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Review Article

Thyroid Disorders-A common Cause of Infertility: A Review

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Abstract:

Undiagnosed and untreated thyroid disease can be a cause for infertility as well as sub-fertility. Both these conditions have important medical, economical, and psychological implications in our society. Thyroid dysfunction can affect fertility in various ways resulting in anovulatory cycles, luteal phase defect, high prolactin (PRL) levels, and sex hormone imbalance. Thyroid hormones are instrumental in reproductive physiology. In hypothyroidism, there is decreased synthesis of factors VII, VIII, IX and XI and estrogen break through bleeding secondary to anovulation, which may explain the frequent, prolonged and heavy menstruation. Hyperthyroidism may be characterized by infrequent scanty menstuation or amenorrhea. Thyrotoxicosis increases the risk of spontaneous abortions and especially if on methimazole, there is an amplified risk of congenital anomalies and aplasia cutis. In males, thyrotoxicosis cause abnormal sperm motility, while hypothyroidism may result in abnormal sperm morphology and both may cause erectile abnormalities.

Key words: Thyroid disorders, Infertility, Hypothyroidism, Hyperthyroidism, Autoimmune thyroid disease.

Introduction :

Infertility is a growing issue around the globe, estimating that 15% of population suffers from it. Reasons of infertility may range from poor reproductive health of either partner of crucial biochemical substances, which are usually overlooked or remain undiagnosed[1]. Hypothyroidism falls in the latter category, where disturbance in thyroid hormones interferes with fertility. Since hypothyroidism sometime remains asymptomatic for a long time, therefore it cannot be easily caught as a contributing factor of infertility. Many women may encounter hypothyroidism which can be primary, secondary or tertiary depending upon the site of lesion. Irrespective of cause, alteration in thyroid hormone levels can influence conception and pregnancy. For instance, sub-clinical hypothyroidism (SCH), also called mild thyroid failure, is diagnosed when peripheral thyroid hormone levels are within normal reference laboratory range, but serum thyroid-stimulating hormone (TSH) levels are slightly elevated (≥4.25 mlU/l). Clinical hypothyroidism, on the other hand, has increased TSH and decreased T_4 serum concentrations[2]. Similarly, autoimmune thyroid disease causes antibodies production against thyroid gland and its products - Hashimoto's disease. In either case, it is the area of concern and major health burden globally. Normal thyroid function is necessary for fertility, pregnancy, and to sustain a healthy pregnancy, even in the earliest days after conception. Thyroid evaluation should be done in any women who wants to be pregnant with family history of thyroid problem or irregular menstrual cycle or had more than two miscarriages or is unable to conceive after 1 year of unprotected intercourse. The comprehensive thyroid evaluation should include T_3,T_4,TSH and thyroid autoimmune testing such as thyroid peroxidase (TPO) antibodies, thyroglobulin/antithyroglobulin antibodies, and thyroid stimulating immunoglobulin (TSI). Thyroid autoimmune testing may or may not be include in the basic fertility workup because the presence of thyroid antibodies doubles the risk of recurrent miscarriage in women with otherwise normal thyroid function[3-5].

Prevalence of hypothyroidism in the reproductive age group is 2-4% and has been shown to be the cause of infertility and habitual abortion[6,7]. Hypothyroidism can be easily detected by assessing TSH levels in the blood. A slight increase in TSH levels with normal T_3 and T_4 indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T_3 and T_4 levels indicate clinical hypothyroidism[8]. Subclinical hypothyroidism is more common. It can cause anovulation directly or by causing elevation in PRL. It is extremely important to diagnose and treat the subclinical hypothyroidism for

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pregnancy and to maintain it unless there are other independent risk factors. Many infertile women with hypothyroidism had associated hyperprolactinemia due to increased production of thyrotropin releasing hormone (TRH) in ovulatory dysfunction[9,10]. It has been recommended that in the presence of raised PRL. The treatment should first be given to correct the hypothyroidism before evaluating other cause of raised PRL. Measurement of TSH and PRL is routinely done as a part of infertility workup.

Hypothyroidism has significant interference, in general, for couples who try to conceive and in particular for those who are undergoing infertility treatments. Developed countries have reported hypothyroidism to be 2-4% in fertile group[11]. SCH has been recognized as major culprit. It is known that hypothyroidism causes increase in thyrotropin releasing hormone, which in turn, alters the level of prolactin and luteinizing hormone (LH) response-both are major contributor towards fertility. Therefore, any correction of hypothyroidism at initial level can be fruitful for the successful treatment of infertility[12]. On the contrary; the state of hyperthyroidism in females also poses hindrance in way of conception due to poor reproductive state. Unlike hypothyroidism, it is a state in which TSH levels are suppressed with elevated T_3 and T_4. It may be caused by Plummers disease, a state in which autonomous nodules are formed on the thyroid gland, which causes the condition of hyperthyroidism. Thyroiditis, a frequent thyroid disorder is yet another condition which results in hyperthyroidism. Another documented reason for hyperthyroidism is an autoimmune condition like Graves's disease, in which antibodies stimulate the thyroid gland, resulting in over production of thyroid hormones[13].

