



Review Article

Role of hypothyroidism and associated pathways in pregnancy and infertility: Clinical insights

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ABSTRACT

Thyroid disorders are the most common endocrine problems in women. In most of the cases, thyroid can lead to infertility or miscarriages. The etiology of infertility is multifactorial with thyroid disorders as the most common presenting factor, hypothyroidism in particular. Infertility in women can lead to emotional and psychological stress. The prevalence of hypothyroidism during pregnancy is estimated to be 0.3%–0.5%. Hypothyroidism and hyperthyroidism can result in menstrual irregularities and anovulatory cycles, thus affecting the fertility. There is a significant high prolactin (PRL) level in infertile women with hypothyroidism when compared to euthyroid patients, indicating the relation between hypothyroidism and hyperprolactinemia. The amount of thyrotropin releasing hormone (TRH) from the hypothalamus is markedly increased by inhibition of pyroglutamyl peptidase II, the enzyme catalyzing TRH. The increased TRH in hypothyroidism causes increased thyroid-stimulating hormone and PRL secretion by pituitary, leading to infertility and galactorrhea. In recent years, a neuropeptide called kisspeptin, encoded by *Kiss1* gene, a potent stimulus for GnRH secretion, has been recognized, which suggests a future direction of treatment with kisspeptin and benefits the fertility induction among hyperprolactinemic infertile patients. Untreated hypothyroidism during pregnancy can lead to subfertility, fetal deaths, premature deliveries, and abortions. Therefore, women planning for pregnancy and infertile women should be assessed for thyroid hormones and serum PRL.

KEYWORDS: *Hyperprolactinemia, Hypothyroidism, Infertility, Pregnancy, Thyroid*

INTRODUCTION

Thyroid disorders were found to be the most common endocrine problems seen in the world. Among various thyroid disorders, the prevalence of hypothyroidism is more with about 4%–5% worldwide. Females are at more risk of developing hypothyroidism than males [1]. In pregnancy, thyroid pathology worsens with a frequency of 6-fold, so pregnancy is seen as a risk factor for thyroid disorders. Hypothyroidism in pregnancy can lead to increased risk of premature delivery, abortions, and intrauterine fetal deaths, which are associated with maternal morbidity [2]. During pregnancy, there will be a great physiological stress on mother and fetus. Physiology of thyroid is modified during pregnancy, which helps prepare the maternal thyroid gland to cope with metabolic demands. Some studies show that hypothyroid women have a decreased fertility rate than normal women, and even if they conceive, the children born will have a significant impairment of IQ levels, learning abilities, and neuropsychological issues [3]. There are several meta-analysis studies and randomized trials, confirming that subclinical hypothyroidism


and thyroid autoimmunity are strongly associated with preterm deliveries and miscarriages during pregnancy and suggesting that treatment with levothyroxine may reduce the risks [4,5]. Pregnancy is affected by thyrotoxicosis at various stages and the conditions named accordingly as gestational thyrotoxicosis, new onset of Graves' disease during pregnancy, postpartum Graves' thyrotoxicosis (PPGD), and postpartum destructive thyrotoxicosis (PPT), with the highest prevalence of PPGD followed by PPT [6].

ROLE OF THYROID-STIMULATING HORMONE IN PREGNANCY

The prevalence of hypothyroidism during pregnancy is estimated to be 0.3%–0.5%. During pregnancy, to meet increased physiological demands of growing fetus, thyroid hormone production is augmented, which leads to increased production of

