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Review Article

A Narrative Review on the Potential Relationship between Fertility and Hypothyroidism

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Abstract: Reproduction is important evolutionary process that is necessary for the maintenance of life. Human fertility depends on a number of endocrine factors, one of which includes the regulation of thyroid hormone**.** The thyroid's role in neurocognitive and fetal development is of key importance. Any disruption in the regulation of the thyroid gives rise to a thyroid disorder. The underactivity of this gland will lead to a condition known as hypothyroidism. The prevalence of hypothyroidism is way more in females, especially during their reproductive period. Infertility in males is also a key concern nowadays. The prevalence of infertility in males is one of the concerning topics for the couple as a whole. The hormonal assessment serves as a guide for the evaluation of fertility. The metabolic activity of iodine in the regulation of thyroid normal function is very essential. The present narrative review aims to evaluate thyroid hormone physiology, hypothyroidism, the major types of hypothyroidism, its correlation with fertility, and with the patients that are suffering from polycystic ovarian syndrome. This review article will discuss the iodine association with hypothyroidism and its potential role in fertility. It will aim to provide a precise understanding of associated thyroid disorders that are majorly linked with male infertility.

Keywords: Thyroid hormone / Hypothyroidism / Infertility / PCOS.

INTRODUCTION

WHO provides the clinical definition of infertility as adysfunction of a reproductive system involving the inability to conceive for the duration of almost 12 months or more despite sexual intercourse on regular basis [1]. The infertility prevalence varies among different countries based on their ethnic backgrounds [2]. On the whole, it is suggested that one out of six couples face difficulty in conceiving. According to the studies, the most recurrent causes of infertility in females include hyperprolactinemia which is 7%, tubal abnormalities which are 11%, pelvic adhesions which is 12%, endometriosis 15%, and ovulatory disorders 25% [3]. The maintenance of life is regulated by the process of reproduction. Human fertility depends on a number of endocrine factors, one of which includes the regulation of thyroid hormone. The thyroid gland is an essential gland responsible for the regulation of human physiology, especially the reproduction function. The thyroid gland is a gland that is located in the human neck and is considered one of the most important glands for human functioning. According to the current studies, thyroid hormone disruption may affect ovulation and it may lead to impaired fertility [4]. The thyroid hormone has the potential to modulate the hypothalamic-pituitary-gonadal axis but as such, there is no scientific evidence available. There is strong evidence for the relation of thyroid disorders with the variable degree of the impaired reproductive system. According to the documentation, both type of hypothyroidism: primary and secondary, produces dysfunction in the gonads [5].

The major function that the thyroid hormone performs in the regulation of normal physiology includes differentiation, development, and regulation of several physiological processes that play a key role in the human body [7]. What actual consequences of thyroid disorder during pregnancy and lactation are yet to be known, but one thing that is for sure includes its role in a variety of associated abnormalities. Studies suggest that in pregnant women thyroid disorder is considered the second most prevalent endocrine disorder. Thyroid disorder is highly associated with poor fetal and mother outcomes because of its

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hypermetabolic nature. During pregnancy number of physiological changes occurs in females' body and such changes make the female body more prone to developing hypothyroidism. Females are more prone to suffer from iodine deficiency because of excessive renal loss during pregnancy [7]. According to the studies, the prevalence of thyroid disorder is more in women that are in their reproductive period. Considering the prevalence of thyroid disorders, almost 1 to 2% have the condition of hyperthyroidism, 2 to 3% of women of their reproductive age have hypothyroidism, while 11% have the condition of thyroid autoimmunity [4]. The incidence of thyroid cancer is increasing in recent years and currently, the most common age for thyroid cancer lies between 20 to almost 39 years of age [6] Around 50% of the women are affected by Hashimoto's and Graves' disease and have complained of infertility.

In this narrative review, we aim to provide the latest research regarding the hypothyroidism role in infertility in women and men, types of hypothyroidism, and its association with iodine intake and PCOS. For this purpose, we studied the published papers from 2020 to 2022 on various electronic databases including Web of Science, Google Scholar, and PubMed.The search yielded around 25 original research articles.

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 [8]. 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 [8].

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 [9]. Studies provide the evidence for 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 [10].

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% [10]. 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 [8].

The prevalence of hypothyroidismin different European countries varies according to ethnic backgrounds, iodine intake, and the population considered [8]. In women subclinical hypothyroidism prevalence ranges from 5 to 7%, thyroid autoimmunity prevalence ranges from 5 to 10%, overt hypothyroidism from 0.2 to 4.5% [11].

