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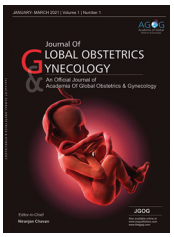
Review Article



Thyroid Dysfunction and Infertility

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ABSTRACT

Thyroid hormones are required for normal ovarian function by regulating the hypo thalamo pituitary ovarian axis along with follicle-stimulating hormone, luteinizing hormone, and prolactin. The prevalence of hypothyroidism is increasing due to better awareness and diagnosis. It is recommended to screen all women seeking evaluation for infertility even though it is controversial. Screening for thyroid antibodies are recommended when serum thyroid-stimulating hormone (TSH) levels are between 2.5 and 4.0 mIU/L, in women with recurrent pregnancy loss and TSH level persistently >2.5 mIU/L. Subclinical hypothyroidism increases the risk of miscarriage rate and decreased pregnancy rate and treatment with levo thyroxine is beneficial in these women. Thyroid dysfunction also affects the semen parameters and these men can present with erectile and ejaculatory dysfunction. It is recommended to have TSH level < 2.5 mIu/l before *in vitro* fertilization for better assisted reproduction treatment outcome. It is recommended to evaluate for thyroid dysfunction in all women seeking infertility evaluation. LT4 treatment is recommended when TSH is >4.0 mIU/L and TSH between 2.5 and 4 mIU/L with TPO-ab positive.

Key words: Hyperthyroidism, Levothyroxine, Overt hypothyroidism, Subclinical hypothyroidism, Thyroid autoimmunity

BACKGROUND

Thyroid hormones are required for regulating the metabolism and reproductive health. In females, ovarian cycle is regulated by synchronized action of thyroid hormones, luteinizing hormone (LH), follicle-stimulating hormone (FSH), and prolactin on hypothalamic-pituitary-ovarian axis.[1] The progesterone release from the corpus luteum occurs only when thyroid hormones act along with FSH, LH and hCG.

Thyroid hormone receptors (TR-∂ 1 and TR - ß1) are seen on ovarian surface epithelium and in oocytes of primordial, primary, and secondary follicles. They participate in complex regulation of ovarian function. In animal models, thyroid hormones synergize with FSH to exert direct stimulatory effects on granulosa cell function, such as morphological differentiation, LH/hCG receptor formation, induction of 3 ß -hydroxysteroid dehydrogenase, and aromatase.[2] They influence fertility by altering the GnRH and prolactin secretion, SHBG levels, and coagulation factors.

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THYROID DISORDERS AND INFERTILITY

Prevalence

The prevalence of thyroid disorders is increasing worldwide probably due to increased awareness and diagnosis. It is more common in the age group of 20–45 years. The prevalence of sub clinical hypothyroidism (SCH) is 5–7%, overt hypothyroidism is 2–4.5%, hyperthyroidism is 0.5–1%, and thyroid auto immunity (TAI) is 5–10%.[3]

Whom to Screen

It is recommended to screen women with signs and symptoms of hypothyroidism, elevated levels of cholesterol, menstrual irregularities, and infertility. However, it is preferred to screen all infertile women for thyroid disorders even though it is controversial. ATA 2017[4] guidelines recommend screening for all infertile women but not so by ASRM (2015).[5] The SOGC committee opinion (2020)[6] suggests that the clinicians who check thyroid-stimulating hormone (TSH) in all infertile women with minor elevations of TSH (4–10 mIU/L) should have repeat test at least 4 weeks later because minor elevations in TSH will normalize. The

recent European Thyroid association (ETA 2021)[7] recommend that all women seeking medical advice for subfertility should be screened for serum TSH and TPOAb. The main justification for this recommendation is to ensure that overt thyroid dysfunction is detected and managed appropriately before pregnancy. Since overt thyroid dysfunction can negatively affect fertility and pregnancy outcomes, this approach has gained support.

