THYROID AND PREGNANCY

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ABSTRACT

Hormonal changes and metabolic needs during pregnancy result in profound changes in biochemical parameters of thyroid function, especially if there is preexsisting autoimmune thyroid disease (AITD). Normal thyroid function is important in order to ensure the best outcome. Many changes in the functioning of the thyroid gland occur during pregnancy, and some diseases of thyroid gland can affect both mother and fetus. Hypothyroidism is the most serious disorder that occurs during pregnancy and can go unnoticed as a „non-specific" problem. Hypothyroidism arises from the reduced ability of the gland to adapt to the increased needs during pregnancy. Mild thyroid dysfunction of mothers in the first trimester, which does not threaten during the pregnancy, can damage the psychomotor development of the child. Measurement of TSH is the most practical, simple and cost-effective screening test for thyroid dysfunction. It is necessary to apply the trimester-specific TSH reference values to correctly interpreted thyroid function during pregnancy. The presence of TPOAb is confirmation of existence of AITD, and predicts increased risk of developing subclinical hypothyroidism (SH). Preconceptional education and adequate diagnosis and treatment of thyroid dysfunction in early pregnancy are of great importance, in order to prevent complications during pregnancy and offspring. Current data indicate an increase in pregnancy loss, gestational diabetes, gestational hypertension, pre-eclampsia and preterm delivery in women with SH in pregnancy. The control of thyroid disease reduce complications of pregnancy.

Keywords: *Thyroid, pregnancy, autoimmune thyroid disease, thyroid stimulating hormone, subclinical hypothyroidism*

THE METABOLISM OF THYROID HORMONE DURING PREGNANCY

Iodine is an essential component of thyroid hormones T3 and T4, produced by the thyroid gland. During early gestation, the fetus depends on the mother's thyroid hormones that cross the placenta because of fetal thyroid function starts at 12-14 week of gestation (wg), while synthesisof fetal TSH occurs around 20th wg Even after the onset of the beginning of the production of fetal thyroid hormones,the fetus continues to rely on the mother's thyroid hormone (1). At birth, about 30% of T4 in the umbilical cord comes from the mother. T3 is the active thyroid hormone,and about 80% of T3 is produced from T4 in liver and muscle. Approximately 99.97% T4 and 99.7% T3 is bound to proteins, primarily on thyroxine-binding globulin (TBG), and to a lesser extent to albumin and transthyretin. The reason for the increased need for thyroid hormone during pregnancy is increased the degradation of T4 and T3; and the effect of human chorionic gonadotropin (hCG) inpregnancy. Serum hCG is a glycoprotein produced by the placenta with a peak at the end of the first trimester, resultsin increased secretion of T4 and T3 and partial suppression of serum TSH (2, 3). Thyroxine of mother crosses the placenta in the first half of pregnancy, while TSH and T3 do not cross the placenta, but TRH crosses the placental barrier (4).

The increase in the need for T4 occurs very early (at 4-6 wg), gradually increasing to 16-20 wg, when reaches aplateau, and is held to the delivery (5). Pregnancy has a significant effect on the thyroid gland and thyroid function. Thyroid gland grow about 10% in size during pregnancy, and up to 20-40% in areas with iodine deficiency. Production of T3 and T4 increases to 50%, with an increase of thedaily requirement of iodine up to 50% (6). Fetal fT4 andT4 reaches adult levels at 36 wg, while fetal TSH is higherthan in the adult (7).

The recommended daily intake of iodine for pregnant women is 229 μg, and for women who are breastfeeding 289 μg(8). TSH provides the most sensitive index for detecting abnormalities of thyroid function. Normal thyroid function is important in order to ensure the best outcome (9). A healthy thyroid gland is able to compensate increased needfor thyroid hormones increasing their secretion and maintaining the level of free hormones in the normal range during pregnancy. However, in situations where subtle pathologic abnormalities of the thyroid gland, such as chronic autoimmune thyroiditis (CAT), or hypothyroid woman onL-thyroxine (LT) replacement therapy, is not present to increase production of the thyroid hormones, entailing the risk of a woman to become hypothyroid. Mild thyroid dysfunction of mothers in the first trimester, which does not threaten during the pregnancy, can damage the psychomotor development of the child (10). In early pregnancy, itis necessary to increase the mother thyroid production of thyroxine, about 50% in comparison to the state prior to conception (11). Many changes in the functioning of the thyroid gland occur during pregnancy and some diseases of the thyroid gland can affect both mother and fetus. Hypothyroidism is the most serious disorder that occurs during pregnancy and can go unnoticed as a "non-specific" problem (12).

