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Maternal Hyperthyroidism and Its Impact on Pregnancy Outcomes: A Review

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Abstract : Hyperthyroidism during pregnancy presents significant clinical challenges, as maternal thyroid hormones play a vital role in fetal growth and neurodevelopment. The most common causes include Graves' disease and gestational transient thyrotoxicosis, which require careful differentiation for appropriate management. Antithyroid drugs such as propylthiouracil and methimazole remain the mainstay of therapy, though their use demands caution due to potential teratogenic and hepatotoxic effects. Uncontrolled hyperthyroidism can result in severe maternal and fetal complications, including preeclampsia, preterm birth, and low birth weight. Preconception counseling, regular thyroid function monitoring, and a multidisciplinary approach are essential for optimal maternal and neonatal outcomes.

IndexTerms **- Hyperthyroidism, pregnancy, Graves Disease, fetal complications**

INTRODUCTION

Among women who are of reproductive age, thyroid diseases are somewhat prevalent. Women are between eight and ten times more likely than men to suffer hashimoto thyroidities or Graves disease, two autoimmune thyroid conditions that peak in early adulthood.(1) The health of both mothers and children depends on thyroid hormone. The fetus thyroid gland does not mature before 18–20 weeks of pregnancy, despite being present and functioning by 10–12 weeks. As a result, during a crucial developmental stage in the early stages of pregnancy, the baby depends on the thyroid hormone that the mother delivers through the transplacental route.(2)

When the thyroid gland produces excessive thyroid hormones, the clinical condition known as hyperthyroidism develops.(3) An elevated production and secretion of thyroid hormone by the thyroid gland results in hyperthyroidism, which is characterized by abnormally high thyroid hormone levels.The term "thyrotoxicosis," on the other hand, refers to "excess of thyroid hormone." This can be caused by hyperthyroidism, which is an increased synthesis of thyroid hormone in the thyroid gland, but it can also happen in patients who do not have hyperthyroidism, such as those who have thyroiditis, which is the leakage of thyroid hormone from the thyroid gland, or excessive thyroid hormone intake.(4)

MATERNAL ALTERATIONS

During pregnancy, the placenta produces a hormone called human chorionic gonadotropin (hCG), which has a mildly thyrotrophic effects and can encourage the growth and development of thyroid nodules.(5) Thyroid stimulating hormone (TSH) release from the pituitary gland is reduced by negative feedback during pregnancy as a result of the mildly thyrotrophic impact of hCG on the thyroid gland, which raises the production of thyroid hormone.(6) Serum TSH levels tend to decrease in early stages of pregnancy when hCG levels are high in comparison to non-pregnant adults. After the first trimester of pregnancy, serum levels of TSH usually rise somewhat, mostly as a result of a drop in hCG levels.(7)

Since serum TSH is the most sensitive indicator of primary thyroid dysfunction, it should be used as the first test to screen for thyroid disorders in pregnant women. Furthermore, overt and asymptomatic thyroid disease can be

differentiated using serum levels of free T4 in the body.[8] Even though low TSH levels can be caused by normal pregnancy physiology, overt maternal hyperthyroidism is a significant differential in the context of low TSH, especially in the early stages of pregnancy. Furthermore, recurrent hyperemesis gravidarum vomiting without the usual thyrotoxicosis symptoms is linked to gestational transitory thyrotoxicosis, which usually goes away by 18 to 19 weeks.[9]

CAUSES AND PATHOPHYSIOLOGY

Graves' disease (GD) is the most common cause of hyperthyroidism in persons under 50, whereas toxic nodular goiter is the most common cause of hyperthyroidism in patients over 50.[10] Of pregnant women, 0.2% have Graves' disease.[11] Given that GD primarily affects female patients during the reproductive period, the patient's reproductive background and the likelihood of present or future pregnancy should be taken into account when managing the condition.[3]

TSH-receptor autoantibodies (TRAb) are a major pathophysiological mechanism of Graves Disease, an autoimmune illness brought on by changes in the immune system.[12] Gestational transitory thyrotoxicosis (GTT) and Graves disease are the two most frequent causes of hyperthyroidism during pregnancy. It is estimated that the prevalence of GTT in pregnant women ranges from 2% to 11%, while the prevalence of new-onset Graves disease is 0.05%.[11] It's critical to distinguish between the two types of pregnancy-related hyperthyroidism since the duration of the condition and available treatments vary. High levels of hCG in the serum during the early stages of pregnancy mediate GTT as hyperemesis is also linked to elevated hCG levels.[13]

GTT is typically accompanied with nausea and/or vomiting symptoms. Laboratory tests will show high thyroid hormone levels and reduced serum TSH levels in both Graves disease and GTT. Because Graves disease causes preferential synthesis of T3, patients with the condition frequently have an elevated ratio of T3 to T4 (≥20:1). In contrast, women with GTT who experience hyperemesis frequently have lower serum levels of T3. Thyrotropin receptor (TRAb)-specific antibodies are typically seen in Graves disease but not in GTT.[11] TSH receptor binding immunoglobulin, a protein which assesses both stimulating and suppressing antibodies equally, can be used to evaluate TRAb. An alternative is to detect thyroid-stimulating immunoglobulin, which quantifies stimulating specifically.[14] Thyrotoxic symptoms, which may have existed before pregnancy, include palpitations, hand tremors, heat sensitivity, and inadvertent weight loss. These symptoms are commonly reported by women with Graves disease. Patients with GTT, on the other hand, rarely experience severe thyrotoxic symptoms and do not exhibit widespread goitre or Graves ophthalmopathy, which are hallmark symptoms of Graves disease. GTT is not linked to unfavorable pregnancy outcomes and resolves on its own when hCG levels drop after roughly 10 to 12 weeks of gestation. Thus, individuals with GTT do not need antithyroid medication therapy, but they can be managed by supportive therapies for nausea, vomiting, and any imbalance of electrolytes or volume depletion if they also have hyperemesis gravidarum.[15]

Pregnancy changes thyroid physiological processes and laboratory testing, antithyroid medications (ATDs) are linked to teratogenicity, and maternal, fetal, and neonatal complications are directly related to GH control and, in some cases, to serum levels of maternal thyroid-stimulating immunoglobulin (TSI). These factors make it difficult to establish the right diagnosis and manage GH during pregnancy.[3]If left undiagnosed and untreated, prenatal and neonatal hyperthyroidism, which affects 1% to 5% of women with active or previous GH, is linked to higher fetal/neonatal morbidity and mortality.[16]

TREATMENT OPTIONS

Thyroidectomy, which had a high rate of fetal loss, was the only treatment for pregnant women who were thyrotoxic prior to the development of thionamides. Between 1947 and 1953, thionamides were created primarily as a result of Dr. Edwin Bennet Astwood's groundbreaking research. Concerns over the use of radioactive iodine (RAI) during pregnancy were raised in 1949 when Chapman and Corner showed that the fetal thyroid concentrated RAI.[17] There haven't been many novel oral treatment options for GD since the discovery of thionamides. The American Academy of Pediatrics has approved methimazole and propylthiouracil (PTU) for use during lactation, despite the fact that both drugs are known to be teratogenic, especially during the first trimester.[18] Since their introduction into clinical practice in the 1940s, antithyroid medications (ATDs) have been the standard treatment for pregnant women with Graves Disease (GD) hyperthyroidism.[19]

Anti-thyroid drugs do not treat gestational transitory thyrotoxicosis. Grave's disease and gestational transitory thyrotoxicosis can be distinguished by a suppressed or undetectable TSH level (<0.01 mU/l), high free T4 and free T3 levels, positive TSH receptor antibodies (TRAB), clinical signs of autoimmunity, and a goitre.[9] Concerns about the diagnosis of pregnant transient thyrotoxicosis should be addressed by determining antibody status, particularly TSH receptor antibodies (TRAb). The goal of starting and titrating anti-thyroid drugs is to keep the free T4 within the upper limit within the non-pregnant reference range.[20] Propylthiouracyl (PTU) is the preferred treatment for patients with overt hyperthyroidism during the first trimester of pregnancy because carbimazole (CBZ) is linked to congenital abnormalities such as oesophageal and choanal atresia, aplasia cutis congenital, and minor facial deformities.[21] Patients on PTU must have their liver function tests monitored every three to four weeks because of the potential for hepatotoxic side effects, which can be made worse by "disease"–drug (pregnancy–drug) interactions. Given the uncommon but serious liver toxicity side effects linked to PTU, CBZ is advised starting in the second trimester. After two weeks and then every two to four weeks after converting 100 mg of PTU to 10 mg of CBZ, patients transferring from PTU to CBZ should have their TFT evaluated.[22] Treatment with radioactive iodine is not advised during pregnancy or within six months of conception. Maternal Graves' illness may necessitate a subtotal thyroidectomy in the second trimester of pregnancy.[23]

COMPLICATIONS

In addition to GTT, untreated overt hyperthyroidism during pregnancy is linked to low birthweight, intrauterine growth retardation, preterm labor, thyroid storm, pregnancy loss, congestive heart failure, preterm labor, preterm labor, and fetal and/or neonatal hyperthyroidism.[24] Growth restriction, hydrops, the presence of fetal goitre, tachycardia, or fetal cardiac failure are all signs of fetal thyroid dysfunction. In the first trimester, PTU treatment is necessary with regular clinical, laboratory, and ultrasound monitoring if fetal hyperthyroidism is identified and deemed a gestational risk.[25] Prematurity, low birth weight, intrauterine growth restriction, thyroid storm, stillbirth, pregnancy loss, pregnancy-induced hypertension, and maternal congestive heart failure are all linked to inadequate management of thyrotoxicosis.[6]

Compared to women without GH, those with uncontrolled GH had a 9.2 times higher chance of giving birth to low-birth-weight babies. They are, however, 2.3 times more likely if the condition is managed throughout pregnancy. Compared to women whose GH was under control, mothers with uncontrolled GH are also 4.7 times more likely to experience severe preeclampsia and 16.5 times more likely to give birth before their due date.[27] During the early stages of brain development, thyroid hormones control a variety of processes, such as myelination, synaptogenesis, differentiation, migration, and proliferation of neurons.[28] They contribute to the formation of brain structures as well as the control of the neurochemical environment. It makes sense that a thyroid hormone deficiency could interfere with these functions, but it is unclear how hyperthyroidism, which is characterized by an overabundance of thyroid hormones, might impact fetal development.[29] Although the crucial role thyroid hormones play in brain development is a significant worry, a disruption in the mother's thyroid function during pregnancy may have effects that go beyond the development of the fetus's brain. Thyroid hormones control several organ functions and are developmental variables. One may conjecture about further fetal development outcomes unrelated to the brain in light of the theory that maternal hyperthyroidism causes fetal programming.[30]

PRECAUTIONS

Preconception counseling should be provided to all women of reproductive age who have GH or a history of GH. In addition to discussing the advantages and disadvantages of each treatment option (pharmacological therapy, 131-I radioactive iodine ablation (RAIA), and surgery), counseling should take into account the woman's preferred time frame for becoming pregnant. It is recommended that women with GH delay getting pregnant and utilize contraception until their GH is under control. Before getting pregnant, women who have trouble controlling their GH while taking large doses of ATD should think about definitive therapy (RAIA or surgery). Pregnancy testing should be performed prior to conception in women contemplating RAIA, and the procedure should be postponed for six months until the woman is euthyroid after starting levothyroxine replacement treatment. After RAIA therapy, TSH Receptor Antibodies (TRAb), which are detectable in 95% of GH patients, may rise and remain high for months to years. Delivering a healthy, euthyroid baby to a healthy mother is the aim of care for women with GH. For the doctor, making the diagnosis of GH can be difficult. The most prevalent cause of pregnancy-related hyperthyroidism, GTT, can be distinguished from GH with the aid of a physical examination, medical history, and occasionally TRAb levels.

The key to lowering the risk of problems for the mother, fetus, and infant is maintaining euthyroidism during pregnancy. ATDs continue to be the mainstay of GH treatment throughout pregnancy. In the first trimester, PTU is recommended. In women with marginally raised TRAb levels and mildly regulated GH on modest doses of ATD, ATD may be discontinued during the final 4–8 weeks of pregnancy. To manage GH symptoms, a short course of β-adrenergic blockers may be employed. Women who are unable to take ATD, who are uncontrolled on high doses of ATD, or who have large goiters may need surgery in the second trimester. When TRAb levels are consistently higher than the 3× upper limit of normal, it is indicative of prenatal thyroid malfunction and necessitates careful monitoring of the fetus and newborn.

Women are susceptible to GH symptom recurrence during the postpartum phase, thus thyroid function testing ought to be assessed six weeks in. For these complicated patients to be successfully managed, a multidisciplinary strategy comprising cooperation between the endocrinologist, maternal-fetal specialist, obstetrician, neonatologist, pediatric endocrinologist, and anesthesiologist is crucial. An effective pregnancy starts with preconception counseling.[31]

DISCUSSION

Pregnancy-related persistently high TRAb levels are predictive of fetal thyroid dysfunction.[32] As a result, women who had extremely high levels of TRAb before becoming pregnant could be better candidates for thyroidectomy. Within months to a year following surgery, TRAb levels drop and return to normal.[33]

Methimazole (MMI) is generally preferred over propylthiouracil (PTU) in women who continue ATD treatment because MMI is administered once daily and PTU has been linked to hepatotoxicity; however, PTU is advised for the first trimester of pregnancy because its teratogenic effects are thought to be less severe than those of MMI, and switching from MMI to PTU in preparation for conception should be taken into consideration.As an alternative, after becoming pregnant, women might convert to PTU. Patients on ATDs should be advised to closely monitor their menstrual cycles and take contraception. In the event of a missing menstruation, a pregnancy test should be performed very away. Weeks 6–10 are when there is the highest risk of birth abnormalities due to ATDs.[34]

Declaration of interest

The authors confirm that there is no conflict of interest associated with this publication, and no financial or personal relationships could have inappropriately influenced the content of this work.

CONCLUSION

To summarize, the treatment of thyroid disease during pregnancy necessitates careful consideration for both mother and child. Pregnancy-specific reference ranges should be used to assess thyroid function in pregnant women because of physiological changes during pregnancy, and because normal thyroid function is important for the health of both mother and child, decisions about how to treat thyroid dysfunction during pregnancy should take both maternal and fetal outcomes into account. Pregnancy-related specific considerations may also be necessary for the diagnosis and treatment of thyroid nodules or thyroid cancer. During the first few months after giving birth, thyroid dysfunction is also common.

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