HYPOTHYROIDISM AND INFERTILITY

In hypothyroidism, serum TSH levels are elevated with normal or low FT4 levels. Subclinical hypothyroidism is association of raised serum TSH levels above the upper limit of normality with normal FT4 with no symptoms of thyroid deficiency. In overt hypothyroidism, in addition to elevated serum TSH level, FT4 is low with symptoms of thyroid hormone deficiency. If this upper limit of normality for the population is not available, then upper limit of reference range of the assay is used. This range varies in each society guidelines. If an age-based upper limit of normal for a third generation TSH assay is not available in an iodine sufficient area, an upper limit of normal of 4.12 mIU/L should be considered.[8] However, this upper limit is 4.5–5.0 mIU/L according to ASRM.[5]

Hence, TSH levels used in different studies to determine the association of thyroid function with fertility problems varied considerably. In general, association with adverse fertility outcomes seem to emerge at TSH levels above 4.0 mIU/L.[9]

EFFECTS OF HYPOTHYROIDISM

Ovulatory Disturbance

Thyroid disorders are associated with disturbed folliculogenesis. It can cause anovulation by its direct and indirect action as depicted in Figure 1.

Menstrual Changes

These women can present with disturbance in cycle length, abnormal uterine bleeding and defects in hemostasis. Menstrual abnormalities are more prevalent in hypothyroid women (25–60%) when compared to euthyroid women (10%) and the predominant menstrual disturbance in these women is oligomenorrhea.[10]

Hormonal Changes

The rate of metabolic clearance of androstenedione and estrone is decreased, but there is increased peripheral aromatization. In addition, there is decrease in plasma binding activity of SHBG. Hence, the plasma concentration of total testosterone and estradiol is decreased with increase in their unbound fraction. There is also a blunted LH response which, in turn, stimulates TRH secretion and increase serum prolactin levels. All these changes lead to ovulatory dysfunction, corpus luteum insufficiency, and low progesterone levels in the luteal phase.[10]

Infertility

This is due to altered estrogen metabolism, hyperprolactinemia, ovulatory dysfunction, and disturbance in GnRH secretion.

THYROID AUTOIMMUNITY AND FEMALE INFERTILITY

TAI is defined as presence of the thyroid autoantibodies – anti thyroperoxidase antibody (Anti TPO -ab), or anti thyroglobulin antibody (Anti Tg- ab). This is the most common cause of hypothyroidism among women of childbearing age.[11]

In women with TPO-ab, the relative risk of female infertility is increased (RR - 2.25; 95% CI 1.02–5.12; $P = 0.045$).[12] Women with recurrent miscarriages have a higher incidence of Tg - ab and / or TPO -ab amounting to as high as 25%.[13]

