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Thyroid hormones and female health: A comprehensive review of endocrine and reproductive implications

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Abstract
Thyroid hormones are essential for controlling growth, metabolism, and reproduction. From puberty to menopause, the complex relationship between thyroid function and reproductive health in women is visible at every stage of life. Menstrual abnormalities, infertility, pregnancy problems, and postpartum disruptions can all be caused by thyroid disorders, especially autoimmune thyroid illnesses, which disproportionately impact women. While hyperthyroidism can result in amenorrhea or oligo menorrhea, hypothyroidism is often linked to anovulation and menstrual disorders. Thyroid autoimmunity and subclinical thyroid disorders have been associated with infertility and poor reproductive outcomes, even in euthyroid people. Pregnancy causes physiological changes that influence the dynamics of thyroid hormones, making close observation more important to avoid problems for both the mother and the foetus. Transient or permanent thyroid dysfunction can be a symptom of postpartum thyroiditis, which is frequently seen after childbirth. When climacteric alterations and thyroid symptoms coexist in menopausal women, a high level of clinical suspicion is required. This review covers the aetiology of thyroid problems, their effects on reproductive health, and a thorough summary of the physiological functions of thyroid hormones in women. Thyroid disorder must be detected early and treated appropriately to maximize a woman's endocrine and reproductive outcomes.

Keywords: Thyroid hormones, reproductive health, hypothyroidism, hyperthyroidism, infertility, female endocrine health

Introduction
Thyroid hormones have a key role in controlling several biological functions, such as development, metabolism, and thermoregulation. The two main hormones that the thyroid gland produces, triiodothyronine T_3 and thyroxine T_4, are vital for preserving homeostasis throughout the body. In females, these hormones have a more intricate function, affecting both the reproductive system and general physiological processes. Variations in thyroid function during puberty and menopause can have a major impact on a woman's health. Thyroid problems are among the most common endocrine illnesses in the world, and they affect women much more frequently than they do men. During critical reproductive phases like menarche, pregnancy, and menopause, when hormonal changes may worsen pre-existing thyroid disorders or lead to the emergence of new dysfunctions, this discrepancy is most noticeable [1, 2]. Hashimoto's thyroiditis and Graves' disease are two examples of Autoimmune Thyroid Disorders [AITDS] that are particularly common in women, indicating a gender-based sensitivity that may be connected to immunological and hormonal interactions [3]. There are many different ways that thyroid hormones and the female reproductive system interact. Menstrual cycle irregularities, infertility, miscarriage, and pregnancy problems are among the reproductive outcomes that have been linked to these hormones, which also affect the hypothalamic-pituitary-gonadal [HPG] axis [4]. Additionally, thyroid conditions that go undetected or are not properly treated can have a negative impact on fertility, lower quality of life, and increase the chance of pregnancy and childbirth. The purpose of this review is to present a thorough analysis of how thyroid hormones affect female health, with an emphasis on the endocrine and reproductive consequences.

The basic physiology of thyroid function, its gender-specific presentation, and its clinical significance in different stages of a woman's life are highlighted in the introduction.

Thyroid Physiology: An Overview

The hypothalamic-pituitary-thyroid [HPT] axis is the primary regulator of thyroid hormone synthesis and release. The anterior pituitary secretes thyroid-stimulating hormone [TSH] in response to thyrotropin-releasing hormone [TRH] from the brain, which in turn encourages the thyroid gland to generate T_4 and T_3. The hormone that is biologically active is T_3, whereas T_4 functions mainly as a prohormone and is transformed into T_3 in peripheral tissues. [5].

These hormones work by attaching themselves to nuclear thyroid hormone receptors and changing the transcription of genes related to development and metabolism. Thyroid hormones interact with the HPG axis to influence menstrual cycle regulation, ovarian function, and sex hormone metabolism in women.

