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Female Fertility through the Lens of the Thyroid Gland: A Review

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Abstract
Fertility is the natural capacity of a couple to conceive a child through an intricate biological process. In females the secretion of optimal levels of thyroid hormones by the thyroid gland, a vital hormone gland which plays a major role in the metabolism, growth, and development of the human body, is necessary for the effectiveness of this process. This review intends to bring to the fore how the thyroid gland impacts fertility in females and the adverse effects of a dysfunctional thyroid gland on the ability of a female to get pregnant or sustain the same to term. Relevant literature on the thyroid gland's regulation of female fertility in various search engines were reviewed. Various studies have helped to establish strong links between the functionality of the thyroid gland and fertility. This is implicated on the secretion of thyroid hormones, especially triiodothyronine (T3), and tetraiodothyronine (T4), and their resultant effect on reproductive processes such as the rate of folliculogenesis and the onset of ovulation. Hypothyroidism and hyperthyroidism are disorders of the thyroid gland that often result in infertility. Studies have proven, by monitoring the genesis of symptoms of infertility and their resolution between periods of thyroid dysfunction and restoration of normal T3 and T4 levels in circulation, that a strong link exists between normal thyroid gland function and the ability to reproduce. The recognition of the mechanisms involved may help to establish preventive measures early enough, aid proper diagnosis of infertility, and increase the effectiveness of therapeutic measures employed in helping infertile females get pregnant.

Keywords: Female Fertility, Thyroid Gland, Review

Introduction

To better understand how the body operates and performs its vital processes, one must consider the very fundamental principles of the body's communication system. Hormones are one of the principal factors in intercellular and inter-organ communication. We have several endocrine glands producing chemical messengers to participate in various physiological functions, and the thyroid gland holds a central place in controlling the physiology of human body (Wagner *et al*., 2008).

The thyroid is a hormonally active gland that is part of the hypothalamic-pituitary-thyroid axis. The axis includes thyroid releasing hormone (TRH) which is secreted by the hypothalamus. TRH stimulates the release of thyroid stimulating hormone (TSH) from the anterior pituitary gland. TSH, in turn, stimulates the thyroid to secrete thyroxine (T4) and triiodothyronine (T3), which are present in a free active form, and a bound inactive form (Fekete and Lechan, 2014; Bates, 2018). Thyroid derangements most commonly arise from primary thyroid dysfunction, rarely being caused by secondary etiologies such as a TSH secreting pituitary adenoma, pituitary failure or hypothalamic failure (Bates, 2018). Thus, hypothyroidism is generally associated with decreased T3 and T4 and increased TSH. In contrast, hyperthyroidism is associated with increased T3 and T4, and decreased TSH levels. Graves' disease and Hashimoto's thyroiditis

(HT) result in autoimmune hyper-and hypothyroidism, respectively. Hyperfunctioning "toxic" multinodular goiter, and hyperfunctioning adenoma are common non-autoimmune causes of hyperthyroidism. Non-autoimmune hypothyroidism often results secondary to surgery, radiation or radioiodine administration for the treatment of hyperthyroidism. Hyperthyroidism results in a hypermetabolic state typified by sympathetic overactivity resulting in tachycardia, tremor, anxiety, diarrhoea and weight loss. Conversely, hypothyroidism is a slowing of physical and mental activity with resultant fatigue, decreased cardiac output, constipation, and weight gain (Maitra, 2015). While the effects of thyroid function on metabolism and anthropomorphic parameters are well known, the effects of these hormones and thyroid disease on sexual functioning have been less thoroughly elucidated. In part, this is due to the long-held belief that genitalia are non-responsive to thyroid hormones. However, recent studies have identified the presence of thyroid hormone receptors in both the male and female genitalia including the testis, corpora cavernosa, ovary, and vagina (Carosa *et al*., 2018).

The thyroid hormones are widely considered to be indispensable to the human body. Thyroid stimulating hormone (TSH) is secreted by the pituitary gland and stimulates the thyroid gland to secrete two different thyroid hormones: tri-iodo-L-thyronine (T3 or triiodothyronine) and tetra-iodo-L-thyronine (T4 or thyroxine). The thyroid hormones are crucial for normal functioning because of their control over body's basal metabolic rate, as well as growth, development, and differentiation of many cells/organs in the body (Wagner *et al*., 2008). Given diverse roles of thyroid in the human body, it would be interesting to explore how the thyroid gland affects the molecular and physiological processes that impact fertility, especially in females.