Hypothyroidism:

Hypothyroidism may lead to failure of sex steroids by disrupting the functioning of hypothalamo-pituitary-ovarian axis. Thus, a clinical picture in close relationship with menstrual irregularity, infertility, miscarriage and complications of unwanted pregnancy may occur[14,15]. The prevalence of hypothyroidism is approximately 2-4%. Even though there are several rare causes of hypothyroidism as post-iodine^{131} treatments, post thyroiditis and drug induced hypothyroidism, the main reason of hypothyroidism is immunological. Low levels of FT_4 is the condition paving the way for symptoms of hypothyroidism and ovulatory dysfunction is the main clinical symptom of hypothyroidism. The condition leads to menstrual dysfunction 3 times more the usual prevalence. The most common type of menstrual dysfunction is oligomenorrhea. There is no consensus over the TSH cut-off values which are a parameter that is used in diagnosis and classification. TSH normal range is a disputed subject among some authors. In a cohort study including 195 cycles in patients getting IVF therapy, when upper normal limit of TSH is considered 2.5, gestational age during delivery and birth weight of newborns were found to be significantly lower in patients having TSH values over this cut-off point. However, even though there's a tendency towards an increase in abortus the difference wasn't significant.

Subclinical Hypothyroidism:

Subclinical hypothyroidism(SCH) is described as absence of hypothyroidism symptoms with normal FT4 and elevated TSH values[16]. Although there's no consensus over upper normal limit of TSH, currently some authors suggest 2.5ml U/L[17]. Incidence of SCH in normal population is estimated at 4-8.5%, but it was determined that in patients with infertility and in advanced age the incidence increase[18]. According to the current literature, treatment of SCH is not established yet. In a prospective randomized study 64 SCH patients with infertility was delivered 50 mcg levothyroxine (LT_4) in the first day of controlled ovarian stimulation and it was shown that having grade 1 and embryo, implantation and live birth rates were higher in the treatment group; but, no difference was found between groups regarding pregnancy rate per cycle. When pregnant groups were evaluated, treatment group with pregnancy experienced significantly less abortion than control group[19]. Feto-maternal effects of hypothyroidism such as abortus during pregnancy and mental retardation was clearly established[20]. Additionally, in recent times association of SCH with unwanted antenatal complications such as premature birth, placental detachment and intrauterine death was demonstrated.

Autoimmune thyroid diseases:

Autoimmune thyroid diseases (AITD); are the most common autoimmune conditions encountered in females in reproductive age characterized by presence of antibodies against to some structure of thyroid gland such as thyroglobulin (TG), thyroid peroxides (TPO) and thyroid microsomal (TM). Excessive immune response which is usually 5-10 times more in females stimulates organ specific or non-specific auto-immunity. Organ specific ATA occurring against TG damages thyroid follicle tissue, ATA occurring against TPO impedes iodination of tyrosine. Non-specific antibodies occur as a result of stimulation of T cells against specific thyroid molecules and subsequently effecting B cells. Abnormal immune response effects release of cytokines such as interferon IL-4 and IL-10 and at the same time prevents successful implantation by altering profile of endometrial T-cells.

Hyperthyroidism:

In women with hyperthyroidism hormonal changes effecting reproductive system may occur. Suthern et al have reported that androstenedione and testosterone production increase in hyperthyroidism and subsequently this leads to elevation of estrogen and estradiol[21]. Both this mechanism and decrease in metabolic clearance of estrogen lead to higher plasma estrogen levels in women with hyperthyroidism[22]. Infertility incidence is about 5-8% in women with hyperthyroidism[23]. Even though in some studies endometrial biopsies proved that women were ovulating, it's still emphasized that hyperthyroidism is related with reduced fertility[24,25]. Additionally, Poppe et al in a study performed in 2002 have reported that suppressed serum TSH levels are more frequent in ATA positive infertile women compared to non-positive ones[26]. Previously menstrual disorders including particularly oligomenorrhea was reported as 50% in people with hyperthyroidism, but Krassas et al found that rate is around 21.5% in thyrotxicosis[27].

Conclusion:

Reproductive function is a vital process for continuation of life and requires an appropriate endocrine, molecular and cellular organization. In every stage starting from maturation of ovarian follicle up to implantation of the embryo, a convenient environment including normal thyroid hormone level is of utmost importance. Thyroid surveillance must be performed in patients with infertility, having history of abortus and replacement therapy should be done even in subclinical cases. Since thyroid functions exert effect over fertility with various mechanisms; particularly in infertile pairs, especially if family history is positive thyroid dysfunction and autoimmunity should be investigated.

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