AUTOIMMUNE THYROID DISEASE (AITD)

Thyroid disease in pregnancy is common, at least 2-3%of women have thyroid dysfunction, and it is estimated that about 5-20% of women of reproductive age suffer from AITD (11). Thyroid antibodies (Ab) may representa marker of generalized autoimmune imbalance which is responsible for the increased rate of spontaneous abortion (SA) (12). AITD is a risk factor for infertility, women with AITD are often older, so older age, per se, may explain theincreased rate of fetal loss (13, 14).

Thyroid autoimmunity is the most common autoimmune disorder in humans. The situation may remain latent, asymptomatic or undiagnosed for years.Approximately 30% reduction in fT4 indicates that nearly half of women who's test is positive, has fT4 below the normal value at the end of pregnancy (15).

Before any clinical decisions based on the basis of TSH 3-4.5 mIU/L, it is necessary to repeat this analysis in a few weeks to turn off transient thyroid dysfunction. Common causes of transient elevated TSH is subacute or postpartum thyroiditis. The presence of TPOAb is confirmation ofexistence of AITD, and predicts increased risk of developingsubclinical hypothyroidism (SH) when TSH >2 mIU/L (16).Studies have shown that the majority of pregnant women with elevated TSH, in the absence of iodine deficiency, withpositive thyroid Ab, indicates that the AITD is the primarycause of decreased thyroid reserve. Studies have shown that about 30-50% women with thyroid Ab develop postpartumthyroid dysfunction (17).

AITD without clear thyroid dysfunction was significantly associated with an increased rate of 3-5 timesof SA. Negro showed that: 1) euthyroid women with thyroid Ab are older when get pregnant; 2) even if in the early pregnant euthyroid, they have a reduced thyroid reserve; 3) have an increased risk for complications of birth (SA and preterm delivery (PD)); and 4) using a LT to normalisethyroid function (14). It was demonstrated the benefit of using LT in patients with AITD, not only correcting the thyroid function of the mother, but also reduce the level ofadverse outcome (AO) (8).

SH is defined biochemically: when the serum TSH is elevated, a thyroid hormone is normal. In about 60-80%of cases, the disorder is associated with positive TPOAb, marker of CAT (18). Women with positive TPOAb who have not developed PPT have a 25% chance to developit after the next pregnancy. During pregnancy, screening to identify women with TPOAb showed 11 times greater risk of PPT (19). CAT that is often only manifest presenceTPOAb and TGAb is associated with 2-4 times higher incidence of PD and SA (20, 21).

EPIDEMIOLOGY OF AUTOIMMUNE THYROID DISEASE

The prevalence of SH among women of reproductive age is 0.5-5%, depending on the criterion reference value (RV) for TSH (18). The prevalence of thyroid autoAb in the population of women of childbearing age varies from 6-45%, in women with SA about 17-33% of women with infertility around 10-31%. It has been shown in studies thatthe presence of thyroid autoAb, especially TPOAb is associated with adverse outcome (AO) (PD, SA, developmentalneurological sequelae in children). The real mechanisms ofthis association are unknown (22). Thyroid disorders are 4-5 times more common in women than men, especially ofchildbearing age. Hormonal changes and metabolic needs during pregnancy result in profound changes in biochemical parameters of thyroid function (23, 24).

The incidence of hypothyroidism is the mother of 0.19-2.5% (25). The need for universal thyroid screeningof pregnant women is controversial. The American College of Obstetricians and Gynecologists (ACOG's) Clinical Guidelines (2002) suggests testing thyroid function only in women with a personal history of thyroid disease, DM1 or the presence of other autoimmune diseases or symptoms of thyroid disease and does not recommend universal screening. Management of Thyroid Dysfunction during Pregnancy and Postpartum: An Endocrine Society Clinical Practice Guideline in 2012 recommended targeted tests on pregnant women (Table 1) (26, 27). American Association of Endocrinologists (AACE) recommends routine screening of thyroid function before pregnancy for all who are planning a pregnancy, or the first trimester (28). AACE and the Endocrine Society did not find sufficient evidence to recommend universal screening for and treatment of SH. Recent results indicate that a limited screening for high-risk women basedon personal or family history may miss the diagnosis of women with hypothyroidism (29, 30).

Table 1. Recommendations for tests of thyroid function in preconceptional period or early in pregnancy (Indications for thyroid function testing during pregnancy)

Women older than 30 years
Women with a family history of AITD and hypothyroidism
The existence of goiter
At positive thyroid (especially TPOAb)
Symptoms or clinical signs of functional disorders of the thyroid gland
Women with DM1 or other autoimmune diseases infertility
Women with a history of previous miscarriage and preterm delivery
Women with previous radiotherapy neck or thyroid surgery
Women who are on estrogen replacement therapy L - thyroxine
Women who live in iodine deficient areas

REFERENCE VALUES (RV) FOR THYROID HORMONE DURING PREGNANCY

Physiological changes during pregnancy often makeit difficult to determine the specific trimester RV for thyroid function. These changes include increased TBG, increased release of T4 and T3 due to the weak agonistic effect of hCG and the consequent decline in TSH. The concentration of TSH in the serum depends on the wg, it is lower in the first trimester as compared to the second and third trimesters of pregnancy. There is substantial data supporting the clinical value of the serum of 2.5 mIU/L and the upper limit during the first trimester, and the lower limit of 0.1 mIU/L (11, 31).

