CHAPTER

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Management of Hypothyroid in Pregnancy

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INTRODUCTION

Pregnancy has a profound impact on the thyroid gland and thyroid function. The gland increases 10% in size during pregnancy in iodine-replete countries and by 20%–40% in areas of iodine deficiency. Production of thyroxine (T4) and triiodothyronine (T3) increases by 50%, along with a 50% increase in the daily iodine requirement. These physiological changes may result in hypothyroidism in the later stages of pregnancy in iodine-deficient women who were euthyroid in the first trimester. The range of thyrotropin (TSH), under the impact of placental human chorionic gonadotropin (hCG), is decreased throughout pregnancy with the lower normal TSH level in the first trimester being poorly defined and an upper limit of 2.5 mIU/L. 10% to 20% of all pregnant women in the first trimester of pregnancy are thyroglobulin (Tg) or thyroid peroxidase antibody (TPOAb) positive and euthyroid. 16% of the women who are euthyroid and positive for TPOAb or Tg antibody in the first trimester will develop a TSH that exceeds 4.0 mIU/L by the third trimester, and 33%–50% of women who are positive for TPOAb or Tg antibody in the first trimester will develop postpartum thyroiditis. In essence, pregnancy is a stress test for the thyroid, resulting in hypothyroidism in women with limited thyroidal reserve or iodine deficiency, and postpartum thyroiditis in women with underlying Hashimoto's disease who were euthyroid prior to conception.

CHANGES IN THYROID FUNCTION ASSOCIATED WITH PREGNANCY

A normal pregnancy results in a number of important physiological and hormonal changes that alter thyroid function. These changes mean that laboratory tests of thyroid function must be interpreted with caution during pregnancy. Thyroid function tests change during pregnancy due to the influence of two main hormones: hCG and estrogen. hCG can weakly turn on the thyroid and high circulating hCG levels in the1st trimester may result in a slightly low TSH (subclinical hyperthyroidism). When this occurs, TSH will be slightly decreased in the 1st trimester and then return to normal throughout the duration of pregnancy (Fig 1). Estrogen increases the amount of thyroid hormone binding proteins which increases the total thyroid hormone levels in the blood since > 99% of the thyroid hormones in the blood are bound to these proteins. However, measurements of "free" hormone (that are not bound to protein, representing the active form of the hormone) usually remain normal. Table 1 lists effects of pregnancy on thyroid physiology.

INTERACTION BETWEEN MATERNAL AND FETAL THYROID FUNCTION

For the first 10-12 weeks of pregnancy, the baby is completely dependent on the mother for the production of thyroid hormone. By the end of the 1st trimester, the baby's thyroid begins to produce thyroid hormone on its own. The baby, however, remains dependent on the mother for ingestion of adequate amounts of iodine, which is essential to make thyroid hormones. WHO recommends iodine intake of 200μg/day during pregnancy to maintain adequate thyroid hormone production.

HYPOTHYROIDISM IN PREGNANCY

Primary maternal hypothyroidism is defined as the presence of an elevated TSH concentration during gestation. Historically, the reference range for serum TSH was derived from the serum of healthy, non-pregnant individuals. Using these data, values greater than 4.0 mIU/L were considered abnormal. More recently, normative data from healthy pregnant women suggest the upper reference range may approximate 2.5–3.0 mIU/L. When maternal TSH is elevated, measurement of serum FT4 concentration is necessary to classify the patient's status as either subclinical (SCH) or overt hypothyroidism (OH). This is dependent upon whether FT4 is within or below the trimester-specific FT4 reference range. The distinction of OH from SCH is important because published data relating to the maternal and fetal effects attributable to OH are more consistent and easier to translate into clinical recommendations in comparison to those regarding SCH.