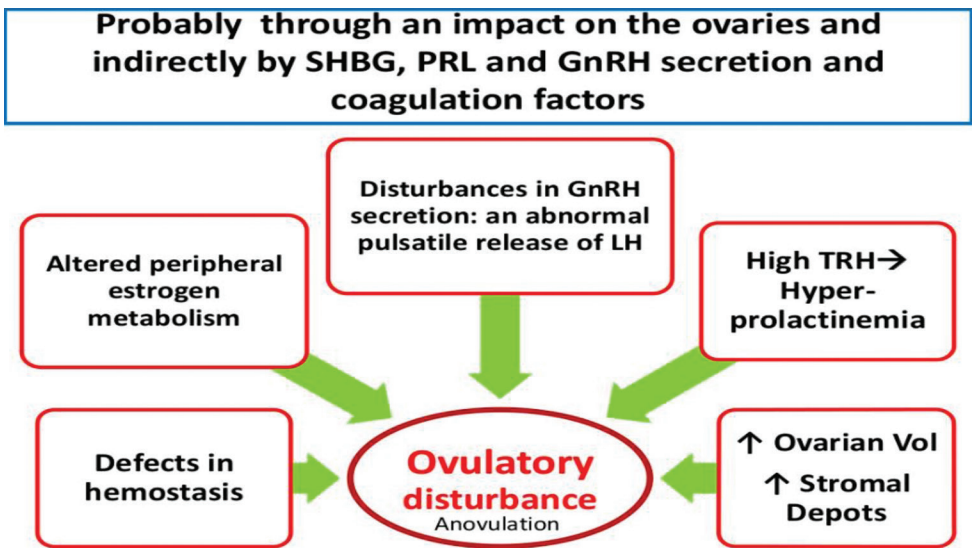

Figure 1: Ovulatory disturbance in thyroid dysfunction

There is 2–3 fold increase in the risk of spontaneous miscarriage among antibody positive women than those who test negative. Among the two antibodies, TPO - ab is considered as a more sensitive marker of TAI.[14]

INDICATIONS FOR TESTING THYROID ANTIBODIES [TABLE 1]

According to American Association of clinical endocrinologists,[8] antibody testing is indicated in women with (a) TSH >2.5 mIU/L on repeated testing, (b) history of recurrent miscarriage, and (c) serum TSH between 2.5 and 4 mIU/L. In addition, ESHRE2015[15] recommends screening in women with diminished ovarian reserve and premature ovarian insufficiency. Recently, ETA (2021)[7] has suggested TPO-ab testing for all women seeking infertility evaluation.

The indications for TAI testing are increasing among the various causes for infertility. A meta-analysis showed that euthyroid patients with thyroid antibodies are associated with unexplained infertility (OR 1.5, 95% CI 1.1–2.0).[16] The other causes linked to TAI are PCOS which can be explained by polymorphism of PCOS-related gene for fibrillin 3, influencing the activity of TGF- ß, and a key regulator of immune tolerance. They contribute to autoimmunity along with lower TGF-ß, Vitamin D levels, and high estrogen-to- progesterone ratio.[17] There is evidence that endometriosis is also linked with TAI as there are immunological changes associated with it.

Table 1: Endocrine societies guidelines for TSH and anti-thyroid antibody testing[24]

Guideline recommendation	ASRM 2015	ACOG	SOGC 2020	ETA 2021
Routine TSH testing	No	No	No	Yes
Routine TPO/TG antibodies	No	No	No	Yes
Treatment if TSH >2.5	No if TSH >4.0	No	No if TSH >4.0	Yes

TSH: Thyroid-stimulating hormone

TAI AND OVARIAN STIMULATION (OS)

During OS, there is rapid and supraphysiologic increase in serum estradiol levels. This results in excess of thyroxine-binding globulin (TBG) production and sialylation by the liver and reduced clearance of TBG. In addition, there is direct effect of raised estradiol levels on TRH. All these mechanisms explain the raise in TSH during OS which is more pronounced in women with TAI. Hence, the overall effect of OS in women with TAI is a decrease in FT4 levels with an increase in TSH levels and this is more evident when TSH level is >2.5mIU/L before OS. Hence, it is suggested to test TSH level 1–2 weeks before OS to keep TSH <2.5 mIU/L and on the day of ß-hCG testing. It is not recommended to monitor serum TSH level during OS as results obtained during the course of OS may be difficult to interpret.[4]

TAI AND ASSISTED REPRODUCTIVE TECHNOLOGY

Women with TAI have increased risk of developing (sub) clinical hypothyroidism.