Pregnancy is a stress on the thyroid, resulting in hypothyroidism in women with limited thyroid reserve or iodine deficiency. Most studies show a significant fall in fT4 as the pregnancy progresses. The largest drop in TSH in the first trimester, and weak, obviously linked to hCG, which is the largest in early pregnancy. TSH gradually increases in the second and third trimesters, but remains lower. Recently, the norms for the upper RV 2.5-3.0 mIU/L(6, 31). The concentration of maternal thyroid hormones, T4 and T3 increases from early pregnancy, with a slight increase of free hormones in the first trimester with corresponding lowering TSH (11). Thyrotropic activity of hCG produces a decrease in serum levels of TSH inthe first trimester, so that pregnant women have a lower concentration of TSH in comparison to women who are not pregnant. Expert opinion is committed to the followingrecommendations for a specific value-trimester TSH: 0.1-2.5 mIU/L (first trimester), 0.2-3.0 mIU/L (the second), and 0.3-3.0 mIU/L (third) (31). Lower physiological limitis 0.1 mI/L for the first, 0.2 mIU/L for the second, and 0.3 mIU/L for the third trimester. It is necessary to apply the trimester-specific TSH RV to correctly interpreted thyroid function during pregnancy (14, 27).

Gestational thyroid hormone reference intervals vary according to population ethnicity, iodine nutrition, and assay method and each population should derive trimesterspecific reference intervals for use in pregnancy (32).

In particular, it was found that 9.0% and 8.9% of euthyroid pregnant women had a positive TPOAb test in the first or second trimester, respectively. It is necessary to regularly monitor thyroid function in TPOAb positive women in order to maintain optimal maternal and fetal health (33).

COMPLICATIONS DUE TO AUTOIMMUNE THYROID DISEASE AND HYPOTHYROIDISM

Hypothyroidism arises from the reduced ability of the gland to adapt to the increased needs during pregnancy. Hypothyroidism during pregnancy is associated with a number AO, the most important being: SA, PD and reduced cognitive function in offspring. During the first trimester, when fetal development depends entirely on the mother's thyroxine is a critical period for the functioning of thyroid hormones on the developing brain (34).

Patients with Hashimoto's thyroiditis (HT) are at greater risk for developing hypothyroidism in early pregnancy due to the increased need for thyroid hormones. A recent study has shown a significant reduction of the number of SA and PD in women who are euthyroid, with HT that were treated with LT for the first ten weeks of gestation compared with a control group of pregnant women who did not receive treatment (13). Pregnancy-induced hypertension (PIH) and small birth weight (SBW) was noted in 15% of pregnant women with SH (18).

The diagnosis of primary hypothyroidism during pregnancy is based upon finding of an elevated serum TSH concentration, defined using trimester-specific TSH reference ranges for pregnant women. The implementation of trimester-specific reference ranges is recommended in order to avoid misclassification of thyroid dysfunction during pregnancy (35).

Progeny in TPOAb and TGAb positive mothers have 2-3 times higher perinatal mortality than negative. AITD detected during the first trimester is independently associated with increased perinatal mortality, probably through PD. Careful monitoring of thyroid function is critical for the prevention of potential complications that can occur during pregnancy (36).

Patients with SH have several slightly clinical signs or symptoms of thyroid dysfunction. Possible consequences include cardiac dysfunction, or adverse cardiac events, increasing cholesterol and LDL, and progression to hypothyroidism (37). There is a connection between hypothyroidism and reduced fertility, which is mainly associated with ovulatory disorders, rather than SA. Women with LT therapy have twice the risk of infertility. Repeated SA are associated with serious autoimmune diseases, such as systemic lupus or the antiphospholipid syndrome (38).

Many studies have shown that gestational diabetesmellitus (GDM) as the most common obstetric metabolic disease and functional abnormalities in the thyroid can have a variety of adverse effects on pregnancy outcomes and offspring. Some studies have shown that there is a correlation between thyroid disease and GDM, whereas others have not found this association. However, a recent meta-analysis showed that the incidence of GDM in patients with subclinical hypothyroidism was 1.35-fold higher thanthe incidence in the control group. In summary, this studyprovides new evidence showing that low thyroid hormonelevels increase the risk of developing GDM in early pregnancy (33).