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serum estrogen up to 500–1000 pg/mL during the first half of gestation. This results in 2–3-fold upregulation of hepatic thyroxine (T4)-binding globulin (TBG) production. Increased TBG levels may alter equilibrium between bound and free T4 (FT4). The T4 in free state is utilized by the body, so the reduced FT4 can increase the levels of thyroid-stimulating hormone (TSH) by feedback mechanism. This elevated TSH in turn leads to hypothyroidism. Another factor is associated with increased human chorionic gonadotropin (hCG). During pregnancy, placental production of hCG reaches a peak of 50,000–75,000 IU/L at 8–11 weeks. Since the first trimester, hCG causes thyroid stimulation by binding to TSH receptors due to structural analogy with TSH, and there is a decrease in serum TSH during the first trimester. Iodine also plays a factor for developing hypothyroidism during pregnancy. To fuel the increased production of thyroid hormones and to compensate the loss of iodine through enhanced renal clearance, there is an increased need of iodine in pregnancy. Hence, the pregnant women are recommended with an average iodine intake of 250–500 µg/day [7,8]. During the second and third trimester, enhanced metabolism of T4 is seen, due to rise in placental type II and type III deiodinase, which converts T4 to T3 [3]. Autoimmune thyroid disease is common in childbearing age women with 5%–18% prevalence. Antibodies to thyroid peroxidase (TPO-Ab) or thyroglobulin are associated with a significant increment in miscarriages [9]. Celik *et al.* conducted a study on 275 pregnant women and examined iodized salt use and thyroid function. The results have shown insufficient iodine intake among them and goiter rate of 19.3%; this study suggested that pregnant women should be supplemented with iodine-containing preparations [10]. According to the Polish Society of Endocrinology recommendations, pregnant and breastfeeding women should be advised to take extra supplementation of iodine (150–200 µg/day) started in pre-conception period to meet increased demand for iodine during pregnancy [11,12]. Practically, the risk of iodine excess in the body does not exist because any excess of iodine is excreted by the kidneys [13].

ROLE OF HYPOTHYROIDISM IN FERTILITY

There is a known association between fertility and hypothyroidism, which is mostly associated with ovulatory disturbances. These observations are confirmed by animal investigations, showing an association between experimentally induced hypothyroidism and menstrual cycle dysfunctions. Autoimmune thyroiditis is the most common cause of hypothyroidism in young women [14]. Thyroid hormones have intense effects on fertility and reproduction. In women of reproductive age group, the prevalence of hypothyroidism is 2%–4%. Infertility and subfertility have important psychological, medical, and economical implications. The normal thyroid function is necessary for fertility in women and also to maintain healthy pregnancy. The thyroid disorders that are left untreated or in some cases undiagnosed can lead to subfertility or infertility, which may be due to high prolactin (PRL) levels, anovulatory cycles, and defects in luteal phase and sex hormones. Women with preexisting family history of thyroid problems are suggested for any possible thyroid abnormalities

before they plan for pregnancy. A study was conducted among 94 women who are infertile and diagnosed with hypothyroidism (with or without hyperprolactinemia). These patients were treated with drugs (adjusted dose based on severity) for hypothyroidism. The patients responded to the treatment and 76.6% of them conceived after the therapy, which also includes the patients with hyperprolactinemia. This study, thus, suggests that by treating the hypothyroidism, the infertility associated with it can be managed easily [15]. A study conducted in 438 infertile women with various causes of infertility found a significant higher prevalence of TPO-Ab. There was a high prevalence of hypothyroidism and hyperthyroidism in the infertile women when compared to healthy fertile women [16]. According to a study conducted by Abalovich *et al.*, in 150 pregnant patients, when treatment was adequate with levothyroxine, 90.5% of subclinical hypothyroid and 100% of overtly hypothyroid patients carried pregnancies to term. Among the levothyroxine treated euthyroid patients the cases of abortions and premature deliveries were found to be 4% and 11.1% respectively. The congenital malformities among the new born children in this study was found to be 6.3%. The output of this study shows that adequate treatment of hypothyroidism during pregnancy minimizes complications and makes pregnancies to be carried to term [17]. There is a well-known association between thyroid and pregnancy; many studies suggest an association between thyroid autoimmunity and adverse outcomes related to pregnancy such as miscarriage and preterm delivery in particular. A study conducted in 1990 found that miscarriages in pregnancy are twice as frequent in women with positive TPO-Ab when compared with negative TPO-Ab [18]. The possible reasons for these associations are subtle thyroid insufficiency, direct effect at placental level by thyroid Ab, and unfavorable autoimmune environment. Roberto Negro conducted a study in women who are trying to conceive with a history of infertility or miscarriage. Thyroid Ab-positive women (chronic autoimmune thyroiditis) were treated with levothyroxine and placebo. The results showed no difference in maternal and neonatal outcomes between the two groups [19]. Levothyroxine is the treatment of choice in hypothyroidism. The patients on levothyroxine should be carefully monitored for blood thyroid profile to maintain them in the recommended ranges before conception and during pregnancy. Hyperthyroid pregnant women are treated with propylthiouracil as a preferred choice during the first trimester and thiamazole during the second and third trimesters. There is a need of controlling maternal thyroid function carefully to avoid fetal hypothyroidism. There is a special entity involving hCG (which is increased during the 1st trimester) related to gestational transient thyrotoxicosis, which usually needs no treatment, but in patients with severe clinical symptoms, anti-thyroid drugs may be useful [20].