Infertility is defined as the absence of clinical pregnancy after at least one year of regular unprotected intercourse (Chai *et al*., 2014). Infertility is a global health issue affecting about 48 million couples (WHO, 2019). The prevalence is higher in sub-Saharan Africa. In Nigeria 10 – 30% of couples are affected (Chimbatata and Malimba, 2016).

There is a close link between thyroid function and female fertility. Physiologically, pregnancy has a significant effect on the thyroid gland, and thyroid dysfunction has long been associated with female infertility with both obstetric and foetal outcomes being well established (Dosiou, 2020; Lazarus, 2011).

Methodology

In this review, a critical, constructive analysis of relevant literature in the subject areas of thyroid gland's regulation of female reproductive function and female fertility was carried out. The literature survey entailed the use of the general search engine (Google); subject specific search engine (PubMed) as well as scholarly literature engine (Google Scholar).

The Thyroid Gland and Fertility in Females

Thyroid hormones (THs) are vital for the normal reproductive function of humans and animals. L-thyroxine (3,5,3',5'-tetraiodothyronine, T4) and L-triiodothyronine (3,5,3'-triiodothyronine, T3) act directly on ovarian, uterine, and placental tissues (specifically in the syncytiotrophoblast and villous cytotrophoblast) via specific nuclear receptors that modulate the development and metabolism of these organs (James *et al*., 2007; Vattai *et al*., 2015; Adu-Gyamfi *et al*., 2020).

In addition, they act indirectly through multiple interactions with other hormones and growth factors, such as estrogen, prolactin (PRL), and insulin-like growth factor (IGF), and by influencing the release of gonadotrophin-releasing hormone (GnRH) in the hypothalamic-pituitary-gonadal axis (Poppe and Glinoer, 200). Therefore, changes in the serum levels of THs, such as hypothyroidism and hyperthyroidism, may result in subfertility or infertility in women (Silva *et al*., 2012). Hypothyroidism usually results from autoimmune thyroiditis, in which the body's own antibodies react against key thyroid proteins, such as thyroperoxidase (TPO) and/or thyroglobulin (Tg), resulting in destruction and the loss of gland function (Thangaratinam *et al*., 2011). The occurrence of hypothyroidism in women and animals is

associated with reproductive disorders, such as delayed onset of puberty, anovulation, ovarian cysts, menstrual irregularity, infertility, increased frequency of spontaneous abortions and the birth of preterm infants with low birth weight and congenital anomalies (Panciera *et al*., 2012). In addition, research has recently shown that these gestational changes also result from compromised placental development, with reduced proliferation and increased apoptosis of trophoblastic cells and a failure of intrauterine migration associated with alterations in the endocrine, immune, and angiogenic profiles at the maternal–fetal interface (Silva *et al*., 2014).

The prevalence of hyperthyroidism in women of reproductive age is 1.3%, and the disease usually occurs because of an increase in antibodies against the thyroid-stimulating hormone (TSH) receptor, which is known as Graves' disease. Data supporting the association of hyperthyroidism with infertility are still sparse and sometimes conflicting (Mintziori *et al*., 2016).

Mechanism of Thyroid Hormone Action on the Female Reproductive System

A well-functioning thyroid is crucial in pregnancy, and it undergoes physiologic changes to sustain foetal growth. There is a notable increase in thyroid gland size during pregnancy, by 10% in women who are well supplied in iodine and up to 20–40% in those who are iodine deficient. The thyroid function changes in two ways: by increase in thyroxine binding globulin (TBG) due to estradiol level, and stimulatory effects of human chorionic gonadotropin (hCG), with repercussion on the hypothalamic–pituitary –thyroid axis (Alexander *et al.,* 2017).

