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Thyroid Dysfunction in Pregnancy: A Literature Review

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ABSTRACT

Due to structural similarities between HCG and thyroid-stimulating hormone, thyroid stimulation during pregnancy starts in the first trimester (TSH). The volume of thyroid hormone distribution increases along with placental metabolism, maternal thyroxine transport, and estrogen-mediated changes in thyroxine-binding globulin (TBG), all of which cause a 20–40% rise in early pregnancy thyroid hormone demand. Due to the human chorionic gonadotropin alpha subunit's cross-reactivity with the TSH receptor, the reference range of laboratory values for TSH is lower. High serum protein levels may alter estimates rather than direct measurements of free thyroxine (FT4), leading to reported results that are inaccurate. The clinical range of thyroid dysfunction during pregnancy can include both hyperthyroidism (Graves' disease and transitory gestational thyrotoxicosis) and hypothyroidism (overt hypothyroidism, subclinical hypothyroidism, and autoimmune thyroid disease). The risk of preterm and infant respiratory distress syndrome is increased by this malfunction.

Keywords: Hyperthyroidism, hypothyroidism, pregnancy, thyroid.

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I. Introduction

Pregnancy is a natural physiological change that hormonal and metabolic changes can follow. These changes can undoubtedly cause various conditions, both physiological conditions and also trigger pathological conditions. One of these changes is the endocrine system, specifically the thyroid. Thyroid disease during pregnancy can cause complications for the mother and the fetus. Therefore, the importance of early recognition and appropriate therapeutic approaches is expected to reduce morbidity and mortality from these complications. So, this literature review will discuss further thyroid dysfunction during pregnancy.

II. An Overview of Thyroid Gland

Thyroid hormone is produced by a complex series of pathways in the hypothalamic-pituitary-thyroid axis. Thyrotropin-releasing hormone (TRH) is secreted by the hypothalamus stimulates thyrotropic cells of the anterior pituitary to produce and secret thyrotropin. Thyroid-stimulating hormone (TSH) is one of the key regulators of thyroid function. The anterior pituitary gland produces the peptide hormone TSH under TRH control. Little variations in the serum levels of thyroid hormone have a big impact on TSH. The production of TRH by the hypothalamus is necessary for this feedback system. The production of TRH is directly inhibited by the thyroid hormone. On the other hand, low levels of thyroid hormone lead to an increase in TRH production in the hypothalamus, which is discharged into the hypothalamic-pituitary system's portal circulation (Fig. 1). Thyrotropin stimulates hyperplasia of the thyroid gland, induces the production of thyroglobulin, and leads to the production of the thyroid hormones triiodothyronine (T3) and thyroxine (T4). Also, by downregulating TRH receptors on thyrotropic cells, this thyroid hormone negates the effects of TRH by inhibiting thyrotropin release at the level of thyrotropic cells. Thyrotropin secretion changes inversely logarithmically in response to changes in thyroid hormone levels; for example, a doubling change in T4 causes a 100-fold change in thyrotropin secretion. Consequently, thyrotropin levels are responsive to subtle and subclinical variations in T4 levels. [1],[2].

This complex relationship is the basis for obtaining thyrotropin levels as a first-line test for thyroid dysfunction. Thyroid-binding pre-albumin (transthyretin), albumin, and thyroxine-binding globulin (TBG) all bind thyroid hormone. Most thyroid hormones have a natural affinity for TBG, which is why TBG is the primary site of binding for most thyroid hormones. Up until a new setpoint is reached by the homeostatic processes that control the hypothalamic-pituitary-thyroid axis, factors that change TBG levels will also affect thyroid hormone availability. These elements include the use of medications, dietary intake, pregnancy, and systemic disease. T3, which is created by taking the 5' iodine out of T4, is the thyroid hormone that is physiologically active. Twenty percent of T3 is released directly from the thyroid gland, and 80% of T3 is created in peripheral tissues from deionized T4. The main thyroid hormone storage form, T4, is not thought to be biologically active. T4 had a binding rate of 99.97%, whereas T3 had a binding rate of 99.7%. Only hormones that are not bound to other molecules are biologically active and accessible to tissues. Consequently, if

total thyroid hormone levels are the only thing measured, thyroid hormone measurements can be difficult to interpret. [1].