Role of hypothalamic–pituitary–thyroid axis

Activity of thyroid is regulated by hypothalamus and pituitary glands. Thyroid gland is influenced by the hypothalamus and pituitary with the help of their secreted hormones, thyrotropin-releasing hormone (TRH) and TSH, respectively. Abnormalities in the levels of serum TSH indicate the presence of thyroid disorders [21]. TRH (a tripeptide amide) has

a major role in the regulation of central hypothalamic–pituitary–thyroid axis. TRH serves as both neurotransmitter and neurohormone [22]. The hypothalamic paraventricular nucleus contains the hypophysiotropic TRH neurons which are responsible for the secretion of TRH. The activity of these neurons can be regulated by thyroid hormones through negative feedback mechanism. Other adverse conditions such as infections can affect the thyroid axis. TRH regulates the release of TSH from the anterior pituitary [23]. Membrane-bound ectoenzyme, pyroglutamyl peptidase II (PPII) primarily synthesized by neurons, catalyze the secreted TRH in the brain and inactivate it. The amount of TRH released from the brain is markedly increased by the inhibition of PPII [24]. PPII is also synthesized in hypothalamus by tanycytes, a specialized glial cell type. Tanycytes also have an active role in neuroendocrine regulation [25]. They regulate hypothalamic–pituitary–thyroid (HPT) axis by expressing TRH inactivating enzyme PPII and also they are thought to be involved in feedback regulation by expressing Type 2 iodothyronine deiodinase which converts T₄ to T₃ (active thyroid hormone) [26,27]. Another regulating body of the thyroid gland is central nervous system by mediating through autonomic nervous system. The thyroid gland is supplied with innervations of adrenergic nerves and the cholinergic axons from vagus nerve.

Blood vessels of the thyroid gland are densely innervated by autonomic nerves and also their axon terminals are found around thyroid follicles [28]. Inhibitory action is seen by sympathetic input due to decreased thyroid blood flow, *in vivo* thyroid hormone secretion is decreased, and stimulatory effects of TSH on thyroid cells *in vitro* are inhibited by noradrenaline [29,30]. In contrast, increased thyroid blood flow is seen with parasympathetic input by electrical stimulation of the thyroid nerve [23]. Axons innervating thyroid gland also contain neuropeptides such as vasoactive intestinal peptide and neuropeptide Y (NPY). Thyroid blood flow and thyroid hormone secretion are increased by vasoactive intestinal peptide. In contrast, thyroid blood flow is inhibited/reduced by NPY present in sympathetic innervation of thyroid gland [31,32].

Role of hypothalamic–pituitary–ovarian axis

Thyroid disorders and menstrual disturbances are frequently associated with each other. This can lead to subsequent infertility [33]. In women, menstrual cycle is associated with hypothalamic–pituitary–ovarian axis, which involves gonadotropin-releasing hormone (GnRH), pituitary gonadotropes, uterus, and ovaries [34]. GnRH acts on gonadotropes of anterior pituitary and releases follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which stimulates folliculogenesis in ovaries. The GnRH pulse generator has a crucial role in normal ovulatory menstrual cycle. Certain conditions such as Kallmann syndrome exhibit delayed puberty and hypogonadotropic hypogonadism (HH) which may be due to incomplete migration of GnRH neurons, leading to decrease/absence of GnRH release [35].

Some lifestyle variables such as psychogenic stress, diet related, and exercise related can also affect the cyclic dysfunction, leading to functional hypothalamic amenorrhea or