Gender differences in thyroid disorders

Epidemiological evidence has repeatedly shown that thyroid diseases are more common in women. Overt and subclinical hypothyroidism are very common; research indicates that women are five to ten times more likely than men to have them [7]. Females are also more likely to have hyperthyroidism, particularly when it results from Graves' illness. Immunological, hormonal, and genetic factors are thought to be involved in the underlying causes of this gender discrepancy, albeit they are not entirely understood [8]. The way that estrogen modulates immunological function is one theory that has been put forth. The formation of autoantibodies is more likely when estrogen increases humoral immunity and B-cell activity. Women are more prone to aitds, which may be explained by this [9]. Significant changes in immunological tolerance are also linked to pregnancy and the postpartum phase, which may precipitate or worsen autoimmune diseases such postpartum thyroiditis [10].

Impact on menstrual and reproductive health

Hormonal Imbalances and Menstrual Irregularities

Hormonal fluctuations especially in estrogen and progesterone play a critical role in regulating the menstrual cycle. Any disruption in the hypothalamic-pituitary-ovarian [HPO] axis can cause irregular, painful, or absent menstruation. Conditions such as hypothyroidism, hyperprolactinemia, or premature ovarian insufficiency can all impact menstrual health and fertility.

Common Symptoms

- Irregular periods
- Missed periods [amenorrhea]
- Heavy or prolonged bleeding [11]

Psychological Stress and Mental Health

High levels of stress can disturb the balance of reproductive hormones by affecting the HPO axis, often leading to irregular or absent menstruation. In addition, mental health conditions such as anxiety and depression can influence reproductive health behaviors and outcomes, including adherence to treatments, sexual activity, and fertility planning.

- Disrupted ovulation
- Shortened luteal phase
- Emotional distress related to infertility or menstrual disorders [12]

Polycystic Ovary Syndrome [PCOS]

PCOS is a hormonal disorder that affects millions of people with ovaries, often causing irregular periods, excess androgen production, and polycystic ovaries. It is a leading cause of infertility and is associated with insulin resistance, obesity, and increased risk of metabolic syndrome.

Symptoms

- Irregular or absent periods
- Acne, hirsutism
- Difficulty getting pregnant[13]

Endometriosis and Chronic Pelvic Pain

Endometriosis occurs when tissue similar to the uterine lining grows outside the uterus. This causes inflammation, scarring, and pain. It significantly affects menstrual health and fertility, and it can also cause heavy bleeding, fatigue, and digestive issues.

Reproductive Impact

- Infertility due to pelvic adhesions or inflammation
- Painful ovulation or menstruation [dysmenorrhea] [14]

Environmental and Chemical Exposure

Environmental pollutants and endocrine-disrupting chemicals [EDCs] such as bisphenol A [BPA], dioxins, and phthalates can interfere with hormone receptors and disrupt reproductive health. Long-term exposure is linked to early puberty, menstrual disorders, miscarriage, and infertility.

Examples of EDCs

- Plastics [BPA]
- Industrial chemicals [PCBs]
- Personal care products [parabens] [15]

Poor Nutrition and Lifestyle Factors

Nutrition plays a vital role in maintaining hormonal and reproductive health. Deficiencies in iron, vitamin D, and omega-3 fatty acids, as well as unhealthy habits like smoking or excessive alcohol intake, can lead to menstrual irregularities and complications in fertility.

Risks

- Obesity and insulin resistance [linked to PCOS]
- Low body weight causing amenorrhea
- Increased risk of miscarriage or infertility [16]

Lack of menstrual hygiene and education

In many developing regions, lack of access to sanitary products, clean facilities, and menstrual health education leads to infections, absenteeism from school/work, and long-term reproductive complications. Taboos and stigma also prevent individuals from seeking timely medical care.

Consequences

- Reproductive tract infections [rtis]
- Poor mental and social well-being
- Missed educational and economic opportunities [17]

Infections and Reproductive Health Conditions
Sexually transmitted infections [stis], if untreated, can lead to pelvic inflammatory disease [PID], ectopic pregnancy, and infertility. Proper reproductive health education, routine screenings, and safe sex practices are crucial for prevention.