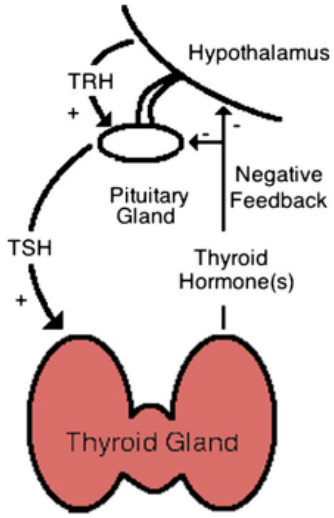

Fig. 1. The Illustration of The Hypothalamic-Pituitary-Thyroid Axis [2].

III. Thyroid Physiological Changes in Pregnancy

Hormones called HCG, which resemble TSH in structure, start stimulating the thyroid in the first trimester. Additionally, during pregnancy, serum TBG concentrations increase by 2-3 times because of an increase in circulation TBG levels caused by estrogen. TBG, one of the many proteins involved in the movement of thyroid hormone (TH) in the blood, has a strong affinity for T4, the level of which rises in the serum several weeks after fertilization and reaches a plateau in the middle of pregnancy. TBG is synthesized more frequently in the liver, which is thought to be the mechanism for this rise in TBG. An increase in TBG levels lowers the amount of free T4, which lowers the amount of free T4 in the body. This causes the pituitary to secrete more TSH, which causes the body to secrete more TH. Increased TBG synthesis has the effect of forcing a new balance between bounded and free TH. As a result, the levels of T4 and T3 in total have significantly increased. Around 20 weeks into the pregnancy, the increase in TH is reached and lasts until term. It reflects modifications in iodine metabolism, which is essential for the production of TH [3], [4].

Pregnancy causes an increase in iodine demand (Fig. 2) because of increased renal excretion and increased maternal iodine supply to the fetus. Iodine excretion in the urine increases during pregnancy due to increased glomerular filtration and renal tubular absorption. Additionally, maternal iodine is transferred to the fetoplacental unit, which adds to the relative iodine deficiency [5].

The effect of the human placenta's production of β-HCG is another factor. The thyrotropic activity of β-HCG causes thyroid stimulation, which overrides the hypothalamic-pituitary-thyroid feedback system's normal operation. TSH has the ability to bind to and transmit signalling from thyroid epithelial cells' TSH receptors. The majority of thyroid stimulating activity occurs up until the first trimester of pregnancy is completed, when β-HCG levels are at their highest. During this time, the level of TSH in the blood becomes depressed. Some women acquire transient hyperthyroidism as a result of β-HCG's thyroid-stimulating action. The thyroid and the mother's thyroid are both potential sources of TH for the fetus. The fetus acquires the ability to synthesize TH in approximately the first trimester of pregnancy. After 12 weeks of pregnancy, the fetal thyroid gland begins to concentrate iodine and synthesize thyroid hormone. During the first trimester of pregnancy, thyroid hormone is very critical for embryonic brain development. Thyroid hormones are vital later in pregnancy because considerable the fetal brain continues to develop long beyond the first trimester. Maternal thyroid insufficiency during the first half of a pregnancy is linked to several pregnancy problems, and also intellectual disability in the offspring. [6], [7].

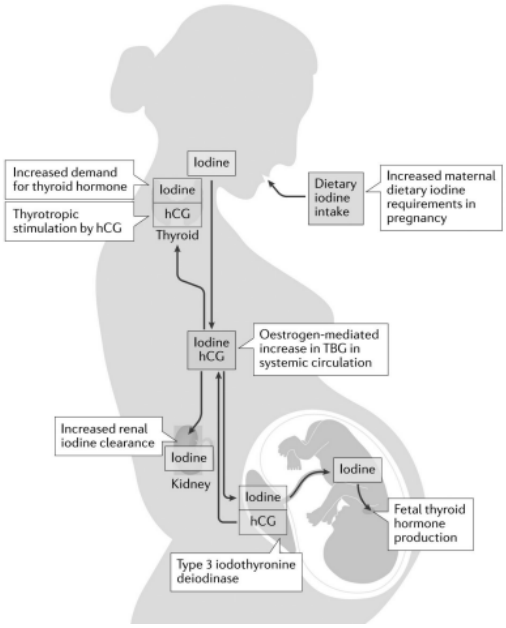

Fig 2. Factors increasing maternal dietary odine requirement in pregnancy [5].