Types of Hypothyroidism

Primary Vs Secondary Hypothyroidism

Primary hypothyroidism Is characterized by disruption in the thyroid level majorly due to deficiency of iodine in the body, malabsorption of iodine from food, autoimmune diseases associated with the thyroid gland, and due to any side effects of procedures such as radiotherapy or operation of the thyroid gland [3]. The term Hypothyroidism can further be classified into two types that include subclinical types and overt types. The slowness of speech and voice Hoarseness are some of the characteristic features of overt hypothyroidism. Hypothyroidism involves a variety of clinical manifestations such as cardiovascular, dermatological, metabolic, gastrointestinal, ocular, neurologic, and gynecological. Hypothyroidism is most frequent in females [12]. The condition gets worsens if left untreated and will ultimately lead to the condition called myxedema coma. myxedema coma makes the individual more prone to mortality and morbidity.

Secondary hypothyroidism on the other hand is characterized by the disturbance at the level of the hypothalamus-pituitary axis. Hhypothalamus produces a Thyrotropin-releasing hormone (TRH) that is a peptide in nature. TRH further stimulates the release of TSH at the level of the pituitary gland and this ultimately triggers the production of triiodothyronine (T3) and thyroxine (T4). The extrathyroidal deiodination of Tthyroxine ultimately causes the production of T3 [12].

The term Subclinical hypothyroidism (SCH) is characterized by an increased level of TSH in the blood but can also occur with normal thyroid hormones. The prevalence of subclinical hypothyroidism is about 5%. Investigations are still in progress regarding the role of subclinical hypothyroidism in infertility [12]. Considering the subclinical hypothyroidism, the patient may present with a symptom or it may be asymptomatic. The chances of SCH being misdiagnosed while the clinical examination is very high. To confirm the diagnosis, thyroid function tests serve as a reliable source. thyroid function tests with an increased level of TSH and normal T4 serve as the guide [12].

The other common type of hypothyroidism includes Congenital hypothyroidism. The term congenital hypothyroidism is further divided into two categories that include permanent and transient [13].

Permanent hypothyroidism occurs due to various primary and secondary causes, one of which includes dysgenesis of the thyroid. On the other hand, transient hypothyroidism occurs due to complications during pregnancy. Various maternal abnormalities such as the passage of TSH receptors blocking antibodies from the mother to the placenta are one of the major causes of transient hypothyroidism.

Maternal hypothyroidism is also one of the common types of hypothyroidism most frequent during pregnancy. The factors responsible for maternal hypothyroidism include preterm delivery, pregnancy hypertension, stillbirth, placental contractions, developmental disorders of the fetal genital system, impaired development of the fetal nervous system, growth restriction during intrauterine life and congenital hypothyroidism [13].

Interference of Hypothyroidism with Female fertility

Hypothyroidismis 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 [15]. 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 [15].

The balance between the hypothalamic-pituitary adrenogenital 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 [16].

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 [16].

Studies suggest that if hypothyroidismis 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 [17]. 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 [17]. 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 [18]. The prevalence of infertility in females accounts 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 [18]. Female of reproductive age remains at high risk for developing thyroid disorder that may act as a source

of infertility [17]. It is suggested that even after thyroid disorder has been treated if the female is unable to achieve pregnancy then the infertility issue is resolved by Assisted reproductive technology (ART) treatment. In case of ovarian dysfunction or male infertility, various techniques such as intra-uterine insemination might be carried out just before performing ART treatment. The mechanism of ART treatment is based on the stimulation of ovaries and this has been done to achieve increased ovaries retrieval rate. The procedure further assists in avoiding the syndrome named hyperstimulation syndrome. Such hyperstimulation syndromes serve as a severe complication of ovarian dysfunction and hence it acts as a major factor in causing thyroid disorder too [18]. It is suggested to timely detect thyroid disorders to avoid reproductive system complications.

Hypothyroidism and Pregnancy

The state of pregnancy can be defined as a state of alteration in the hormonal and metabolic physiology in female. Most important changes include the change in thyroid hormone level in the body. The failure to adapt such alterations result in severe consequences on the developing fetus in the mother womb [13]. The role of the thyroid hormone is of key importance not only during intrauterine life but also after birth. The thyroid hormone acts as a key hormone for boosting the growth of an individual [14].The thyroid disorder brings major complication in during the gestational period as it has been established that role of thyroids highly significant in the synthesis of special enzymes required by the fetus as well as it is very critical in synthesizing the fetal DNA and RNA of developing fetus. Studies conducted regarding the role of hypothyroidism in pregnant female suggests that thyroid hormone plays a significant role in the development of a baby's emotional capacity. If thyroid hormone would be deficient in the mother, the baby will be lacking its emotional and functional capacities [15].