TREATMENT OF HYPOTHYROIDISM DURING PREGNANCY

International guidelines advocate using population based reference ranges; however, if these are unavailable the recommended fixed upper threshold for TSH concentration is 2.5 mIU/L during the first trimester and 3.0 mIU/L during the second and third trimesters (31). According to these diagnostic criteria, is estimated to affect up to 15% of pregnancies in the US and 14% in Europe. This represents a fivefold increase in prevalence comparedwith the 2-3% prevalence of SH before these criteria were established, raising the possibility of overdiagnosis of SH and discussions at the 2016 Endocrine Society meeting about increasing the TSH cut-off limit to 4.0 mIU/L in theupcoming American Thyroid Association guidelines (31). A recent meta-analysis of 18 cohort studies found that pregnant women with untreated SH are at higher risk for pregnancy loss, placental abruption, premature rupture ofmembranes, and neonatal death compared with euthyroidwomen. Current guidelines recommend LT treatment in pregnant women with SH (39).

It is estimated that approximately 1-2% of pregnant women receiving LT for hypothyroidism. Epidemiological studies suggest that 0.4% of pregnant women have TSH>10 mU/mL of 15-18 wg (38).

For women already diagnosed as hypothyreoidism, it is recommended to adjust the dose to a TSH of pregnancy was <2.5 mIU/L, and in the first trimester, while the second and third should not exceed 3 mIU/L (31). To achieve these results, LT dose should be increased at the beginning of pregnancy (after conception) by 30-50%, depending on the cause of hypothyroidism. Increasing the dose is important at thebeginning of pregnancy, although it may be necessary to continue to increase during the second and third trimester. HATwith euthyroidism does not require the application of LT, oron the basis of the risk of hypothyroidism, strict supervisionis necessary during pregnancy (40). In order to minimize thecomplications of hypothyroidism for the mother and fetus,women need to quickly return to the euthyroid state. It is desirable that TSH was maintained at 1.2 mIU/mL (31).

Ideally, women with primary hypothyroidism should be counseled before pregnancy about the appropriate dosageof LT during pregnancy. It is necessary to increase the dailydose of 25-50 mg. There is a consensus that it is necessary tocheck hormone 4-6 weeks, it seems that the need to increasethe dose to half of pregnancy, which is held until delivery (1).The progression of the SH is predictable based on TSH and TPOAb in the first trimester. These parameters areuseful markers for the identification of women at high risk,and careful monitoring of thyroid function during pregnancy. Pregnancy is associated with an increased risk ofthyroid pregnant women with AITD, so that the potentialrelationship between pregnancy and thyroid disorders(41). SH arising before conception or during gestationshould be treated with levothyroxine. The goal of levothyroxine treatment is to normalize maternal serum TSHvalues within the trimester-specific pregnancy referencerange (35). After delivery, the dose of LT should be continued with a dose of a non-pregnant, and is not changedunless there is evidence of a hypo or hyperthyroidism (42).Thyroid hormone treatment was associated with decreased risk of pregnancy loss among women with subclinical hypothyroidism, especially those with pre-treatment TSH concentrations of 4.1-10 mIU/L (39).

TREATMENT OF HYPERTHYROIDISM DURING PREGNANCY

Carbimazole should be avoided in the first trimester of pregnancy due to risk of congenital anomalies, but recent studies would suggest that this risk is present to a lesser magnitude with propylthiouracil. Current international guidelines recommend the use of propylthiouracil in the first trimester and switching to carbimazole for the remainder of pregnancy but the benefits and practicalities ofthis approach is unproven (32).

Graves' disease often shows a characteristic course in pregnancy with amelioration of thyrotoxicosis in the second half of pregnancy and exacerbation after delivery. In addition transplacental passage of maternal TSH receptor antibodies may lead to thyrotoxicosis in the fetus and/or newborn (43).

Both hypothyroidism and thyrotoxicosis may impair the course of pregnancy and may negatively affect the fetus. In particular, maternal hypothyroidism may lead to irreparable and detrimental deficits in the neurocognitive development of the fetus (31, 43).

CONCLUSION

During pregnancy, proper thyroid function of the mother is important for both mother and child. This is particularly important in the first trimester, when fetal development completely dependent on the mother's hormones that are essential for optimal development.

Recommendation for the upper limit for TSH 2.5 mIU/L in the first, and 3.0 mIU/L in the second and third trimester. Lower physiological limit is 0.1 mIU/L for the first and 0.2 mIU/L for the second, and 0.3 mIU/L for the third trimester

Preconceptional education and adequate diagnosis and treatment of thyroid dysfunction in early pregnancy are of great importance, in order to prevent complications during pregnancy and offspring.

In summary, universal screening of TSH, fT4, and TPOAb is essential during the first trimester and second trimester of pregnancy. Taken together, we support implementation of a universal screening strategy for thyroid disorders in pregnant women.

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CONFLICT OF INTEREST

The author declare no financial or commercial conflictof interest.

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