IV. Pathological Spectrums of Thyroid Function in Pregnancy

A. Hypothyroidism

Hypothyroidism is characterized by insufficient thyroid hormone (TH) production (primary) and decreased stimulation of the pituitary (secondary) or hypothalamic (tertiary) glands. TH deficiency can range from mild to severe. Overt hypothyroidism (OH) occurs when the TSH exceeds the upper limit of normal and the FT4 falls below the reference range. Subclinical hypothyroidism (SCH) occurs when TSH levels are above normal upper limits but FT4 levels are within the reference range. Isolated hypothyroxinemia was characterized as maternal TSH and FT4 levels below the reference range [8].

Thyroid dysfunction during pregnancy includes OH and SCH, which have a relative incidence of about 0.4% for OH and 3% for SCH, and subclinical thyrotoxicosis, which has a relative incidence of about 0.2%. In addition, there is a spectrum of other disorders, namely autoimmune thyroid disease (AITD), ranging from 5-20%, with an average of 7.8%. In pregnant women, AITD is a major cause of hypothyroidism. Hypothyroidism affects approximately 4-10% of women, including the majority of women of

reproductive age. However, it should be noted that iodine deficiency is the leading cause of hypothyroidism in pregnant women globally. Significant hypothyroidism affects only about 5% of all women with high TSH levels [9].

The pregnancy-related normative reference range for TSH (which will be reduced by β-HCG at this time) should be used to diagnose hypothyroidism in the first trimester. Thyroid function examinations in healthy pregnant women differ from those in healthy nonpregnant women due to the increased metabolic demands during pregnancy. In 2012, the ATA proposed a pregnancy-specific and, ideally, trimester-specific reference within the TSH and FT4 intervals. TSH levels higher than the upper range expected during pregnancy (>4.0 mIU/L) and lower serum FT4 concentrations are considered primary manifest hypothyroidism during pregnancy, as are TSH levels of 10.0 mIU/L or more, regardless of FT4 levels. A serum TSH level between 4.0 and 10 mIU/L with an average FT4 level was defined as subclinical hypothyroidism in pregnancy. In pregnancy, isolated hypothyroxinemia was defined as a standard TSH value with an FT4 concentration in the 2.5-5th percentile lower than the reference range. Given the wide geographic and ethnic variation in pregnancy TSH concentrations, the new ATA guidelines recommend determining the best reference range for each population, hospital, or laboratory. Assume, however, that this is not available during the first trimester. The upper limit TSH value is used as a reference. That is 4.0 mIU/L in that case, with a gradual return to the TSH range in nonpregnant thyroid disease-free individuals (0.45-4.5 mIU/L) in the second and third trimesters [10], [11].

To avoid obstetric complications and adverse pediatric neurodevelopmental outcomes, pregnant women with overt hypothyroidism should be treated with LT4. Mono-LT4 therapy is recommended for the treatment of pregnancy hypothyroidism. Because T3 does not cross the placenta, despite normal maternal thyroid function, using T3, T3/T4 combination therapy may result in insufficient thyroid hormone availability to the fetus. The use of LT4 to treat hypothyroidism or subclinical hypothyroxinemia in pregnant women is debatable [12]. If the TPO antibody is positive, treatment of SCH is recommended for TSH values greater than 4 mIU/L and greater than 10 mIU/L if TPO antibody is negative [10]. The ACOG guideline recommends starting treatment if the free T4 level is low and only for overt hypothyroidism [13].