During intrauterine life, the fetus gets its dose of thyroid hormone from its mother through the passage of the placenta. [15]. The embryo in its first trimester is fully dependent on the thyroid hormone (T4) of the mother until mid of the pregnancy period is achieved (14). The T4 hormone is delivered to the fetus while being protected in the amniotic fluid for almost four weeks. This ultimately protects the fetus's brain from any damage. With time the concentration of free T4 in the fetus which is called FT4 increases, and to determine FT level one can consider the mother's serum level. When the fetus starts secreting its thyroid hormone, the transmission of mother T4 continued and ultimately increases the concentration of fetal T4 levels in the fetal serum [14]. Hence it is to be considered that any disruption in the regulation of thyroid hormone results in severe consequences for the pregnancy.

Hypothyroidism and Polycystic Ovarian Syndrome

Polycystic Ovarian Syndrome is a broad term involving hormonal imbalance and implies a variety of reproductive system complications. PCOS mostly targets females of childbearing age. The major proper PCOS women face is the inability to ovulate in a proper manner. Hypothyroidism plays a major role in PCOS females. Because of the ability of thyroid hormone to be get delivered to all parts of the body through blood, any disruption in thyroid hormone regulation ultimately causes the disturbance. It has been established through studies that thyroid disorders such as hypothyroidism are more common in females suffering from PCOS [25]. It is further implicated that an increased level of TSH in a patient with hypothyroidism has key importance in activating the follicle-stimulating hormone receptor FSHR. The association of PCOS with insulin resistance and obesity is very strong. Studies suggest that almost 44% of female suffering from PCOS suffers from obesity and this is also based n the geographical and ethical background of the individual [25].

The symptoms of the patient suffering from Hypothyroidism and PCOS are very common and both shares a strong association with fertility. Studies have provided evidence regarding the mechanism behind morphological changes in the polycystic ovaries due to hypothyroidism [25]. It suggests that hypothyroid Individual has an increased level of TRH in their bodies and such an elevated level stimulates the production of increased prolactin in the body. Such an elevated level of prolactin hormone in the body disturbs the menstrual cycle by altering the level of LH and FSH hormones in the body. It has also been found that due to hypothyroidism, the collagen gets deposited in the female's ovaries resulting in the alteration of the normal morphology of female ovaries and making them polycystic. Hence it is implicated that time management, as well as diagnosis of hypothyroidism, is the key component in reducing the frequency of infertility in females as well as in preventing females from becoming infertile. It is further suggested that in hypothyroidism individuals, the elevated TRH causes the formation of cysts in the ovaries by reducing egg production and formation [25]. This ultimately disturbs the balance ratio between LH and FSH.

Iodine Role in Fertility

Iodine is considered one of the most significant nutrients essential for regulating the reproductive system of humans and serves a vital role in the growth and development of a fetus as well. The balance of iodine content in the body is essential for the maintenance of fertility, it should not be in deficiency and also it should not be in excess. The recommended requirement of iodine on daily basis is suggested to be around 150 mg per day, while the demand increase during the phase of breastfeeding and in the whole pregnancy around 200–250 mg and 200–290 mg

respectively [23]. The role of iodine in female fertility is of key significance. Iodine deficiency due to hypothyroidism during pregnancy results in severe complications. If such a condition remains untreated it ultimately leads to adverse perinatal outcomes and makes the female more prone to miscarriages [23]. Maternal iodine is very important for the cognitive and neurological development of the fetus. It plays a key role in the production of thyroxine (T4), triiodothyronine (T3), and prohormone in the mother in the fetus. If the mother lacks iodine then it would cause rapid T4 to T3 conversion, overall reducing T4 levels in the body. For the proper cognitive and neurological development of the fetus, T4 is the key element, its reduced level ultimately causes disruption in the neurological development of the fetus.

The term IDD called "iodine deficiency disorders" has a variety of its manifestations, considering infertility, and impaired development of the fetus in the womb as the most important ones. Various complications arise due to deficiency of iodine during pregnancy including congenital anomalies in the babies, abortions, and stillbirths. Studies conducted suggest that females that have reduced iodine levels in their body had reduced fertility ranging from about 46%. It is also suggested that iodine deficient females take more time to get pregnant [24]. Hence it is implicated from the above studies that iodine has a significant impact on fertility because of its involvement in thyroid hormone regulation.

