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Farah Kausar

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Hyperthyroidism and Its Implications for Diagnosis and Management of Complications During Pregnancy

Farah Kausar

Department of Zoology, University of the Punjab, Lahore, Pakistan

*Corresponding author: farahqasam8@gmail.com

Abstract

Thyroid dysfunction alters the physiological events of pregnancy that may have serious outcomes if left untreated. Hyperthyroidism (a thyroid disease) is related to complications during pregnancy. A challenging task for the physician is to correctly diagnose and properly manage hyperthyroidism in pregnant women. Hyperthyroidism is an autoimmune disease caused by excessive production of thyroxin hormone. The objective of this paper is to review the research in detection and management of Graves' disease (thyrotoxicosis) during and after pregnancy. This paper discusses thyroid receptor antibodies, etiology of Grave's disease (thyrotoxicosis), pregnancy related complications, infants' thyrotoxicosis management, as well as post-partum management, guidelines and counseling offered to pregnant women. Literature search was conducted using the keyword 'hyperthyroidism' in conjunction with pregnancy, anti-thyroid drugs and birth defects in Pubmed, Google Scholar and Medline. Maintaining thyroid gland may reduce the complications of pregnancy. At the beginning of pregnancy, low doses of anti-thyroid drugs are usually recommended to women by endocrinologists. However, the use of these drugs is completely stopped after 4 – 8 weeks of gestation. Propylthiouracil is the preferred anti-thyroid drug used in the first trimester in case of preconception to decrease the risk of teratogenicity. Carbimazole may be used in the first three months. Early diagnosis and maintaining normal hormone concentration by reducing the level of thyroid receptor antibodies as well as anti-thyroid drugs is essential in order to prevent maternal and fetal complications. Counseling and guidelines provided by endocrinologists constitute the key to a healthy and successful pregnancy.

Keywords: anti-thyroid drugs, Grave's disease, neonate hyperthyroidism, post-partum management, thyroid receptor antibodies

1. Introduction

Thyroid diseases are the subject of endocrinopathy and constitute the second major class of endocrine disorders after *diabetes mellitus* [1]. Thyroid disorders have been associated with complications in pregnant women and they also complicate the neurophysiological development of newborn babies [2]. Maternal thyroid disorders can affect both the mother and the fetus during pregnancy and

postpartum. Treatment is necessary to ensure good prenatal care, otherwise it may cause miscarriage, growth impairment and hypertension disorder [3, 4].

Graves' disease causes hyperthyroidism [5]. This is a pathological disorder responsible for the excessive production and secretions of thyroid hormone from the thyroid gland. It is identified through normal or high uptake of radioactive iodine by thyroid gland [6]. Generally,

thyrotoxicosis without hyperthyroidism is an excessive production of thyroid hormone due to its increased biosynthesis in the thyroid gland. The excess thyroid hormone originates from the thyroid gland as a result of the lesion [7].

Hyperthyroidism can be overt or subclinical. Overt hyperthyroidism is characterized by reduced concentrations of thyroid-stimulating hormone (TSH) and increased concentrations of thyroid hormones including thyroxin (T4), triiodothyronin (T3), or both. However, low serum level of TSH but normal serum level of both T3 and T4 are characterizations of subclinical hyperthyroidism. A diffused toxic goiter (Graves' disease), toxic multi-nodular goiter (Plummer's disease), and toxic adenoma are considered the most obvious forms of hyperthyroidism [8].

Graves' hyperthyroidism (GH) occurs due to the excessive production of thyroxin hormone. Generally, 0.2% of pregnant women are affected by this thyroiditis [9]. GH has an adverse effect on pregnant women because of the use of anti-thyroid drugs in pregnancy, which can lead to teratogenicity, maternal, fetal and neonate malformation [10]. It is essential that guidelines and counselling are provided to women of reproductive age with GH [11].

The key term 'hyperthyroidism' was used in conjunction with pregnancy, anti-thyroid drugs and birth defects to search the literature published during the years 1997-2019 in Medline, Google Scholar and Pubmed.

2. Etiology of Hyperthyroidism

The etiology of hyperthyroidism is extensive. Most common forms of hyperthyroidism /are diffused toxic

goiter (Graves' disease), toxic multinodular goiter (Plummer's disease), and toxic adenoma. Gestational transient thyrotoxicosis (GTT) is a condition of mild hyperthyroidism that does not cause adverse pregnancy complications and generally is not treated with anti-thyroid drugs [12].

About 5% of pregnant women are affected by GTT early in their pregnancy [13]. Common signs of GTT include palpitation, heat intolerance and depression. Hyperemesis gravidarum is a severe form of GTT characterized by nausea, vomiting and weight loss. GTT is correlated with human chorionic gonadotropin (hCG) levels that increase in the 7th week of pregnancy [14].

