THYROID FUNCTION AND FERTILITY IN WOMEN

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SUMMARY

Thyroid hormones, by affecting prolactin and sex hormone-binding globulin levels and oocyte maturation, significantly affect reproductive function in women. Subclinical or overt hypothyroidism is most common, and hyperthyroidism is less common. Approximately 10% of women show immunological thyroid disorders with increased antibody levels. There is no conclusive data that fertility disorders accompany hyperthyroidism. Hypothyroidism in pregnancy is a factor in its risk, as therapy in the first trimester is proposed propylthiouracil. In contrast, thiamazole is recommended in the second and third trimesters due to its hepatotoxic effects. Breastfeeding should occur immediately after taking the drugs and 3 hours before the next feeding. Abnormalities in monthly bleeding and ovulation accompany hypothyroidism and are the most common cause of fertility and pregnancy disorders, especially when accompanied by elevated levels of anti-TPO antibodies. Medications used to treat hypothyroidism are not contraindicated for breastfeeding during pregnancy, and screening tests in the form of TSH, FT4, and anti-TPO determination are recommended for women planning pregnancy and who are pregnant.

Keywords: Thyroid, fertility, pregnancy, hyperthyroidism, hypothyroidism

INTRODUCTION

Thyroid hormones are essential for the proper development and differentiation of all human body cells and affect the female reproductive organ. Directly affecting the ovary and endometrium during the luteal phase and the trophoblast and placenta via the TH receptors (TRs): TRa1, TRa2, and TRb1.[1, 2, 3] Combined with FSH, triiodothyronine enhances granulose cell proliferation and inhibits granulose cell apoptosis by the protein kinase B pathway. Leukemia inhibitory factor (LIF) is involved in embryo implantation and expressed in the mid-secretory endometrium. TSH

significantly upregulates LIF expression in endometrial cell cultures, suggesting a potential role of TSH in the implantation process.[1, 2, 3] Thyroid hormones also regulate the secretion of prolactin and probably kisspeptin, which, in turn, affect pulsatile gonadotropin-releasing hormone secretion and hypothalamic-pituitary-gonadal axis function. Also, it was shown that thyroid hormones stimulating the synthesis of SHBG influence free sex hormone levels.[1, 2, 3] For that reason, we can expect that in women of reproductive age, thyroid dysfunction and/ or autoimmunity have independently been associated with adverse fertility and pregnancy outcomes in the case of spontaneous conception or after assisted reproductive technology (ART).[1, 2, 3] How pregnancy affects thyroid function: estrogen stimulates the synthesis of thyroxine-binding globulin (TBG), which causes a decrease in free thyroxine (FT4) and free triiodothyronine (FT3). In response, TSH secretion increases and FT4 and FT3 synthesis physiologically increases, and the size of the thyroid gland increases. At the same time, it is essential to remember the thyrotropic effect of βhCG. The concentration of hCG increases in the first trimester and peaks around the 10th week of pregnancy. It can cause TSH suppression, which is sometimes misinterpreted as hyperthyroidism. The thyrotropic effect of βhCG leads to pregnancy-related transient thyrotoxicosis in only about 2% of patients. At the same time, the peripheral metabolism of thyroid hormones is altered to maintain homeostasis and ensure the proper supply of maternal thyroid hormones to the fetus. When the availability of thyroxine decreases, the activity of 5'-deiodinase type 2 in the placenta increases to maintain a sufficiently high concentration of triiodothyronine in the placenta. In turn, 5'-deiodinase type 3, which converts thyroxine to the inactive reverse of triiodothyronine and inactivates triiodothyronine, protects against excess thyroxine. [1, 2, 3]

Hyperthyroidism, and Fertility Disorders, and Pregnancy

In hyperthyroidism, serum concentrations of sex hormone binding globulin (SHBG) and estradiol increase compared to pregnant women with normal thyroid function. This is associated with increased conversion of androgens to estradiol and estrone and increased secretion of LH. An increased risk of miscarriage accompanies this. It has been shown that lowered TSH in pregnant women is more often accompanied by elevated antibody levels compared to women with lowered TSH who are not pregnant.[6] Menstrual cycle abnormalities in women with hyperthyroidism occur in 65% compared to 17% of the healthy population.[7] Hypomenorrhea, polymenorrhea, oligomenorrhea, and hypermenorrhea are the most common menstrual abnormalities. Endometrial biopsy results indicate that most women with hyperthyroidism maintain ovulatory cycles.[8] In women with hyperthyroidism in pregnancy, we can expect several complications like Preeclampsia: OR 1. 78, Preterm birth: OR 1. 81 and Intensive care unit admission OR 2. 08 Superimposed preeclampsia OR 3. 64.[1, 2, 3] How to diagnose hyperthyroidism in pregnancy? Taking into account the previously described changes in TSH under the influence of HCG in the first trimester, the diagnosis of hyperthyroidism should include the determination of FT4 and FT3 levels because only elevated levels of these hormones with low TSH are the basis for initiating therapy for hyperthyroidism. Due to the passage of antithyroid drugs through the placenta, subclinical hyperthyroidism is not an indication for pharmacotherapy in pregnancy, as the risks of antithyroid medications outweigh the benefits. To determine the etiology of hyperthyroidism, measuring the level of antibodies to the receptor for TSH (TRAb) is recommended. Determination of antibody levels