B. Hyperthyroidism

Hyperthyroidism is less common than hypothyroidism, affecting 0.1-1.0% of pregnancies. At least 80% of these cases are caused by Graves' disease, with other causes including solitary or multiple autonomic nodules. In pregnancy, hyperthyroidism is a serious condition that increases the risk of, stillbirth, miscarriage, premature birth, and intrauterine growth restriction. Fetal hyperthyroidism with fetal tachycardia, goiter, and hydrops are potential causes of miscarriage. Furthermore, TSH receptor antibodies transferred from the mother's blood to the infant cause neonatal hyperthyroidism in 1-5% of infants born to Graves' disease mothers. Although this condition usually resolves on its own, it can cause significant neonatal morbidity, which can be fatal. Recognizing neonatal hyperthyroidism in the absence of thyroid examination can be difficult, especially in infants born to mothers with undiagnosed hyperthyroidism. The increase in TBG caused by estrogen and the weak thyroid stimulating action of β-HCG result in an increase in total thyroid hormone and a corresponding decrease in TSH. Meanwhile, unlike Graves, there are no antibodies to the TSH receptor, goiter, abnormal thyroid texture on ultrasound, or ophthalmopathy. Recognizing neonatal hyperthyroidism can be difficult, especially in infants born to mothers with undiagnosed hyperthyroidism [14].

This transient thyrotoxicosis occurs in 1.7-3.0% of women who are pregnant during the first trimester, when β-HCG levels are at their peak. Because there are significant maternal complications, it is critical to correctly interpret thyroid function tests in order to avoid missing the diagnosis. A TSH receptor activating mutation inherited predominantly from the mother can also cause neonatal hyperthyroidism. Transient neonatal central hypothyroidism is caused by poorly controlled Graves' disease, which causes suppression of the fetal pituitary thyroid axis due to T4 transfer through the placenta [4].

Anti-thyroid drugs (ATD) are used to treat TH concentration increases that are more severe. The lowest dose should be used to prevent fetal hypothyroidism since the medication can slightly crosses the placenta and decrease fetal TH production. ATDs like PTU and methimazole (MMI) are efficient treatments for hyperthyroidism but both have potential side effects. Both ATDs have the potential to elevate serum levels of liver enzymes, which typically return to normal following drug discontinuation. The prevalence of cholestasis between the 2 ATDs was not significantly different in a more recent study, despite the fact that PTU has been linked to a higher incidence of liver injury. PTU can cause fulminant liver failure, even in pregnant women, despite its low prevalence (1:10,000). MMI is typically preferred over PTU in cases devoid of pregnancy for this reason. The teratogenicity of ATD should be taken into account during the early stages of pregnancy when organogenesis is occurring because MMI and PTU cross the placenta. Since the 1970s, MMI has been linked to congenital disorders, while PTU has long been thought to be safe during early pregnancy [3], [12].

TABLE I: CLINICAL MANIFESTATIONS DUE TO GENETIC DISORDERS ASSOCIATED WITH CONGENITAL HYPOTHYROIDISM [12]

Test	Nonpregnant	1st trimester	2nd trimester	3rd trimester
TSH (mIU/L)	0.3-4.3	0.1-2.5	0.2-3	0.3-3
TBG (mg/dL)	1.3-3	1.8-3.2	2.8-4	2.6-4.2
FT4 (ng/dL)	0.8-1.7	0.8-1.2	0.6-1	0.5-0.8
Total T4 (mcg/dL)	5.4-11.7	6.5-10.1	7.5-10.3	6.3-9.7
FT3 (pg/mL)	2.4-4.2	4.1-4.4	4-4.2	-
T3 total (ng/dL)	77-135	97-149	117-169	123-162

Women with a high risk of thyroid disease

Women with a history of thyroid dysfunction and/or thyroid surgery
Women with a family history of thyroid disease
Women with a goiter
Women with positive thyroid antibodies
Women with symptoms or clinical signs suggestive of hypothyroidism
Women with Type I diabetes
Women with a history of miscarriage or preterm delivery
Women with other autoimmune disorders are frequently associated with autoimmune thyroid dysfunction, including vitiligo, adrenal insufficiency, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, systemic lupus erythematosus (SLE), and Sjögren's syndrome
Women with infertility
Women with prior therapeutic head or neck irradiation
Women with morbid obesity
Women aged 30 years or older
Women treated with amiodarone
Women treated with lithium
Women with recent exposure to iodinated radiological contrast agents

Fig. 3. The Criteria For Women With A High Risk Of Thyroid Disease [14].