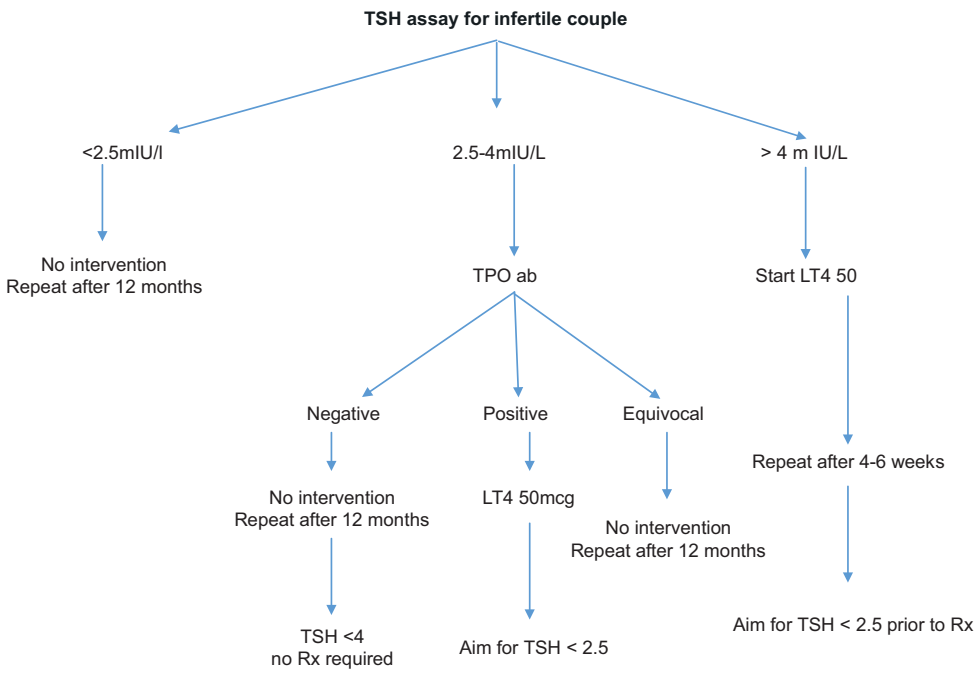

Figure 2: Algorithm for evaluation of infertile women with suspected thyroid dysfunction

TAI is associated with adverse pregnancy outcome such as increased risk of miscarriage, preterm delivery in both spontaneous and assisted reproduction treatment (ART) pregnancies. A study by Zhong *et al.*[18] comparing *in vitro* fertilization (IVF) outcome in TAI positive and TAI negative women revealed that TAI positive women had a significantly lower fertilization rate (64.3% vs. 74.6%), implantation rate (17.8% vs. 27.1%), pregnancy rate (33.3% vs. 46.7%), and a higher risk of miscarriage rate (26.9 vs. 11.8%) following IVF-ET compared to their TAI negative counterparts.[18] This can be explained by alteration in endometrial receptivity that affects the fetal allograft, changes in profile of endometrial T cells with reduced secretion of interleukin - 4 and 10 along with hyper secretion of interferon-γ have been reported. The hyperactivity and increased migration of cytotoxic natural killer cells may also alter the immune and hormonal response of the uterus in women with TAI.[19] However, a prospective study by Sakar *et al.*[20] showed comparable pregnancy and miscarriage rates between 49 TAI positive and 202 TAI negative women after IVF.

Thyroid antibodies can have an unfavorable effect on oocyte and embryo quality. Since thyroid hormones play an essential role in oocyte maturation and implantation, it has been hypothesized that the decline in thyroid function induced by the stimulation protocol in women with TAI may negatively influence pregnancy rate in ART. Hence, it is preferred to keep TSH < 2.5mIU/L before starting infertility treatment in these women.

SCH AND ART OUTCOME

SCH increases the risk of miscarriage when compared to euthyroid women in spontaneous pregnancies. A meta-analysis among women with SCH and euthyroid before 20 weeks of pregnancy showed a higher prevalence of miscarriage in SCH than euthyroid women (RR - 1.45, 95% CI1.07–1.96, *P* - 0.02) (95%CI 1.07 ± 1.96, *P* - 0.02).[21]

According to ASRM,[5] there is insufficient evidence that SCH (TSH >2.5 mIU/L with normal FT4) is associated with infertility and miscarriage. However, there is fair evidence that SCH (TSH >4 mIU/L) is associated with miscarriage and levothyroxine treatment is associated with increase in pregnancy rate and decrease in miscarriage rate.[5] Most of evidence suggests that ART outcomes do not differ between women with serum TSH <2.5 mIU/L and those with very mild TSH elevations, defined as a TSH between 2.5 and 4.0 m IU/L.