An important role in the central and peripheral crosstalk is also played by adipokines (in the hypothalamic-pituitary-gonadal axis); specifically, kisspeptin, which is essential for human reproduction acting on the hypothalamus and stimulating GnRH production. It may also stimulate TSH (Jayasena *et al*., 2014). Furthermore, leptin, which is produced by adipocytes and regulates food intake and energy storage, influences the hypothalamus–pituitary– thyroid axis by regulating the expression and stimulating thyrotropin-releasing hormone (TRH) (Mantzoros *et al.*, 2011).

These conditions result in different thyroid-stimulating hormone (TSH) and free T4 (fT4) reference range than in the period out of gestation. In fact, TSH level decreases in the first trimester of pregnancy by 20–50%, due to hCG stimulatory effect on TSH receptor, leading to an fT4 increase in the same trimester, reaching maximum concentrations by 16 weeks of gestation, and consequently TSH increasing and fT4 lowering throughout the rest of gestation. In 15% of pregnant women during the first trimester, TSH level is below the lower limit of reference range of 0.4 mU/L (Lazarus, 2011). In multiple pregnancies, it is expected that TSH level is even more suppressed due to higher hCG concentration (Sapin *et al*., 2004). Previous data proposed TSH upper reference limit of 2.5 mU/L in the first trimester and 3.0 mU/L in the second and third trimester (Lazarus *et al*., 2014); recent studies proposed wider ranges, and societies now recommend using the reference range for each trimester adjusted for the population (local laboratory ranges), and T4 instead of fT4 as more specific for the pregnancy, although, as this is not readily available in all countries, many clinicians rely on TSH to monitor thyroid function throughout pregnancy. When population- and trimester-specific reference ranges for TSH are not available, an upper reference of approximately 4 mU/mL may be used (Alexander *et al*., 2017).

The importance of thyroid hormones in the female reproductive system has been highlighted since the evidence of TSH and thyroid hormone receptors (TR-a1 and TR-b1) on ovarian and oocytes surface (Zhou *et al*., 2019), so its role in folliculogenesis, fertilization, embryogenesis, and in implantation, and maintaining pregnancy is inevitable. Furthermore, the expression of TSH receptor in human granulosa cells as well as the increase of cyclic adenosine monophosphate (cAMP) upon TSH stimulation have been described (Aghajanova *et al*., 2009). Consequently, thyroid hormones impairment could affect markers of ovarian reserve, including anti-Mullerian hormone (AMH) (Kabodmehri *et al.*, 2021). Moreover, alterations in thyroid hormones signaling could also have detrimental effects on the placenta, possibly even causing abortion; however, the molecular

mechanisms involved have not been completely understood (Adu-Gyamfi *et al.,* 2020).

Thyroid hormones act indirectly through multiple interactions with other hormones and growth factors, such as estrogen, prolactin (PRL), and insulin-like growth factor (IGF), and by influencing the release of gonadotrophin-releasing hormone (GnRH) in the hypothalamic-pituitary-gonadal axis (Poppe and Glinoer, 2003). In this regard, in vitro studies suggest that thyroid hormones promote FSH-induced preantral follicle growth, activating the protein kinase B (Akt) pathway (Zhang *et al.,* 2011). Thyroid hormones and hormone receptors also regulate the endometrium receptivity, which is the stage where all the actors, including thyroid hormones, cooperate to prepare and allow the implantation window of the blastocyst, with variations during the menstrual cycle (Mazzilli *et al.,* 2023).

Thyroid Disorders and Female Infertility

A Nigerian study by Emokpae *et al. (2011)* reported an overall prevalence of thyroid disorders in women at 23.4%, consisting of subclinical hypothyroidism (14.9%) and subclinical hyperthyroidism (7.5%). In Europe, the prevalence of thyroid disorders in women aged 20–45 years varies between 5% and 7% for subclinical hypothyroidism (SCH), 0.2–4.5% for overt hypothyroidism (OH), 0.3–1% for hyperthyroidism and 5–10% for thyroid autoimmunity (TAI). Hypothyroidism is generally associated with decreased T3 and T4 and increased TSH. In contrast, hyperthyroidism is associated with increased T3 and T4, and decreased TSH levels (Maitra, 2015; Carosa et al., 2018).