is also recommended in cases of fetal tachycardia or the presence of goiter. The finding of more than fivefold elevation of TRAb levels is associated with the risk of fetal or neonatal hyperthyroidism. [1, 2] The most common cause of hyperthyroidism in pregnancy is Graves-Basedow disease. The differential diagnosis should include gestational thyrotoxicosis, gestational trophoblastic disease, subacute thyroiditis, and excess exogenous thyroid hormones. Rare causes include ovarian goiter and secondary hyperthyroidism due to a pituitary tumor. Treatment of hyperthyroidism in pregnancy is based solely on pharmacotherapy, excluding the "block and replace" method. Radioiodine treatment is contraindicated. In the first trimester, propylthiouracil (PTU) is used. Due to the hepatotoxic effects of PTU, therapy in the second and third trimesters is continued with thiamazole. The therapeutic goal is to maintain FT4 and FT3 levels in the upper range of reference values. Initially, it is recommended to monitor therapy every two weeks and after reaching euthyroidism every 2-4 weeks. Liver enzymes and white blood cell counts should be monitored during PTU treatment. Iodine prophylaxis is not contraindicated in hyperthyroidism in pregnant women. At a dose of methimazole ≤ 20 mg/day and PTU ≤ 300 mg/day, breastfeeding is not contraindicated. The drugs should be administered immediately after feeding, with an interval of 3 hours before the next feeding. [1, 2]

Hypothyroidism, and Fertility Disorders, and Pregnancy

Hypothyroidism is accompanied by an increased risk of fertility disorders and complications during pregnancy. [1, 2, 9] These are a consequence of hormonal changes in the form of a decrease in metabolic clearance of androstenedione and estrone and changes in SHBG levels leading to a reduction in testosterone and estradiol, with an increase in the free fraction of these hormones. The stimulatory effect of LH on TRH secretion and an increase in prolactin levels have also been shown in hypothyroidism. Elevated prolactin levels lead to ovulation disorders and corpus luteum insufficiency with low progesterone secretion in the luteal phase of the cycle. [1, 2, 3] Menstrual cycle disorders occur in 25-60% of women with hypothyroidism in relation to 10% of the healthy population. The most common is oligomenorrhea. There is no clear opinion on subclinical hypothyroidism vs fertility disorders, which is partly related to the different TSH cutoff values and the lack of prospective studies. A retrospective study in Denmark involving 11,254 women showed an increase in fertility disorders in subclinical hypothyroidism diagnosed at TSH levels below 3. 7 mIU/ml. [10] Analyzing the results of many papers, it is suggested that a TSH value below 4. 0 mIU/l may be a risk factor for fertility disorders. [1, 2] A significant factor that disrupts fertility is autoimmune thyroid disorders, which occur in about 10% of women. Many studies have shown that the presence of antibodies in euthyroid women was associated with fertility disorders.[1, 2] Elevated levels of anti-TPO antibodies are considered the most sensitive test for evaluating autoimmune disorders. It should be mentioned the presence of autoimmune thyroid disorders is a risk factor for miscarriages and premature births as well as in pregnancies achieved by ART. [1, 2] Overt hypothyroidism in pregnancy is diagnosed with TSH values above 2. 5 mIU/ml and decreased FT4 or TSH above 10. 0 mIU/ml regardless of FT4 values. In contrast, subclinical hypothyroidism is diagnosed with TSH values of 2. 5 – 10. 0 mIU/ml and normal FT4 levels. For women planning pregnancy, it is suggested to obtain TSH values below 2. 5 mIU/ml, preferably around 1. 0 mIU/ml. To achieve a TSH level of 2. 0-2. 5 mIU/ml, it is advisable to administer l-thyroxine, mainly if an elevated titer of anti-TPO antibodies is found. Once pregnancy is achieved, the dose of l-thy-

roxine should be increased by 30-50%. The TSH level should be checked every four weeks. After delivery, return to the starting dose and check TSH every 4-6 weeks. The use of L-tyroxine is not a contraindication to breastfeeding. [1, 2] In summary, in a woman who is planning a pregnancy or is pregnant to assess thyroid function, TSH, FT4, and FT3 determination should be performed; if hypothyroidism is shown, anti-TPO antibody level should be determined, and in case of hyperthyroidism TRAb. In the case of hyperthyroidism and pregnancy, you can use drugs according to the recommendations discussed above; in the case of hypothyroidism, there is no contraindication to the use of medications during pregnancy.

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