DEFINITIONS OF OH AND SCH IN PREGNANCY

Elevations in serum TSH during pregnancy should be defined using pregnancy specific reference ranges. OH is defined as an elevated TSH (>2.5 mIU/L) in conjunction with a decreased FT4 concentration. Women with TSH levels of 10 mIU/L or above, irrespective of their FT4 levels, are also considered to have OH (0.2%). SCH is defined as a serum TSH between 2.5 and 10 mIU/L (in 80-90%) with a normal FT4 concentration. TPOAb may be positive in 60-80%. SCH is more common in women (7.5% against 2.8% in men) and is found in 2.3% of pregnant women. SCH is common in diabetes, goiter, and spontaneous abortion.

TPOAb positivity is seen in 10.8% of all pregnant women.

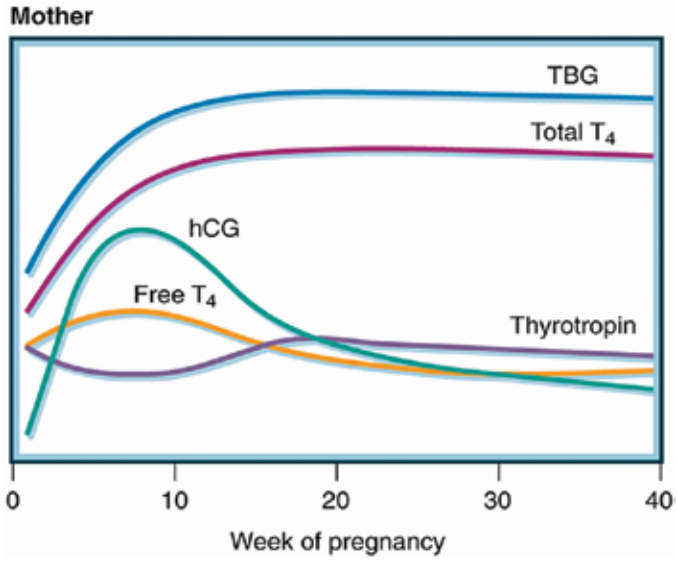

Fig. 1: Thyroid hormone levels during pregnancy

Infertility and miscarriage are more common if TPO positive.

COMMON CAUSES OF HYPOTHYROIDISM IN PREGNANCY

Hypothyroidism can occur during pregnancy due to the initial presentation of Hashimoto's thyroiditis, inadequate treatment of a woman already known to have hypothyroidism from a variety of causes, or over-treatment of a hyperthyroid woman with anti-thyroid medications. Postablative hypothyroidism following radioactive iodine or surgical therapy and iodine deficiency may be seen. Table 2 lists the causes of hypothyroidism in pregnancy.

RISKS OF MATERNAL HYPOTHYROIDISM TO THE BABY

Even mild (subclinical) thyroxine deficiency in early pregnancy is detrimental to mother & fetus. Thyroid hormone is critical for brain development in the baby. Untreated severe hypothyroidism in the mother can lead to impaired brain development in the baby. This is mainly seen when the maternal hypothyroidism is due to iodine deficiency, which also affects the baby. Children born with congenital hypothyroidism can have severe cognitive, neurological and developmental abnormalities if the condition is not recognized and treated promptly. These developmental abnormalities can largely be prevented if the disease is recognized and treated immediately after birth. Consequently, all newborn babies in the United States, Europe and Japan are screened for congenital hypothyroidism.

There is 20% incidence of maternal and perinatal complications with untreated, or inadequately treated hypothyroidism viz anemia, CHF, pre-eclampsia, gestational hypertension, placental abruption, preterm birth, LBW, congenital malformations, impaired intellectual and psychomotor development and fetal death. With subclinical hypothyroidism the same problems exist, but they are one-third as common.

SCREENING FOR HYPOTHYROIDISM DURING PREGNANCY

At this time universal screening is not recommended for patients who are pregnant or are planning pregnancy, including assisted reproduction. The policy is for "aggressive case finding" ie in women with past history of thyroid disease, PPT, or thyroid lobectomy, with a family history of thyroid disease, with a goiter, known positive thyroid antibodies, with symptoms or clinical signs suggestive of thyroid hypofunction or hyperfunction, including anemia, elevated cholesterol, and hyponatremia and with type 1 diabetes.

