have only been a few in-vitro and in-vivo studies of peripheral thyroid metabolism and signalling in the ovary [36]. The possibility of crosstalk between the various mechanisms involved in Functional Ovarian Reserve (FOR) preservation has been clearly shown by in-vitro system [37]. Additionally, relationship between gonadotropins and thyroid pathways are initiated by them, specifically TSH, and the development of the gonadal organs [37]. By connecting with additional signalling pathways like Anti-Mullerian Hormone (AMH), Growth Differentiation Factor 9 (GDF9), Bone Morphogenetic Protein 15 (BMP15), IGF, or other endocrine hormones (such FSH, LH), the TH/TR complexes may in fact contribute to the onset of Primary Ovarian Insufficiency (POI) [38]. As already mentioned, in-vitro research has been done on these factors. The production of GDF9, BMP15, and AMH during the maturation phases of follicles is necessary for the activation of signalling pathways that are specifically involved in FOR preservation [39].

The interaction of the aforementioned pathways with intracellular T3 signalling has not been explored in ovarian cell lines with the deletion of one or more genes from the ensemble of components involved in cellular TH metabolism and signalling [37]. Due to increased transcription of the Follicle Stimulating Hormone (FSH) receptor (FSH-R) gene, the role of T3 in the amplifying of FSH-R signalling during the differentiation of swine Granulosa Cells (GCs) was first demonstrated [40]. The combination of FSH and T3 signalling was then validated by Tsang et al., to raise FSH-R levels in rat pre-antral follicles via GDF9. As a result of enhanced expression of cytochrome P450 lanosterol 14-demethylase (Cyp51), a mediator of T3 and FSH-induced follicular growth, T3 and FSH co-treatment also increased steroid synthesis [41]. These results suggested that the ovaries' TH and gonadotropin signalling crosstalk may be involved [42]. The link between Transforming Growth Factor-β (TGF-β) family of proteins and THs was also inferred indirectly in an in-vitro study using bovine cumulus cells activated with GDF9 and BMP15. Cells produced more circular Ribonucleic Acid (RNA) after stimulation, which was housed in TRAP80, a part of several multi-subunit complexes that aids them in their function as transcriptional factors, including TRs [43]. The synthesis of thyroid-specific genes and the activation of the MAPK pathway are all controlled by the TSHR/IGF1R cross-talk [44]. The authors highlight the existence of both receptors in the tissue, despite the fact that this interaction has not yet been studied in the ovary. Gonadotropin-driven cyclic Adenosine Mono-Phosphate (cAMP) cascade enhances and oestradiol production inhibits TSH-R expression in cultures of rat follicles and primary GCs. Last but not least, the primary TSH-R activator of the ovary is recognised to be thyrostimulin, which is produced by oocytes [45]. Hyperthyroid women have been found to have higher levels of circulating LH, which is paradoxical [46]. In the trials indicated above, it was suggested that THs affected steroidogenesis and the expression of oestrogen receptors in the ovary through modulating LH transcription as well as FSH [47]. The data demonstrate the significance of TH signalling in FOR preservation because to its interplay with other signalling pathways involved specifically in ovarian health.

CONCLUSION(S)

The proper functioning of the entire organism, especially the reproductive system, is compromised by fluctuations in the blood concentration of TH, which are involved in the control of numerous physiological processes. Subfertility or infertility, menstrual/estrous irregularity, anovulation, abortion, preterm birth, intrauterine growth restriction, and mental disability in offspring are well-documented consequences of maternal thyroid dysfunction. TH impact female reproductive mechanisms, affecting menstrual cycles, sexual behaviour, ovulation, pregnancy maintenance, and breastfeeding. Hypothyroidism reduces oestrogen sensitivity in uterine cells, slowing cell division. Hypothyroidism is associated with delayed sexual maturation, irregular periods, impaired sexual development, and ovulatory disorders in women, including menorrhagia and hirsutism.

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