Women with twin pregnancies have increased hCG levels for a prolonged period of time which leads to increased production of T4 levels and suppression of TSH stimulating hormone. [15]. GTT is also identified by a reduced level of TSH with an elevated level of FT4. Thyroid receptor antibodies (TRAbs) are absent and the level of TSH is suppressed for several weeks. Beta-blocker anti-thyroid drug may mitigate the thyroiditis problem during pregnancy [16]. In pregnancy, propranolol is preferable for GTT patients as compared to atenolol. To some extent, atenolol decreases the newborn's birth weight [17, 18]

3. TSH Receptor Antibodies (TRAbs)

TRAbs are antibodies that bind to thyroid stimulating hormone receptors. They are widely used in the diagnosis and management of pregnancy. They cross the placenta, enter into the fetus and may induce fetal hyperthyroidism. Their excessive production has the potential to induce fetal and neonatal hyperthyroidism [19].

TRAb assay has two categories:

- 1) TSH binding inhibiting I_g / thyrotropin binding inhibitory immunoglobulin assay (TBII) detects TRAbs (stimulating, blocking, and neutral) in patient's serum. Antibodies completely bind with TSHR and act as competitors.
- 2) TSI is a bioassay that detects cAMP generation in thyroid cells and measures TRAbs in patient's serum [20].

The development of advanced bioassays may help to analyze the stimulators or inhibitors of TRAbs [21]. Basically, TBII has 97% sensitivity and 99% specificity for GH. However, due to an excessive level of thyroid receptor antibodies, TBII does not sense stimulatory or inhibitory antibodies in a thyroiditis patient [22].

It has been reported that thyroid peroxidase is very helpful in the production of thyroid hormone and it is a major autoantigen in autoimmune thyroid disorders [23]. Thyroid peroxidase is a heme-containing, membrane bounded glycoprotein enzyme located at the apical surface of thyrocyte and constitutes a major auto-antigen [24]. The level of anti-thyroid antibodies can be seen in all forms of autoimmune thyroid disease including Hashimoto's thyroiditis, Graves' disease and post-partum thyroiditis disease. However, thyroid peroxidase antibody (TPO-Ab) positively increases the risk of abortion as well as premature delivery. Moreover, TPO-Ab is a non-specific marker of thyroiditis that has no predictive value for infants [22].

4. Pregnancy Related Complications

GH is associated with miscarriage, hypertension, premature delivery, uterine growth impairment, weight loss,

uncontrolled thyroid storm and in an extreme condition, heart failure occurs due to it [25]. Specifically, hyperthyroid women have infants that are nine times more associated with low birth weight as compared to healthy pregnant women. Uncontrolled GH poses 16.5 times more risk of premature delivery and it is 4.7 times more associated with the development of preeclampsia in pregnant women [26].

About 3-5% of women with GH experience both mild and severe side effects of anti- thyroid drugs. A clinical study showed that the most common side effect was an allergic reaction and severe side effects included granulocytosis and liver failure that occurred very rarely [27]. Andersen and others [28] reported the effects of anti-thyroid drugs propylthiouracil (PTU) and methimazole, (MMI) which are highly effective, cross the placenta barrier and induce fetal defects. For women who take a daily dose of anti-thyroid drugs (ATDs), MMI is generally preferred to PTU because the latter is associated with hepatotoxicity. However, PTU has traditionally been preferred over MMI in the first trimester in order to compensate for birth defects [29]. A meta-analysis study showed an increased risk of birth defects due to methimazole as compared to propylthiouracil [30]. The harmful effect of ATDs is maximum in the last month of the first trimester during pregnancy [31]. Besides birth defect, no other differences between PTU and MMI have been reported. [32].

Thyroid storm (TS) is the condition in which GH becomes uncontrollable. It was found that TS occurs in those patients who face additional stress and TS stimulating events (such as pregnancy infection, preeclampsia, labor pain, surgery). Patients with TS

experience tachycardia, thermic imbalance, mental retardation and heart failure [33]. Biochemical analysis demonstrated that TS patients have a reduced level of TSH and an elevated level of T4. In critical condition, patients should be admitted to ICU where proper medication and intubation may help them to stabilize.

5. Fetal Thyroid Function

In the fetus, thyroid gland starts to develop in the second month of the first trimester and releases thyroxin hormone in the third month of pregnancy [34, 35]. TH production is limited in the initial 18-20 weeks of the gestation period [36]. Fetal TSH levels rise in the 28th week of gestation and continuously increase by the end days of pregnancy. Before the induced fetal TH, the fetus depends on mother's TH transmitted through the placenta [37]. After birth, newborns have an increased level of thyroid secretions that gradually decreases to the optimum level in 3-5 days [38, 39].

Hyperthyroidism in the fetus can be monitored by maternal serum thyroid receptor antibodies titer. Antibodies cross the placenta and block fetal thyroid hormone production. They may also cause hyperthyroidism with 100% sensitivity and 43% specificity [10, 40]. The probability of neonatal hyperthyroidism is high in babies of those mothers who take anti-thyroid drugs and have an increased concentration of thyroid receptor antibodies, even during the last days of pregnancy [41].