Interference of Hypothyroidism with Male Fertility

The male infertility issue has been trending over recent years and its prevalence has increased to a great extent [20]. Globally infertility has not only affected females but it has targeted males as well. The mechanism of causation of infertility in males needs to be studied to its core. The endocrine system of the human body plays a significant role in the regulation of all the reproductive functions of humans. Any disruption in this would cause severe consequences.

Considering the male reproductive functions, there is various hormone crosstalk involved. The hypothalamus performs the function of releasing Gonadotropin-releasing hormone (GnRH). This release promotes the secretion of luteinizing hormone (LH), follicle-stimulating hormone (FSH), and gonadotropins from the anterior pituitary. The function of FSH includes action on Sertoli cells to promote the maturation of sperms. The function of LH involves action on the Leydig cells that ultimately promotes the production and release of testosterone [20]. In order to achieve normal spermatogenesis, the level of testosterone in testes must be in greater proportion than that available in the serum. The increased level of testosterone in the ovaries increases the maturation of germ cells in an indirect manner by acting on the Sertoli cells. Studies suggested that the prevalence of infertility in males due to endocrinopathies ranges from about 1% to 2%), and if such endocrinopathies get treated with a proper treatment approach one can restore his ability to fertilize [19].

	Hypothyroidism
Prepubertal testicular volume and function	↑ Early onset of spermatogenesis
Sperm count	Normal or ↓
Testicular germ cell count	↓
Sperm motility	↓
Sexual function	Impaired
Erectile function	↓
Free testosterone level	↓
LH and FSH levels	↓
E2	↓

↑ = increase, ↓ = decrease.

Figure 1: Interference of hypothyroidism with Male Fertility

Thyroid hormone regulation plays an essential role in male fertility. Studies have been conducted to understand the linkage of hypothyroidism with male infertility (Figure1) [20].

It has been established that hypothyroidism plays a significant role in reducing the level of total serum testosterone and sex hormone-binding globulin (SHBG). In contrast with hyperthyroidism, hypothyroidism is considerably related to reduced free testosterone levels in the body [20]. The response of

hypothyroid individuals toward the release of exogenous GnRH is also very diminished.

In some investigations, it has been noted that hypothyroid individuals have hypothyroidism mediated diminutive levels of FSH and LH in their bodies [20]. It has been established that if such a condition remains for a prolonged period in prepubertal males then it would lead to diminished function of Sertoli cells as well Leydig cells in males. Hence overall it would reduce the ability of sperm to mature in male testes. There would be no effect on sperm count but the number of sperms that are matured decreases to a great extent. This mechanism accounts for the increased testes size in a patient with hypothyroidism and also it shows a strong connection with a reduced level of germ cells available in seminiferous tubules [21].

For a better understanding of the connection between male fertility and hypothyroidism, research has been conducted on rats. According to the research, the rat model with induced hypothyroidism has shown a reduced number of mature sperms and they had lighter teste with reduced seminiferous tubules and their sperm parameters had deteriorated [21].It has been established that before the role of thyroid hormone was discovered, hypothyroidism had majorly been linked with diminished erectile dysfunction as well as reduced libido. Furthermore, a study suggests that individuals with an increased level of thyroxine in their blood have significantly increased sperm concentration rates.

On the other hand, a hypothyroid individual has shown to have a disruption in the motility of the sperm, decreased volume of semen, and reduced concentration of sperm with normal morphology. One study also suggested that once the hypothyroidism has been treated in the individual then he would have sperm with normal morphology and relatively higher concentration also and this accounts for almost 76% of the individuals [22].

According to investigations the mechanism behind the association of hypothyroidism with male infertility involves the histological dysfunction of the cell of the testes. It further provides insight into the theory that says reduced FSH and LH level in male with hypothyroidism cause abnormality in the maturation of germ cell that lies in the seminiferous tubules of males [22]. From the demonstration of different cases being studied, it's safe to say that the treatment of hypothyroidism increases the semen production parameters. Considering the existing information from all the findings it is implicated that there is definitive relation between hypothyroidism and male infertility.

CONCLUSION

Recent studies since 2020 provide insight into the complex interaction between fertility and thyroid hormone regulation. It is implicated that hypothyroidism adversely affects both female and male reproductive systems hence reducing their ability to conceive. The precise understanding of female and male infertility due to endocrine disruption plays a significant role in the timely management and treatment of such a pathological state.

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