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 menstruation 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. 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, subclinical 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 T₄ serum concentrations. Similarly, autoimmune thyroid disease causes antibodies production against thyroid gland and its products – Hashimoto’s disease.

Prevalence of hypothyroidism in the reproductive age group is 2-4% and has been shown to be the cause of infertility and habitual abortion. Hypothyroidism can be easily detected by assessing TSH levels in the blood. A slight increase in TSH levels with normal T₃ and T₄ indicates subclinical hypothyroidism whereas high TSH levels accompanied by low T₃ and T₄ levels indicate clinical hypothyroidism. 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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Hypothyroidism can be fruitful for the successful treatment of infertility. On the contrary, the usual prevalence of menstrual dysfunction is 1-2 times more than that in normal menstruating women. 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 above 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. Although there's no consensus over upper normal limit of TSH, currently some authors suggest 2.5mIU/L. 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. According to the current literature, treatment of SCH is not established yet. In a prospective randomized study 64 SCH patients with infertility were delivered 50 mcg levothyroxine (LT4) 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. Feto-maternal effects of hypothyroidism such as abortus during pregnancy and mental retardation was clearly established. 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 autoimmune. 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$^{9}$. 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 thyrotoxicosis$^{27}$.

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.

References: