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REVIEW ARTICLE - BIOLOGY

A review: Maternal hypothyroidism during pregnancy

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Abstract

The thyroid gland in pregnant women undergoes significant structural and physiological changes. One example is the universal enlargement of the gland in pregnant women in countries with sufficient and deficient body iodine levels. In addition, an increase of 50% occurs in both the production of the thyroid hormones and the daily need for iodine. Such alterations also continuously occur in women in general, but the pathological reactions taking place during pregnancy may lead to various aspects of dysfunction of the glans, including hypothyroidism which is commonly observed in pregnant women who might be seriously affected, along with the developing fetus. The situation can become complicated with other physiological disorders, including gestational hypertension, premature delivery, and fetal growth restriction. About 3 to 5 % of pregnant women develop hypothyroidism, making it the main form of thyroid dysfunction in this group of women. As compared to the overt form, subclinical hypothyroidism occurs in a higher frequency. It is diagnosed when the level of the thyroid-stimulating hormone (TSH) in the serum is higher compared to the pregnancy-specific reference range. Hormone levels higher than 2•5 mIU/L in the 1st trimester and 3 mIU/L in the 2nd and 3rd trimesters are also indicative of this condition. However, a number of studies reported serum TSH values of 5-10 and >10 mIU/L to diagnose subclinical and overt hypothyroidism, respectively. Close monitoring is especially important during the first trimester because untreated hypothyroidism during this time might lead to irreversible disorders in the nervous system of the developing fetus.

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1. Introduction

The hormones secreted by the thyroid gland are essential for the fetus to properly develop and maturate. Maternal T4 passing through the placenta is utilized by the fetus until synthesizing own hormone [1]. Factors such as the increase of the combined metabolism rates of the mother and the infant as well as the elevated level rate of glomerular filtration in the kidneys contribute to the observed increased demand on iodine in pregnant women [2,3]. Therefore, physiological alterations required to fulfill this increase in the metabolism rates must be taken into account the thyroid is functionally tested along the pregnancy period [4]. Reduced levels of thyroid hormones result from decreased activity of the gland, which is diagnosed as hypothyroidism that significantly affects the mother and her fetus. The brain of the fetus is usually developed under significant impact from the thyroid. This is the reason conditions as preterm birth, low birth weight, and child cognitive disorders are observed upon hypothyroidism in pregnant women. Maternal hypothyroidism affects 2-3% of pregnancies and could take place due to several reasons, including autoimmune disease, lack of iodine and previous thyroid surgery. Hypothyroidism can also develop during pregnancy due to an increased need for thyroid hormones [5]. Symptoms of hypothyroidism in pregnant women could have similarities with those in non-pregnant women and may include fatigue, weight gain, constipation, and sensitivity to cold. However, these symptoms can also be due to the normal changes of pregnancy, making it difficult to diagnose hypothyroidism during pregnancy without proper testing [6]. The American Thyroid Association recommends screening of pregnant mothers in order to identify possible thyroid dysfunction during the 1st trimester of pregnancy. If hypothyroidism is diagnosed, thyroid replacement therapy is often recommended for securing optimal concentrations of the thyroid hormones and

reducing the risk of any complications in pregnant mothers [7]. Treating hypothyroidism during pregnancy can help improve pregnancy outcomes and the cognitive development of children. However, the study also highlights the importance of close monitoring and individualized treatment planning for pregnant women with hypothyroidism to ensure optimal management. Overall, hypothyroidism in pregnant mothers must be properly diagnosed and managed so that the lowest risk of complications is reached and healthy development of both mother and fetus is promoted [8].

The placenta is actively involved in modulating maternal contribution of thyroid support and promoting fetal thyroid function as well. Placenta and fetal pancreas are a significant source of thyroid releasing hormone (TRH) [9]. The relationship between TRH from these sources and the maturing fetal hypothalamic pituitary axis is poorly understood, despite the suggestion that it plays a role in prematurity and fetal lung maturation [10].

The thyroid is a gland with the shape of butterfly and a location at the anterior the neck. As part of the endocrine system, it is known for the production of two hormones (T3 and T4) that are responsible for the regulation of several processes, such as those of the metabolism (e.g. thermal regulation and energy production), growth, and development. The thyroid is regulated by the brain-based pituitary gland through the actions of the thyroid-stimulating hormone (TSH) which controls the production of the thyroid hormones [11].

At the molecular level, a number of key genes have been suggested to be implicated in hypothyroidism pathogenesis. These genes along with their descriptions are summarized in the below table (table1).

Table 1: Genes implicated in hypothyroidism pathogenesis

Gene	Description	Category	Reference
TPO	Thyroid Peroxidase	Protein Coding	[12]
TSHR	Thyroid Stimulating Hormone Receptor	Protein Coding	[13]
ENO1	Enolase1	Protein Coding	[14]
TG	Thyroglobulin	Protein Coding	[12]
ALB	Albumin	Protein Coding	[15]
CKMT2	Creatine Kinase, Mitochondrial 2	Protein Coding	[16]
CKMT1B	Creatine Kinase, Mitochondrial 1B	Protein Coding	[17]
CKB	Creatine Kinase B	Protein Coding	[18]

1.1 Physiological features of the thyroid in pregnant mothers

Pregnant mothers undergo an increase in metabolic demands, which leads to physiological alterations in the thyroid that can be reflected in alterations observed during functionally testing the gland. Chorionic gonadotropin (hCG) and estrogen are the major hormones responsible for such altered results of thyroid functional tests in pregnant mothers[19]. The hCG exerts a weak stimulatory impact on the thyroid; however, this hormone is found in high concentrations during the 1st trimester, possibly leading to reduced levels of TSH, which can restore normal levels along the pregnancy period. These alterations occur alongside increase in estrogen, leading the thyroid binding globulin (TBG) to be increasingly produced and decreasingly cleared, resulting in an overall net increase in its level in the serum[20]. Reports indicated elevated affinity (by 50%) of T4 (thyroxine) / T3 (tri-iodothyronine) to TBG during the first half of pregnancy. This results in an elevation in the overall T4/T3 concentration by 50%, while that of the free T4/T3is consequently reduced , which plateaus at 20 weeks of gestation[21].

1.1.1 Changes in iodine requirements

Iodine is a crucial nutrient for the production of thyroid hormones. During pregnancy, an increase in the need for iodine is observed, as it is needed to support the increased production of thyroid hormones. Women, before and during pregnancy, are advised to consume higher amounts of iodine, usually through iodine-rich foods or supplements. Certain mothers have the risk of developing autoantibodies against their thyroid at some point of the pregnancy course, which can lead to a condition called autoimmune thyroid disease[22]. This condition can affect the production of thyroid hormones and require treatment[23]. Several maternal physiological adaptations occur in response to foetal physiology and fetal thyroxine requirements. At around 12 weeks, the fetal thyroid is functional; however, it begins the production of sufficient thyroxine only at 18–20 weeks gestation. Importantly, adequate supply of thyroxine is crucial for the developing fetal brain [24, 25].

The thyroid is responsible for a number of metabolic alterations that are noticed in pregnant mothers. Thus, understanding these alterations to properly manage possible thyroid disorders in these mothers is of a crucial importance. Both overt and subclinical maternal hypothyroidism, regardless of antibody status, require effective treatment to avoid adverse clinical consequences for the mother and her fetus [24]. Along the course of pregnancy, spontaneous hypothyroidism is observed in approximately 2%-3% of the overall population of pregnant mothers, among which about 0.3% - 0.5% are diagnosed to have hypothyroidism and 2% - 2.5% to have subclinical hypothyroidism [25]. Iodine is a trace element that is essential for both the thyroid of the mother to act normally and the thyroid of the fetus to develop and act properly. Pregnant mothers should consume about 250-300mcg of iodine per day[26] , whereas both the conditions of excessive and deficient iodine are accompanied by higher risk of thyroid nodules development [27].

The hormonal milieu in pregnant women shows an association with the conditions where new thyroid nodules are developed and existing ones are further grown. As illustrated by ultrasound screening, such nodules are prevalent in about 3-21% of women during pregnancy [28]. A study of 221 pregnant women in china demonstrated increased frequency and size of these nodules in pregnant women. Repeated sonography revealed higher nodule size, in 15% of pregnant women with existing nodules, whereas newly developed ones were found in 13% of the study sample. After delivery, the percentage of mothers exerting nodules showed an elevation from 15% to 24% [29].

Postpartum thyroiditis (PPT) refers to a damaging autoimmune disorder that takes place at one year post-partum in mothers who did not show thyroid disorders before pregnancy. PPT can lead to

thyroid disease, both in its transient and permanent forms. It was proposed that this disease has the following three clinical manifestations: (1) transient hyperthyroidism (32% of cases), (2) transient hypothyroidism (43% of cases), and (3) transient hyperthyroidism followed by hypothyroidism and then recovery, also known as the classical type of PPT (25% of cases). PPT accompanies the appearance of autoantibodies directed against thyroid peroxidase (TPO). The risk to develop PPT in pregnant mothers with positive anti-TPO autoantibodies early in pregnancy was estimated to be between 30% and 52% [30, 31].

Critical periods in terms of physiological changes include pregnancy, during which mothers provide thyroid hormones and iodine to the fetus via the placenta, and lactation, during which this supplementation occurs via the milk. This higher demand on these biologically essential materials during pregnancy imposes the need to ensure their sufficient supply to mothers during pregnancy and breastfeeding [32]. However, it is unfortunate that reports of their insufficiency and deficiency in these female populations are frequent [33]. For example, it was demonstrated that diet of 2.5% of women in their pregnancy and breastfeeding periods has insufficient content of iodine [34].

1.1.2 Hypothyroidism prevalence in pregnant women

Hypothyroidism is considered as a common chronic condition in mothers during pregnancy, the time period during which thyroid hormones from the mother provide essential support for the fetal body to grow and brain to develop. It occurs in both forms of overt and subclinical [35]. Pregnant mothers diagnosed with overt hypothyroidism manifest a number of adverse complications, such as miscarriage, preeclampsia, preterm labor, and fetal death [36]. Nevertheless, it is not possible to readily recognize hypothyroidism due to the fact that its symptoms are not specific. Subclinical hypothyroidism does not occur frequently during pregnancy, being observed only in about 2–3% of cases. It has also adverse complications in pregnant mothers, such as gestational diabetes mellitus, preeclampsia, placental abruption, and preterm delivery. Mothers with earlier diagnosis of subclinical hypothyroidism show higher risk to develop conditions such as stillbirth and gestational diabetes mellitus if they become pregnant in the future [37].

The functions of thyroid hormones include the regulation of cardiovascular activities and blood pressure, while long-term thyroid hormone disorder leads to cardiovascular disorder [38]. In clinical terms, both the conditions of excessive and deficient thyroid hormone could lead to the induction or exacerbation of cardiovascular disorders, which might include atrial and ventricular arrhythmias, atherosclerotic vascular

disease, dyslipidemia, and heart failure[39]. Hence, thyroid hormone disorders might contribute to higher risk of premature morbidity and death [40].

1.1.3 Impacts of hypothyroidism of pregnant mother on the fetus

Deficient iodine levels in pregnant mothers, along with altered blood estrogen levels, are among the common causes of gestational hypothyroidism [41]. Hypothyroidism could result in adverse impacts during pregnancy (Fig.1). Since thyroid hormone plays an essential part for the fetus to develop normally, hypothyroidism is accompanied by adverse obstetric and child neurodevelopment complications. For these complications to be avoided, with the drug levothyroxine has to be used to treat women who exert hypothyroidism during pregnancy [42], a condition that can result in lower values of gestational age and birth weight [43]. The type of congenital anomalies with the highest frequency in newborns is represented by cardiovascular defects, which impose more extensive screening and monitoring during pregnancy, along with decreased birth weight and neonatal jaundice [44].

Preterm birth is a complication that is most frequently observed in pregnant women showing subclinical hypothyroidism in comparison with those with eu-thyroidism. Pregnant women with hypothyroidism are more frequently prone to premature delivery, a condition that can stop the neonates from being intellectually and psychomotorly develop in a proper way [45, 46]. Reduced thyroid functioning in the mother leads to infantile low value of intellectual quotients, as well as retarded development. When the thyroid hormone is lacking in pregnant women, the infantile brain develops in a slower rate, while the value of the intelligence quotient is lower[47, 48]. Thyroid dysfunction in mothers can result in a similar condition in the fetus, as well as alterations in the metabolism [49].