Moreover, much contradiction exists in current literature as regards the impact of hyperthyroidism on female fertility. That there are effects cannot be questioned, but arriving at definite conclusions appears to be further removed from us as compared to what is now known of the impacts of hypothyroidism.

Hyperthyroidism

The most common cause of thyrotoxicosis, a clinical syndrome resulting in exposure to thyroid hormone excess, is hyperthyroidism, which, in reproductive age, is usually due to autoimmune Graves' disease (GD). GD occurs in 0.4–1.0% of women before pregnancy and about 0.2% during pregnancy. It is crucial to differentiate it from relatively common, hyperemesis gravidarum, which occurs in 0.3–1% of the cases. Other causes, such as toxic multinodular goiter and toxic adenoma, as well as subacute thyroiditis, are less common, and others are very rare. It is, therefore, important to distinguish these clinical manifestations to apply an adequate treatment (Zhou *et al*., 2019). Gestational transient thyrotoxicosis is more frequent than GD. A rare cause of hyperthyroidism in pregnancy is the mutation of the TSH receptor gene with functional hypersensitivity to hCG. Due to the stimulating effect of hCG on TSH receptor, serum TSH may decrease in the first trimester, with a peak of hCG between 7- and 11-weeks' gestation. Even TSH levels lower than 0.1 mU/L may occur approximately in 5% of women by week 11 of pregnancy (Alexander *et al*., 2017).

Impact on Spontaneous Conception

Thyrotoxicosis results in increased serum levels of sex hormone binding globulin (SHBG) due to increase in estradiol levels, and a reduction of the metabolic clearance rate of estradiol. In women with hyperthyroidism, testosterone and androstenedione levels increase due to a higher production rate. Furthermore, the ratio of the conversion of androstenedione to estrone, as well as of testosterone to estradiol, increases. These hormonal alterations result in menstrual cycle disturbances 2.5 times more frequent than in the general population (Krassas *et al*., 2010).

Hypothyroidism

The term Hypothyroidism is defined as the disturbed hormonal level of thyroid stimulating hormone and tetraiodothyronine, there is an increased level of TSH in the blood and decreased level of T4 in the blood. There are various factors involved in hypothyroidism, the main one is Hashimoto's disease. “Hashimoto's disease” is an autoimmune disorder that majorly affects the enzyme named thyroid peroxidase. Thyroid peroxidase performs the function of oxidation of iodine which is considered the initiative for the synthesis of thyroid hormone. The diseases include the formation of autoantibodies against the macro-protein that is

named thyroglobulin. It is composed of a total of 115 tyrosine residues and about 5000 amino acids (Seifi *et al.,* 2022).

The diagnosis of hypothyroidism due to Hashimoto's thyroiditis can be confirmed by analyzing the lab report values as they serve as a guide in this procedure. The elevated value of anti-thyroglobulin in the serum or peroxidase antibodies may be responsible for delayed puberty in females. It is highly responsible for decreased fertility and various menstrual disorders. The disturbed level of the hormone causes the prevention of ovulation while ultimately leading the female toward developing PCOS (Thapa and Khanal, 2021). Studies provide evidence for the association of hypothyroidism with insulin resistance in humans. The studies also suggest that females with hypothyroidism have increased levels of testosterone in their bodies. The elevated level of testosterone serves as a disturbing factor for the menstrual cycle. This also challenges the female's ability to ovulate (Naeem *et al*., 2022).

Considering the thyroid disorder: Hypothyroidism is highly responsible for several reproductive disorders. These include ovulation disorder, amenorrhea, hyperprolactinemia, menstrual disorders, spontaneous abortion, and infertility. Hypothyroidism clinical manifestation is very vast and diverse and is dependent on several factors such as duration of disease, age of individual, and severity of reduction of thyroid hormone. According to the available studies, the prevalence of hypothyroidism in males is about 0.2% while in females it is 2% (Naeem *et al*., 2022). Studies also provide evidence that women that have small figures at the time of birth as well as during their childhood are at greater risk of developing the condition of hypothyroidism (Seifi *et al.,* 2022).