Common Infections
- Chlamydia
- Gonorrhea
- Human papillomavirus [HPV] [18]

Contraceptives and Assisted Reproductive Technologies [ART]
Hormonal contraceptives can regulate cycles and treat conditions like endometriosis and PCOS. However, some may experience temporary menstrual changes or fertility delays after stopping use. ART [e.g., IVF] offers hope for infertility but can be physically and emotionally demanding.

Considerations
- Contraceptives may cause spotting, mood changes, or amenorrhea
- ART can be expensive and emotionally taxing [19]

Climate Change and Reproductive Health
Climate change, especially extreme temperatures and air pollution, may affect menstrual health and fertility. Increased heat exposure can reduce ovarian reserves and increase pregnancy complications.

Emerging Risks
- Heat-induced fertility reduction
- Air pollution linked to shorter menstrual cycles [20]

Thyroid function and pregnancy:
The thyroid gland plays a critical role in metabolism and hormone regulation. During pregnancy, thyroid function becomes even more important as it supports both maternal health and fetal development, particularly in the early stages when the foetus is entirely dependent on maternal thyroid hormones [21]

Physiological changes in thyroid during pregnancy
- **Increased Hormone Demand:** Pregnancy increases the demand for thyroid hormones by 30-50%.
- **Effect of hCG:** Human chorionic gonadotropin [hCG] stimulates the thyroid, especially in the first trimester.
- **Estrogen Influence:** Higher estrogen levels increase thyroid-binding globulin [TBG], leading to elevated total T_3 and T_4 levels.[22]

Hypothyroidism in Pregnancy
- Commonly due to Hashimoto's thyroiditis [autoimmune].

Effects on Pregnancy
- Increased risk of miscarriage
- Preeclampsia
- Preterm birth
- Low birth weight
- Impaired fetal brain development [23]

Hyperthyroidism in Pregnancy
- Most often caused by Graves' disease [autoimmune hyperthyroidism].

Risks
- Miscarriage
- Hypertension and preeclampsia
- Low birth weight
- Foetal hyperthyroidism or hypothyroidism [if maternal antibodies cross the placenta] [24]

Diagnosis and monitoring
- **Tests Used**
  - TSH [Thyroid Stimulating Hormone]
  - Free T_4
  - Thyroid antibodies [tpoab, trab]
- Trimester-specific TSH reference ranges are necessary, as levels naturally vary during pregnancy [25].

Treatment of thyroid disorders in pregnancy
Hypothyroidism
- Treated with levothyroxine [T_4]
- Dosage is often increased during pregnancy

Hyperthyroidism
- Propylthiouracil [PTU] is used in the first trimester
- Methimazole may be used in the second and third trimesters
- Beta-blockers may be used for symptom control [with caution] [26]

Impact on fetal development
- Maternal thyroid hormones are essential for fetal brain development, especially in the first trimester.
- Untreated hypothyroidism can result in low IQ, developmental delays, and reduced motor skills in children [27].

Postpartum and Menopausal Considerations
A temporary thyroid condition that manifests within the first year following delivery, Postpartum Thyroiditis [PPT] is regarded as a type of autoimmune thyroiditis in most cases, it manifests as a biphasic pattern, with initial hyperthyroidism followed by hypothyroidism and, finally, remission. Nonetheless, a considerable percentage of women may develop hypothyroidism that is persistent [28]. Because PPT and postpartum mood disorders share symptoms, diagnosis is frequently overlooked or delayed.
Thyroid function and decreasing estrogen levels interact in a way that becomes more significant after menopause. Weight gain, mood swings, and exhaustion are some signs of hypothyroidism that could be mistaken for menopausal transition, which could postpone diagnosis. Additionally, postmenopausal hypothyroidism has been linked to elevated risks for osteoporosis and cardiovascular disease, highlighting the necessity of close observation in this age range.