6. Neonates' Thyrotoxicosis Management

Common symptoms of neonatal thyroiditis include heart related diseases and accelerated bone maturation at an advanced age [42]. It was reported that

the level of antibodies remains the same in blood for four months. Resultantly, infants become symptomatic for postnatal hyperthyroidism. Parents should weekly visit the clinic and laboratory until their neonate thyroid receptor antibodies test is negative [43]. The main aim of neonatology team is to educate women under treatment about thyroid disorder and its consequences [44]. However, consultation with pediatric endocrinologists may help to reduce the effects of anti-thyroid drugs and to maintain the level of thyroid receptor antibodies in the circulatory system [10].

7. Post-partum Management

Postpartum thyroiditis is an autoimmune thyroid disease in which women regain hyperthyroid after delivery. ATDs should be dripped at the time of birth as well as during breast feeding. If properly not cared for, then chances for developing hyperthyroidism increase within 4-12 months after delivery [44]. For breast feeding mothers, the recommended dose of methimazole is 20 mg and propylthiouracil is 300 mg daily. [46]. TSH and free thyroxine (FT4 levels should be monitored routinely in the first 12 months after birth. In case of an unclear diagnosis, an uptake of radioactive iodine (¹²³I radio) helps to distinguish thyroiditis [47]. After scanning for thyroid, mothers should discard feeding up to 2-4 days [10].

8. Diagnosis and Treatment

The earliest sonographic sign is the appearance of solid neck mass that leads to fetal goiter [48]. Common symptoms observed in the fetus are high blood pressure, fetal goiter, advanced bone maturation, heart attack and death [44]. Fetal goiter produces different complications including reduced

swallowing ability and fetal airway blockage [49].

It was reported that hyperthyroid women taking anti-thyroid drugs during pregnancy can develop fetal hyperthyroidism [42]. It was also observed during experimental studies that the injection of intra-amniotic levothyroxine into pregnant women sufficiently reduced the level of anti-thyroid drugs and resolved the fetal goiter [50].

There are many methods involved in the diagnosis of fetal hyperthyroidism. Cordocentesis involves the intervention of a needle into fetal blood stream via cord site. Through this method, the level of thyroid hormone can be measured in the amniotic fluid sac [32, 36]. Repeated cordocentesis might help to change the size of fetal goiter and the level of polyhydramnios [48, 51]. Alexander and his colleagues [10] reported that the risk of fetal complications by these identification methods is very low, hardly 1% if performed at well-experienced clinics. A minimum use of ATDs during pregnancy might help to restore normal fetal thyroid function [37].

9. Counseling

Preconception counseling of women should address the benefits and risks of all treatment options. Hyperthyroid women should be advised to defer pregnancy and use contraception until the thyroid gland regains its normal function. Women with difficult to control GH should take therapy treatment (RAIA or surgery) prior to conceiving [11].

It was reported that about 95% of patients showed a reduced quantity of TSH Receptor Antibodies (TRAb) after

taking ¹³¹I radioactive iodine ablation therapy (RAIA). An elevated level of TRAbs increases the chances of fetal thyroiditis. If their level continuously increases then thyroidectomy is the best option to normalize thyroxin secretions. Thyroidectomy is an operation that involves the surgical removal of all or part of the thyroid gland. TRAbs' level returns to normal within months after surgical excision [52, 53, 54].

10. Conclusion

The aim of this review was to understand Graves' disease of hyperthyroidism, its consequences, and adverse outcomes before and after pregnancy and ultimately, its control and management. The most challenging task for physicians is the diagnosis of Graves' diseases in pregnant women. According to the literature, it is possible to distinguish Graves' diseases from mild thyrotoxicosis through the measurement of thyroid receptor antibodies titer in pregnant women. Maintaining thyroid gland may reduce the complications of pregnancy. At the beginning of pregnancy, low doses of anti-thyroid drugs are usually recommended to women by endocrinologists. However, these drugs are completely stopped after 4 – 8 weeks of gestation. Propylthiouracil is the preferred anti-thyroid drug in case of preconception. It is used in the first trimester to decrease the risk of teratogenicity. Carbimazole may be used in the first three months. In case of severity, if the condition becomes uncontrollable, then a partial or full surgical excision of thyroid gland is needed. Patients should use an iodine rich diet on a daily basis. Many foods and fruits contain iodine such as prunes, strawberries, dry fruits, shrimps, cod as well as dairy products including cow-milk, yogurt and butter. Moreover, a

multidisciplinary approach is essential while collaborating with the gynecologist and pediatric endocrinologist for control and management of Grave's disease among pregnant women.

11. Abbreviations

ATDs= Anti-thyroid drugs; cAMP= cyclic adenosine monophosphate; FT4 = Free thyroxine; TSI= Thyroid-stimulating Ig; TRAbs = Thyroid receptor antibodies; GH= Grave hyperthyroidism; GTT= Gestational thyrotoxicosis; PTU= Propylthiouracil; MMI= Methimazole; T3= Triiodothyronine; TBI= TSH- binding inhibiting I_g; TBII= thyrotropin binding inhibitory immunoglobulin; TH= thyroid hormone; TS = thyroid storm; TRAbs = Thyroid receptor antibodies; TRP-Ab= thyroid peroxidase antibody; TSH= Thyroid stimulating hormone

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