In other studies, women of advanced reproductive age and TSH levels >3.0 mIU/L, significantly reduced level of anti-Müllerian hormone (AMH) levels were measured, compared to women with TSH levels <3.0 mIU/L (Aghajanova *et al*., 2009; Kabodmehri *et al.,* 2021). A retrospective study in 2568 Chinese women initiating ART showed significantly lower AMH concentrations, antral follicle counts (AFC) and higher FSH levels in women aged ≥ 35 years with SCH (Kabodmehri *et al*., 2021).

The prevalence of infertility in women with (subclinical) hypothyroidism has not been investigated in longitudinal studies, but only in a few retrospective ones. In one study from 1993, the authors stated that primary and secondary infertility was present in 6% of women, a prevalence compared with that in the general population at those days (Adu-Gyamfi *et al*., 2020). In another study, the prevalence of infertility, defined as the absence of pregnancy in sexually active women having regular unprotected intercourse for an exposure period of at least 12 months, was 47% in women with autoimmune hypothyroidism; significantly higher compared to the prevalence in the general population (ranging from 7.4 to 24.0% in population-based studies) (Selva and Hammond, 2009). In the same study, the number of pregnancies was determined in women prior and after the diagnosis of hypothyroidism. Following the diagnosis, it was 0.67 and prior 1.48 (P = 0.02). Noteworthy is that no differences were present between baseline variables and hormonal parameters between fertile and infertile women with hyperthyroidism or hypothyroidism (Krassas et al., 2010).

Interference of Hypothyroidism with Female fertility

Hypothyroidism is more prevalent among females as compared to males and it brings along complications in the reproductive life of females. These complications include irregularity in the menstrual cycles, abnormal development of sexual organs, early or premature menopause, and infertility. The mechanism involved behind the menstrual abnormalities due to hypothyroidism includes disruption in the hypothalamic-pituitary-ovarian axis. This disruption ultimately leads to an alteration of the TSH response as well as the alteration in the TRH. Altered TRH causes the production of increased prolactin which then induces the alteration in GnRH. All these factors attribute to the defective response of the LH hormone resulting in ovulatory dysfunctions and

abnormality in the luteal phase of menstrual cycles (Pirahanchi *et al.*, 2021).

The balance between the hypothalamic-pituitary-adrenogenital (hypothalamic-pituitary-gonadal) axis is responsible for the maintenance of fertility. Any disruption in this balance results in dysfunction and leads to infertility. Fertility problems associated with hypothyroidism in the reproductive period include frequent miscarriages, abnormality in the menstrual cycle, and delay in the onset of puberty. Studies suggest various endocrine factors responsible for infertility such as Cushing's syndrome, PCOS, diabetes mellitus, and hyperthyroidism, but the most common endocrine cause includes hypothyroidism (Chua *et al.*, 2020).

Hypothyroidism plays role in infertility by disturbing the balance between sex hormones, raising the level of prolactin, and causing dysfunction in the ovulatory as well as the luteal phase of the menstrual cycle. Studies provide evidence that hypothyroidism is highly associated with interfering with the process of ovulation. The elevated level of TRH stimulates the pituitary gland to release estrogen and TSH. When the estrogen remains elevated for a prolonged period, the release of LH and FSH gets disturbed leading to dysfunction of the ovaries. Elevated prolactin levels and reduced SHBG act as the key factor in reducing the potential of ovaries to work (Chua *et al.*, 2020).

Studies suggest that if hypothyroidism is present from the time of birth then it plays a significant role in reducing the number of Graafian and primordial follicles resulting in so defective folliculogenesis. Evidence has been found that changes in the release of GnRH cause reduced secretion of LH that serves as inhibiting factor in ovulation, folliculogenesis, and the synthesis of estrogen while exerting its luteolytic effects overall. Hence the role of the thyroid in the regulation of fertility is of key significance. The role of hypothyroidism in the maintenance of pregnancy is another thing that needs to be considered. It may adversely affect the outcomes of pregnancy to a great extent, some of these include stillbirth, reduced fertility, abruption of the placenta, increased risk of gestational hypertension, frequent abortions, and impaired developmental, cognitive, and learning abilities. It is stated that there is a strong correlation between Hypothyroidism and hyperprolactinemia and this hyperprolactinemia state is considered one of the key factors in causing infertility. The endocrine society's recommendations act as a guideline for the screening of thyroid-associated disorders in females facing the problem of infertility. The detection rate of infertile females associated with thyroid disorders has increased to a great extent. The prevalence of infertility in females account for about 35%, for males, it accounts for 30%, and for the combined factor it is about 20%. In about 15% of the cases, the cause behind infertility has been idiopathic. Female of reproductive age remains at high risk for developing thyroid disorder that may act as a source of infertility (Dhillon-Smith *et al.,* 2022; Rao *et al*., 2020).