Hypothyroidism complications in females
Thyroxine T_4 and triiodothyronine T_3 are the two main thyroid hormones that are insufficient in women with hypothyroidism, a common endocrine condition. In particular, the reproductive, cardiovascular, neuropsychiatric, and metabolic systems can all be

significantly impacted by the illness, which can manifest as either overt or subclinical.

Menstrual and Ovulatory Dysfunction

Numerous menstrual irregularities, such as oligomenorrhea, menorrhagia, polymenorrhea, and amenorrhea, are closely linked to hypothyroidism [29]. These disorders are caused by the hypothalamic-pituitary-ovarian [HPO] axis being disrupted. Alterations in luteinizing hormone [LH] and follicle-stimulating hormone [FSH] output can result from hypothyroidism's impact on gonadotropin-releasing hormone [GNRH] pulsatility, which in turn impacts follicular development and ovulation [30]. Anovulation may also result from increased prolactin secretion caused by enhanced thyrotropin-releasing hormone [TRH], which further inhibits gonadotropin-releasing hormone [31].

Infertility

Fertility can be seriously hampered by insufficient thyroid hormone. Early embryonic development and implantation are hampered by hypothyroidism's effects on the corpus luteum, luteal phase problems, and decreased ovarian reserve [32]. Additionally, women who have positive thyroid peroxidase antibodies or subclinical hypothyroidism have demonstrated lower success rates with assisted reproductive technologies such *in vitro* fertilization [33].

Pregnancy Complications

There are several detrimental effects on both the mother and the fetus when hypothyroidism during pregnancy is left untreated or not well controlled. Preterm birth, low birth weight, placental abruption, preeclampsia, gestational hypertension, and spontaneous miscarriage are among the risks that are elevated [34]. Impaired neurodevelopment is one of the fetal outcomes; children of hypothyroid mothers have been found to have developmental delays and lower IQ scores [35]. In order to restore the mother's thyroid function, overt hypothyroidism during pregnancy is a high-risk condition that requires prompt levothyroxine treatment [36].

Postpartum Thyroiditis

Postpartum thyroiditis [PPT], which usually manifests 6-12 months after delivery, is more common in women with hypothyroidism, especially those with autoimmune thyroid disease. In up to 30% of instances, PPT can develop to permanent thyroid dysfunction. It frequently follows a biphasic course, with initial temporary hyperthyroidism followed by hypothyroidism [37].

Metabolic and Cardiovascular Effects

Women who have hypothyroidism may experience weight gain, dyslipidemia, and an elevated risk of metabolic syndrome. A greater risk of cardiovascular disease is a result of these alterations. [38]. The disorder is linked to elevated triglyceride and low-density lipoprotein cholesterol [LDL-C] levels, which can raise the risk of ischemic heart disease and encourage atherosclerosis [39].

Cognitive and Psychological Impact

Numerous neuropsychiatric symptoms, such as exhaustion, sadness, memory problems, and difficulty concentrating, can be experienced by women who have hypothyroidism. During menopause in particular, these symptoms are frequently mistaken for other illnesses, which delays proper diagnosis and treatment [40]. Women's cognitive impairment and higher rates of depressive symptoms, particularly in older age groups, have been linked to even mild hypothyroidism [41].