functional hypothalamic chronic anovulation. In this condition, the activity of GnRH is reduced which leads to decreased LH release. The abnormal LH can cause anovulation which in turn affects the normal menstrual cyclicity and reproduction [36]. The patients with psychological or emotional stress are prone to chronic amenorrhea. These factors influence increased secretion of cortisol and suggest association between increased activity of hypothalamic–pituitary–adrenal (HPA) axis and reduced GnRH. There are experimental studies in nonhuman primates, suggesting the concept of alterations in hypothalamic function leading to stress-induced functional hypothalamic amenorrhea [37]. The relation between corticotrophin-releasing hormone (CRH) and inhibition of GnRH pulse generator is not well known. For instance, CRH antagonists can prevent immune stress-associated inhibition of LH secretion, which activates HPA axis [38]. Hypothyroidism is the mostly seen endocrine problem in female population. Hypothyroidism affects physiological activities of the body such as menstruation and fertility. Proportion of abnormal menstrual cycles was more in the hypothyroidism group, rather than the euthyroid group. And also, the subfertility in hypothyroidism is high than that in euthyroid [39]. Hypothalamic–pituitary–ovarian axis is physiologically similar/related to HPT axis. Hypothyroidism and hyperthyroidism can result in menstrual irregularities and anovulatory cycles and increase in fetal wastage [40]. Thyroid hormones synergize with follicle-stimulating hormone and stimulate granulosa cell differentiation, followed by normal follicle development which is necessary for ovulation and corpus luteum formation. Thus, thyroid hormones in adequate levels are necessary for induction of ovulation [41]. Menorrhagia is the most common irregularity observed in women with thyroid disorders. Hypothyroidism in more particular is associated with menstrual disorders [42]. In a study of 50 hypothyroid women, 40% showed menorrhagia, 18% oligomenorrhea, 6% with amenorrhea, and 22% had normal menstruation. This indicates menorrhagia as a major menstrual dysfunction in hypothyroid patients [43]. Cases of thyrotoxicosis onset before puberty have reported delay in onset of menses. Oligomenorrhea is the most common menstrual irregularity seen in hyperthyroidism, with less frequent polymenorrhea [44]. Benson and Dailey conducted a study in 221 hyperthyroid patients and found that 58% of the patients are with oligomenorrhea and 5% with polymenorrhea [45].

ROLE OF THYROID ON PROLACTIN

Assessment of thyroid hormones and the levels of serum PRL has been considered an important component in women with infertility [46]. The levels of TRH secretion is increased by hypothalamus due to feedback mechanism in hypothyroidism condition. The increased TRH affects the PRL and TSH levels by increasing their secretion by pituitary [47]. The increased TRH in hypothyroidism causes rise in PRL levels, and subsequently, the patients may have galactorrhea [48]. Impairment of pulsatile secretion of GnRH and interference with ovulation are the reasons that affect fertility associated with hyperprolactinemia [49]. A study conducted by Binita *et al.*, in 160 primary infertile women, showed a positive relation between serum levels of TSH and PRL among

infertile women. Among the total study participants, 60% of infertile women showed menstrual disorders and 41% hyperprolactinemia. The infertile women with hypothyroidism have showed significant high levels of PRL when compared to euthyroid patients [50]. According to a study conducted by Bahar *et al.*, in 481 participants with subclinical hypothyroidism, the hyperprolactinemia prevalence was found to be 20.4% [51]. In a cross-sectional study on 200 infertile women, the levels of TSH values and PRL with infertility status was compared. Abnormal TSH and PRL levels were found to be 36 and 79, respectively, in infertile women, with none in fertile women. This shows a significant relation between hyperprolactinemia, hypothyroidism, and infertility [52]. In a study conducted by Snyder *et al.*, the hypothyroid patients were given thyroid-releasing hormone (TRH) 400 µg, T3 and T4. To the well-known fact that TRH has been shown to be a potent stimulus of PRL release, the results showed that TRH directly stimulated PRL secretion, whereas T3 and T4 inhibits it. Change in PRL response to TRH is associated with changes in normal T3 and T4 levels. TRH-induced PRL release is increased by subnormal serum T3 and T4 levels [53]. There is a high crude prevalence of hypothyroid-associated hyperprolactinemia in infertility. This stresses the fact that all infertility cases should be subjected for the estimation of serum PRL. The results of a study by Sharma *et al.* among patients with subclinical hypothyroidism (ScH) and primary hypothyroidism showed a positive correlation between TSH and PRL. A high specificity of >90% in detecting hyperprolactinemia is seen in female patients with TSH ≥ 7.51 mIU/L. The prevalence of hyperprolactinemia is higher in primary hypothyroidism compared to ScH [54]. A case of hyperprolactinemia due to ScH was treated by thyroid hormone replacement with levothyroxine; the patient's TSH levels and serum PRL levels returned to normal, indicating importance of thyroid hormone replacement therapy in managing hyperprolactinemia [55]. Changes in pituitary structure and pituitary endocrine cell hyperplasia are seen secondary to primary hypothyroidism [56]. Low levels of thyroid hormones lead to overproduction of TRH, followed by hypertrophy and hyperplasia of thyrotrophic cells and pituitary gland [57]. Thyroid hormone T3 was found to reduce PRL mRNA levels in pituitary; therefore, hypothyroidism leads to synthesis of more PRL. In primary hypothyroidism, reduced sensitivity to dopamine inhibitory effect on receptors is seen

in pituitary [58]. Clearance of PRL from circulation is reduced in hypothyroidism [59].