V. Thyroid Dysfunction Screening in Pregnancy

The reference limits of thyroid parameters used to diagnose thyroid dysfunction during pregnancy are no longer valid in the presence of pregnancy-induced thyroid physiologic changes. Given the serious consequences of maternal thyroid dysfunction on pregnancy outcomes and fetal health, this is a critical issue that requires special attention. As a result, numerous attempts to establish a pregnancy reference range for thyroid function tests have been made in recent years. It is necessary to review the regular physiologic changes of the laboratory value references (Table I) [15].

Thyroid dysfunction is clinically diagnosed utilizing serum FT4 and TSH levels, as well as related antibodies. Thyroid function testing with venous blood samples is a standard and appropriate procedure. Because FT4 and TSH have an inverse logarithmic relationship, tiny changes in T4 induce substantial changes in TSH, making TSH the most sensitive and specific measure of thyroid health in both obvious and subclinical thyroid disease. Unlike TSH, the presence of pregnancy-modified plasma proteins can impede FT4 measurement during pregnancy [14].

The presence of an estrogen-mediated increase in TBG, an increase in the volume of thyroid hormone distribution, and placental metabolism and maternal thyroxine transport results in a 20-40% increase in thyroid hormone requirements in early pregnancy. Because the human chorionic gonadotropin alpha subunit and the TSH receptor interact cross-reactively, the reference range for TSH is lower during pregnancy. Elevated serum protein concentrations can affect estimates-based free thyroxine (FT4) measurements, leading to reported values that are incorrect. Serum TSH levels are a more accurate indicator of the maternal thyroid status when the preferred FT4 assay technique is not available. Total thyroxine and the FT4 index can also be measured in its place. Definitive screening is performed only in high-risk pregnant women (Figure 3) using serum TSH measurements [16],[17]. One study found that selective screening for high-risk women will be lost 30% of those with subclinical hypothyroidism. However, universal screening does not reduce adverse outcomes in a randomized control trial of 4,562 women [18].

VI. Perinatal Outcomes

Maternal TSH levels >4 mIU/L were linked to an increased risk of prematurity (RR 2.17 [95%CI 1.15-4.07] P=0.016) and neonatal respiratory distress syndrome (RDS) (RR 2.83 [95%CI 1.02-7.86] P=0.046) compared to a TSH level of 4 mIU/L, according to a study by [19] with a sample of 8,413 pregnant women. TSH levels above 4 mIU/L were also linked, though not statistically significantly, to a higher risk of fetal loss, preeclampsia/eclampsia, and low birth weight. TSH levels above 4 mIU/L are not linked to placental abruption, preterm birth, gestational hypertension or diabetes, cesarean section, or admission to the neonatal intensive care unit [19]. In addition, maternal TSH >4 mIU/L was significantly associated with postpartum thyroiditis (OR=3.55, 95% CI, 1.43-8.81) [20].

The incidence of neonatal hypothyroidism has been reported to be one in every 3000-4000 births. Iodine deficit or excess (paradoxical impact), anti-thyroid medications and goitrogens during pregnancy, and transplacental TAb inhibiting thyroid stimulating hormone receptors (TSHR) from the mother can all cause transient hypothyroidism. However, even transient hypothyroidism can have negative consequences, particularly changes in infant neurologic development, so early detection and treatment are essential. Women who are pregnant and have autoimmune thyroid illness, such as Hashimoto's thyroiditis, are more prone to develop fetal and neonatal problems. The type and amount of TAb that crosses the placenta affects the clinical and hormonal characteristics of the infant. There is evidence that maternal autoimmune thyroid illness is linked to temporary congenital newborn hypothyroidism. Close monitoring of neonates with TSH and FT4 is advised at 48 hours of birth, with repeat measures between 2 and 4 weeks for those with baseline TSH >6 mUI/L, especially in situations of mothers with autoimmune thyroid disease [21].

VII. Conclusion

Thyroid hormone is produced from a complex series of pathways involving the hypothalamic-pituitary-thyroid axis. During pregnancy, there is thyroid stimulation, which begins in the first trimester by hormones β-HCG because it has some

structural similarities to TSH. In addition, there is an increase in thyroxine-binding globulin (TBG) levels in the blood, which is mediated by estrogen. Pathological abnormalities of the thyroid in pregnancy can be hypothyroidism and hyperthyroidism. Screening is done by looking at laboratory values references based on gestational age and is considered in women with a high risk of developing thyroid disease.

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