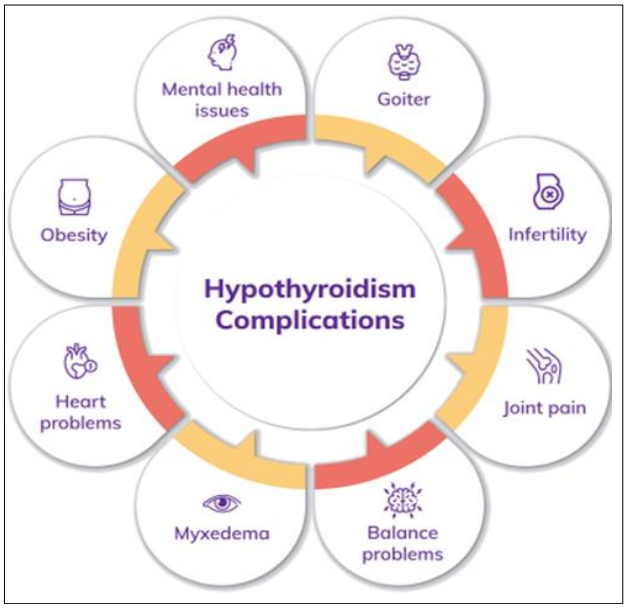

Fig 1: Hypothyroidism complications in females

Hyperthyroidism complications in females

During their reproductive years, women are much more likely than males to suffer from hyperthyroidism, a disorder marked by an excess of thyroid hormones. A number of physiological systems can be affected by the hormonal imbalance brought on by thyrotoxicosis, with consequences being particularly noticeable in females. These include problems with reproduction, hazards associated with pregnancy, heart problems, and psychological impacts.

Menstrual Irregularities and Reproductive Dysfunction:

Menstrual irregularities such oligomenorrhea, hypomenorrhea, or even amenorrhea are common in women with hyperthyroidism [42]. The hypothalamic-pituitary-ovarian [HPO] axis is affected by excess thyroid hormones, which causes these disturbances increased sex hormone-binding globulin [SHBG] due to elevated thyroid hormones modifies the ratio of free estradiol to testosterone, disrupting ovulatory cycles [43]. Defects in the luteal phase and anovulation are frequent and can reduce fertility [44].

Infertility and Fertility Treatment Challenges:

Due to ovulatory malfunction and hormonal disruption of the menstrual cycle, hyperthyroid women may have trouble getting pregnant. In vitro fertilization [IVF] and other assisted reproductive methods may also be less successful if hyperthyroidism is not controlled. [45]. Increased levels of gonadotropins and estradiol are also linked to thyrotoxicosis, which results in a hormonal environment that is not conducive to implantation and the maintenance of an early pregnancy [46].

Pregnancy-related complications

During pregnancy, untreated hyperthyroidism can cause major problems for both the mother and the fetus. Preterm labor, placental abruption, intrauterine growth restriction, preeclampsia, and miscarriage are among them [47].

Additionally, maternal thyrotoxicosis raises the likelihood of fetal hyperthyroidism, particularly when Graves' illness is present and there are positive thyroid-stimulating immunoglobulins cross the placenta [48]. To prevent these negative effects, thyroid function must be regularly monitored during pregnancy.

Postpartum thyroid dysfunction

Previously hyperthyroid women, especially those with autoimmune thyroid disorders, may experience postpartum thyroid dysfunction. The beginning of postpartum thyroiditis or a recurrence of hyperthyroidism may be caused by substantial variations in thyroid function during the postpartum phase. [49]. Maternal mental health and breastfeeding may also be impacted by these variations.

Cardiovascular effects

A hyperdynamic cardiovascular state brought on by hyperthyroidism can increase heart rate, cardiac output, and oxygen consumption. This can worsen cardiovascular strain and raise the incidence of arrhythmias, especially atrial fibrillation, in women, particularly during pregnancy or menopause [50]. Diastolic dysfunction and left ventricular hypertrophy may also be caused by chronic hyperthyroidism [51].

Neuropsychiatric manifestations

Symptoms including anxiety, irritability, mood swings, sleeplessness, and emotional instability are frequently reported by women with hyperthyroidism. These neuropsychiatric symptoms can mimic or exacerbate pre-existing mood disorders, making them particularly problematic during hormonal transitions such as menopause or pregnancy [52]. Additionally documented are cognitive problems like memory loss and trouble focusing, especially in elderly female patients [53].