MANAGEMENT OF HYPOTHYROIDISM

The aim of starting levothyroxine (LT4) is to improve the obstetric and neonatal outcome following treatment. The indications to start LT4 includes (a) overt hypothyroidism, (b) serum TSH levels >4.0 mIU/L irrespective of TAI, and (c) serum TSH level between 2.5 and 4.0 m IU/L with TPO-ab positive.[7]

LT4 treatment is not recommended in euthyroid women with TAI undergoing IVF/ICSI and serum TSH level between 2.5 and 4.0 m IU/L with TPO-ab negative.[6] This is supported by the TABLET trial which did not show any beneficial effect of LT4 on live birth rate in these women.[22]

LT4 is started in the dose of 25–50 mcg/day for 4 weeks based on clinical and biochemical assessment and serum TSH levels are monitored. The dose is increased every 4 weeks by 25 mcg based on serum TSH levels Figure 2.

ROLE OF GLUCOCORTICOIDS IN TPO AB POSITIVITY

It is not recommended to start glucocorticoids in women with TPO ab positive until further information on risks and benefits of steroids in early pregnancy is available.[6]

Overtreatment

With LT4 is not recommended as it has deleterious effect during early pregnancy on offspring and brain morphology in childhood. It can lead on to subclinical hyperthyroidism in 14–21% of women and there is increased risk of preterm deliveries and gestational diabetes.[23]

Hyperthyroidism and Female Infertility

Epidemiological evidence regarding potential link between infertility and thyrotoxicosis is scarce and inconclusive. The prevalence of hyperthyroidism is 0.5–2%. Sub clinical hyperthyroidism is diagnosed if serum TSH is suppressed with normal FT4, without any symptoms. If serum TSH is suppressed with high FT4 or FT3 and if patient is symptomatic, they are labeled as overt hyperthyroidism.

There is increased concentration of SHBG, LH, plasma androgens, and serum estradiol levels. Menstrual disturbances are common in these women of which hypomenorrhea, polymenorrhea, oligomenorrhea, and hypermenorrhea are more prevalent.

These women should postpone pregnancy for at least 6 months after starting treatment. The anti-thyroid drugs used are Methimazole (10–20 mg initially and maintenance dose of 5–10 mg after 4–8 weeks) and Propylthiouracil (PTU) (100–600 mg /day in three divided doses per day) and when pregnancy is planned, should be changed to PTU. Other drugs which are tried are lugol's iodine and radioactive iodine. Surgery is indicated only if not tolerating the drugs and in non-compliant patients.

THYROID DYSFUNCTION IN MALES

It is less common in men when compared to women and its effects on reproductive function are less delineated. Hypothyroidism in men is associated with reduced libido, impotence, affects spermatogenesis, and sperm morphology. They have reduced SHBG, testosterone, DHEA, and pregnenolone sulfate.

In hyperthyroidism, linear motility is the most common semen parameter which is affected; they can also present with erectile dysfunction in up to 70% and is reversible after treatment. These men have increased SHBG, estradiol, and testosterone levels.

According to ETA 2021 guidelines,[7] universal screening of all males presenting for evaluation is not recommended. They

suggest screening for thyroid dysfunction in men with erectile and ejaculatory dysfunction and with altered semen parameters. It is recommended not to delay IVF/ICSI in case of subclinical or overt hypo or hyper thyroidism in males as long as sperm parameters are not strongly affected.

CONCLUSION

It is recommended to evaluate for thyroid dysfunction in all women seeking infertility evaluation. LT4 treatment is recommended when TSH is >4.0 mIU/L and if TSH between 2.5 to 4 mIU/L with TPO-ab positive.

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