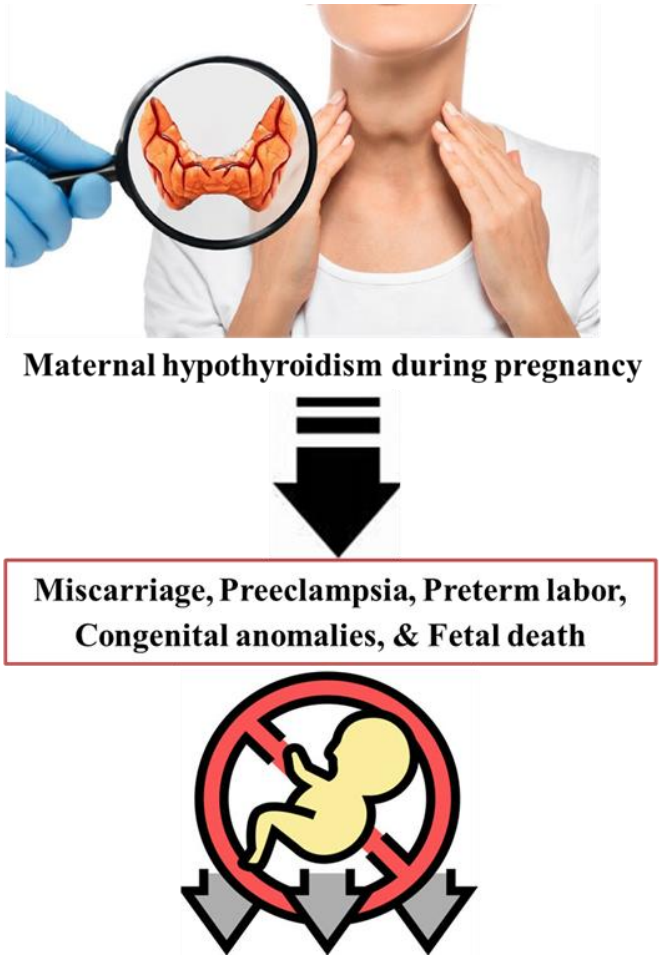

Fig1: The impact of gestational hypothyroidism on pregnancy outcome.

1.1.4 Special consideration for women with a history of Hashimoto's disease.

Hashimoto thyroiditis can be defined as an autoimmune disorder that leads to the destruction of the thyroid tissues through mechanisms that involve both cell-mediated and antibody-mediated immune responses. This type, also has the term of chronic autoimmune thyroiditis and chronic lymphocytic thyroiditis, is considered as the most frequent hypothyroidism form recorded in the developed countries[50]. The pathological events include the production of anti-thyroid autoantibodies that target the thyroid tissue, resulting in progressive fibrosis [51]. It is also associated with insufficient formation of thyroid hormone[52], whereas elevated thyroid-TSH were recorded as a result of low levels of freely available T4, confirming the occurrence of primary hypothyroidism [53].

There is little understanding to the etiology of Hashimoto disease. The majority of the patients exert the development of autoantibodies against various thyroid antigens, especially anti-TPO. A large fraction of patients also develop antithyroglobulin (anti-Tg) and TSH receptor-blocking antibodies (TBII), which attack the intact tissues of the gland, consequently resulting in insufficient formation of thyroid hormone

[54, 55]. Hashimoto disease is believed to develop as a result of autoimmune reactions, the most typical of which are lymphocyte infiltration and fibrosis. Nevertheless, information related to the pathogenetic roles of anti-TPO antibodies in autoimmune thyroid disease is seldom[56]. These antibodies are capable of complement fixation, along with ability of binding and killing the thyrocytes in vitro. Nevertheless, studies conducted on humans revealed that disease severity is not correlated to the serum levels of anti-TPO antibody, except for one study that reported a correlation with the active phase of the disease[57, 58].

Hypothyroidism with pregnancy is typically seen with Hashimoto's thyroiditis. Typically, affected mothers are presented with fatigue, cold intolerance, and weight gain. While the risk profile is similar to that seen in hyperthyroidism (increased likelihood of preterm birth, preeclampsia, placental accidents, stillbirth, and miscarriage), while adequate control with medication greatly diminishes the risk [58]. Currently, the risk of miscarriage is significant with poorly controlled hypothyroidism. Various studies estimate the risk of miscarriage to be three- to four-fold higher with uncontrolled Hashimoto's thyroiditis [59].

Conclusions

Since hypothyroidism significantly impacts the life quality pregnant women and their fetuses, it is highly recommended for healthcare professionals to closely monitor thyroid function during pregnancy, particularly in women with a history of thyroid disease, and to adjust drug doses as needed to maintain normal thyroid hormone levels. The control of thyroid disease in pregnant women requires careful consideration for both the mother and her fetus. Overt maternal hypothyroidism or subclinical maternal hypothyroidism, regardless of antibody status, requires treatment to avoid adverse clinical outcomes.

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