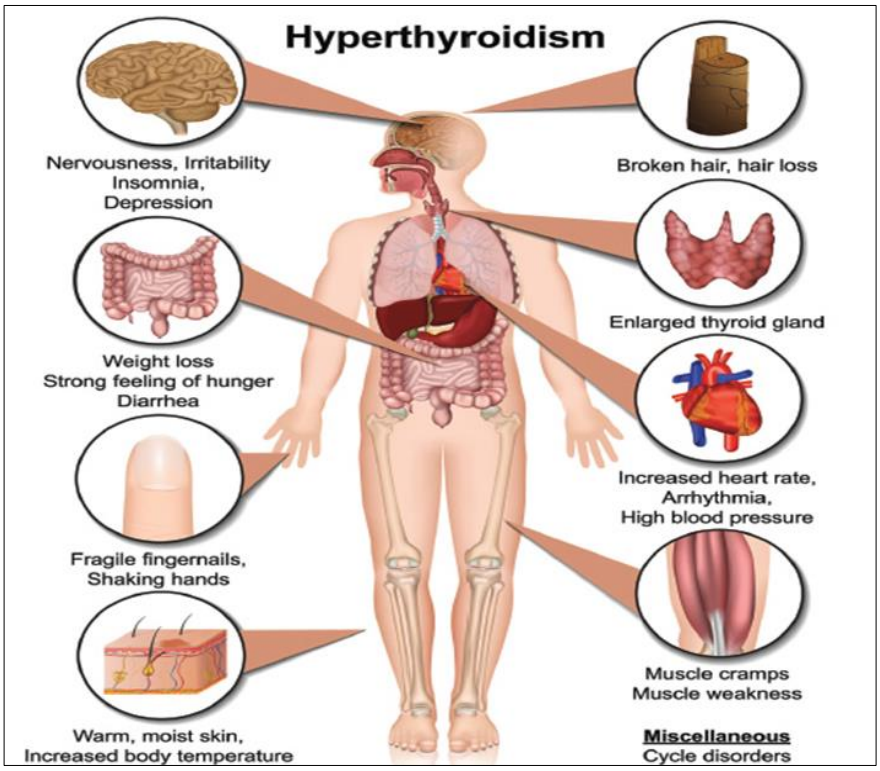

Fig 2: Hyperthyroidism complications in females

Conclusion

From adolescence through menopause, thyroid hormones have a profound impact on female physiological and reproductive health making them essential regulators. The higher vulnerability of women to thyroid diseases, especially during hormonally active phases like puberty, pregnancy, and the postpartum period, is explained by the special interaction between thyroid function and the female endocrine system. Menstrual cyclicity, ovulatory function, and fertility are all severely disrupted by hypothyroidism and hyperthyroidism, which frequently result in issues that can lower quality of life and reproductive success.

Infertility, irregular menstruation, miscarriages, and long-term cardiovascular and metabolic effects are all linked to hypothyroidism, whether it is overt or subclinical. Likewise, hyperthyroidism promotes reproductive difficulties and raises the possibility of unfavourable pregnancy outcomes, such as foetal hyperthyroidism and premature labour. Usually autoimmune in origin, postpartum thyroid diseases exacerbate the clinical picture and frequently go undiagnosed because of their vague symptoms.

Thyroid dysfunction in women requires prompt diagnosis and effective treatment due to the wide range of problems and their potential to affect both the health of the mother and the fetus. In clinical practice, screening should be prioritized, especially during pregnancy and in women who report with irregular menstruation or infertility that lacks an explanation. Furthermore, enhancing access to endocrine treatment and raising knowledge of gender-specific symptoms will greatly lessen the burden of thyroid-related morbidity in women.

Additionally, the burden of thyroid-related morbidity in women will be significantly reduced by expanding access to endocrine treatment and increasing awareness of symptoms particular to gender.

Conflicts of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this article.

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