Infertility in Euthyroid Women with Thyroid Autoimmunity

A prospective US study in 436 patients reported lower AFCs in women with unexplained infertility, diminished ovarian reserve and increased thyroid peroxidase antibodies (TPOAb) levels (- 2.3 follicles, 95% CI: - 3.8 to - 0.5; P = 0.01) (Karl *et al*., 2009).

The presence of TAI can lead to infertility via several factors directly and/or indirectly related to the presence of the antibodies. An indirect mechanism is via the higher mean age in women with TAI compared to that in women without (Yorke, 2022). Age is an independent risk factor for a decreased ovarian reserve and in later stages for miscarriage too. However, in a recent study by Poppe et al., infertile women with TAI were not older compared with women without TAI, nor was there a difference in the use of tobacco (Poppe *et al*., 2021).

The presence of TAI is probably also a reflection/marker of an immune imbalance that might lead to or be associated with implantation failure (Lee *et al*., 2009). Infertile women with TAI might have a higher prevalence of antiphospholipid antibodies (aPL), and the presence of aPL as such has been associated with implantation failure (Budenhofer et al., 2013). However, in studies investigating pregnancy outcomes in women with TAI in which the

presence of aPL was excluded a priori, higher miscarriage rates remained present; an argument against the impact of aPL (Razvi *et al*., 2019).

In other studies, in women with TAI and recurrent implantation failure (RIF), abnormal T-lymphocyte function and higher numbers of endometrial T-cells have been reported, as well as decreased percentages of T-cytotoxicity cells (Tc) and an increased Th/Tc ratio ($P < 0.05$) (Toloza *et al*., 2020). The prevalence of thyroid dysfunction, the absolute number and percentage of T-cells, T-helper (Th) cells, B-cells and natural killer (NK) cells were not different between women with and without TAI (Allan et al., 2000). Since no difference in serum oestradiol or progesterone levels were observed between groups, these findings could indicate that TAI induces a non-receptive endometrial milieu that may underlie the detrimental effects on embryo implantation (Michalakis *et al.,* 2011).

However, in most clinical studies similar implantation rates were noted between women with – and without TAI, although with more first-trimester miscarriages in women with TAI (Jokar *et al.*, 2018). Bottom-line, implantation failure remains a problem that is difficult to document and is due to several altered parameters, including male factors (Fumarola *et al.,* 2013).

Future studies should aim to investigate whether the prevalence of infertility in euthyroid women with TAI is higher compared with that in age-matched women without thyroid disorders. Whether higher levels of increased TPOAb or thyroglobulin (TgAb) in euthyroid women correlate with ovarian reserve and/or implantation and pregnancy rates remain to be investigated too. In daily practice, the presence of TAI may remain unaware since 5–10% of women will have antibodies with a normal function and therefore and will not be screened for it (Vander-Borght and Wyns, 2018).

Conclusion

In the last two decades, increasing amounts of research efforts have been dedicated to looking into thyroid's effect on fertility and infertility. While there is some definite connection between thyroid disease and infertility, much contradiction still surrounds the understanding of the actual mechanisms involved. A lack of research exists in this area, further enhancing the contradictions that are present. It is an established fact concerning females that thyroid hormones play an important role in normal reproductive function both through direct effects on the ovaries and indirectly by interacting with sex hormone binding proteins. Thyroid dysfunction can lead to (reversible) menstrual irregularities and infertility. When thyroid dysfunction is detected, L-thyroxine treatment may help to restore normal fertility and reduce the likelihood of an ART procedure.

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