HYPERPROLACTINEMIA AND INFERTILITY

PRL-secreting adenomas can also be a cause of hyperprolactinemia which can lead to infertility. This condition is generally treated with dopamine receptor agonist cabergoline and bromocriptine to restore fertility [60]. Elevated PRL due to any reason can cause HH and infertility. Hyperprolactinemia leads to direct suppression on GnRH neurons to suppress GnRH release [61]. Elevated PRL levels in hyperprolactinemia through inhibitory action reduce the levels of LH and FSH by inhibiting GnRH neurons in hypothalamus [62]. In recent years, a neuropeptide called kisspeptin, encoded by *Kiss1* gene, a potent stimulus for GnRH secretion, has been recognized, having important value in pubertal maturation and regulation of reproductive function [63]. In a study, hyperprolactinemic mice were administered with intraperitoneal injections of kisspeptin once daily for 20 days. Interestingly, the results showed restoration of estrous cyclicity and increased LH and FSH levels. These results can implicate that the treatment with kisspeptin can benefit the fertility induction among hyperprolactinemic infertile patients [64]. Endometriosis is also seen as a risk factor for infertility. There is an anatomical basis for infertility in women with severe endometriosis, whereas in patients with mild endometriosis, the infertility cause is not been clearly defined [65]. According to some studies, the endometriosis-related infertility can be due to fluctuations in PRL secretion [66]. In contrast, some authors demonstrated normal basal PRL levels in the patients presented with endometriosis-associated infertility; however, these levels were altered after a TRH stimulation test, indicating an association between infertility in endometriosis patients and altered secretion patterns [67]. Infertile women with normal PRL levels when exposed to TRH stimulation test or metoclopramide (dopaminergic antagonist) have shown abnormal PRL secretion with exaggerated response to the interventions [68]. A case-control study to analyze the relation between endometriosis and altered PRL and growth hormone levels by Cunha-Filho *et al.* showed higher levels of PRL in infertile endometriosis women after TRH administration when compared to fertile patients without endometriosis. PRL levels showed no difference between the groups after the dopaminergic blockage. These

Table 1: Role of hypothyroidism and prolactin in infertility

Hormonal condition	Comments	References
Hypothyroidism	The need of thyroxine was increased among the pregnant women with primary hypothyroidism. This was concluded by the increased serum thyrotropin levels among pregnant	Mandel <i>et al.</i> [70]
Hyperprolactinemia + hypothyroidism	There was a significant incidence of hypothyroidism among hyperprolactinemia patients, the serum prolactin levels were found to be significantly high in infertile women	Turankar <i>et al.</i> [71]
Hyperprolactinemia	The hyperprolactinemia infertile women have shown higher serum prolactin and TSH levels with low T3 and T4 levels. This suggests the role of thyroid and prolactin as contributing hormonal factors among infertility women	Bassey <i>et al.</i> [72]
Hyperprolactinemia + hypothyroidism	There was a positive correlation between the serum prolactin and TSH levels among secondary amenorrhea. This concludes the role of hyperprolactinemia and thyroid dysfunction as contributory hormonal factors among amenorrhea women. Amenorrhea can be a risk factor for infertility	Shrestha <i>et al.</i> [73]
Hyperprolactinemia	There was a prevalence of 18% hyperprolactinemia cases among the newly diagnosed subclinical hypothyroidism suggesting the relation between serum TSH and prolactin levels	Sirohi and Singh [74]

TSH: Thyroid-stimulating hormone

results suggest relation between PRL secretion alterations in endometriosis patients and excluded the involvement of dopaminergic system [69]. The correlation between hypothyroidism and PRL in inducing infertility is summarized in Table 1.

CONCLUSION

Thyroid disease requires special care in pregnant women or those desiring pregnancy. Untreated hypothyroidism during pregnancy can lead to infertility/subfertility, fetal deaths, premature deliveries, and abortions. Assessment of serum thyroid profile and PRL levels should be done in women desiring pregnancy and at early stage of infertility. Early intervention with appropriate therapy can avoid the fetal complications in pregnancy due to hypothyroidism and to improve fertility rate among infertile women. The tests for hyperprolactinemia and thyroid disorders should be made routine in pregnant and infertile women.

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Conflicts of interest

There are no conflicts of interest.

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