THE OPTIMAL METHOD TO ASSESS FT4 DURING PREGNANCY

The optimal method to assess serum FT4 during pregnancy is measurement of T4 in the dialysate or ultra-filtrate of serum samples employing on-line extraction/ liquid chromatography/tandem mass spectrometry (LC/MS/ MS). If FT4 measurement by LC/MS/MS is not available, clinicians should use whichever measure or estimate of FT4 is available in their laboratory, being aware of the limitations of each method. Serum TSH is a more accurate indication of thyroid status in pregnancy. In view of the wide variation in the results of FT4 assays, method-specific and trimester-specific reference ranges of serum FT4 are required.

TREATMENT OF HYPOTHYROIDISM DURING PREGNANCY

Apart from symptomatic improvement benefits of treatment are prevention of progression to overt hypothyroidism, reduction in lipid levels with a subsequently lower risk of cardiovascular events and prevention of poor developmental outcomes in children born to women with subclinical disease.

The treatment of choice is levothyroxine (LT4). Once hypothyroidism is diagnosed (overt or subclinical) treatment should be started with LT4 in doses of 50 µg daily with gradual increments of 25 µg every week, until the serum TSH level becomes normal.

For women on thyroid replacement therapy before pregnancy check serum TSH level as soon as pregnancy is confirmed with a preemptive dose increase by 25 mg. Higher doses may be required for postablative and postsurgical hypothyroidism.

TARGET LEVELS OF TSH AND MONITORING DURING PREGNANCY

Emphasize pre conceptional control (TSH<2.5 mU/L) in known hypothyroid women. The goal of LT4 treatment is to normalize maternal serum TSH values. The upper limit of the normal range should be based on trimester-specific ranges for that laboratory. If trimester-specific reference ranges for TSH are not available : the targets are <2.5 mIU/L in the first trimester, <3 mIU/L in later pregnancy. For previously diagnosed hypothyroid women, monitor TSH every 3-4 weeks during the first half of pregnancy and every 6-8 weeks thereafter. After delivery decrease LT4 dose to pre pregnancy dose and check TSH in six weeks. If the original indication for T_4 therapy is unclear this can be sorted out by stopping it for 6 weeks postpartum for re-evaluation.

Table 1 : Effects of pregnancy on thyroid physiology

Physiologic Change	Thyroid-Related Consequences
↑ Serum thyroxine-binding globulin	↑ Total T_4 and T_3; ↑ T_4 production
↑ Plasma volume	↑ T_4 and T_3 pool size; ↑ T_4 production; ↑ cardiac output
↑ Deiodinase expression in placenta and (?) uterus	↑ T_4 production
First trimester ↑ in hCG	↑ Free T_4; ↓ basal thyrotropin; ↑ T_4 production
↑ Renal I^- clearance	↑ Iodine requirements
↑ T_4 production; fetal T_4 synthesis during second and third trimesters	
↑ Oxygen consumption by fetoplacental unit, gravid uterus, and mother	↑ Basal metabolic rate; ↑ cardiac output

Table 2 : Causes of hypothyroidism during pregnancy

Primary hypothyroidism

- Thyroid destruction (Hashimoto's disease)
- Circulating TSH-receptor-blocking antibody

Asymptomatic (euthyroid) autoimmune thyroid disease

Postpartum thyroid disease

- Hyperthyroidism
- Hypothyroidism
- Combinations

Graves' disease

- Pre-existing
- Gestational exacerbation and remission PP exacerbation

Separate iron, calcium, soy products by at least four hours after LT_4 ingestion to ensure adequate absorption.

Women who are TPOAb positive are susceptible to subclinical hypothyroidism. They should be monitored during pregnancy and postpartum for the development of thyroid dysfunction.

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