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Systematic Review

Graves' Disease in Pregnancy: A Systematic Review

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Abstract

Introduction: Graves' disease is an autoimmune disease that is associated with thyroid gland involvement and is most common in young women. During pregnancy, it is the main cause of hyperthyroidism, as the thyroid gland volume and thyroid hormone synthesis increase. Changes in the immune system during pregnancy can affect the onset of disease. During pregnancy, the pathological cause of Graves' disease is immune deficiency. This study investigated changes in the thyroid gland occurring during pregnancy, the causes of Graves' disease during pregnancy, and its diagnosis and treatment.

Methods: A search of Google scholar, Ovid, and MEDLINE was conducted with the search terms Graves' disease, pregnancy, and treatment.

Results: A total of 65 titles were initially identified with the search strategy described. Twenty-five publications were excluded. Out of the remaining articles, 19 articles were used in terms of content. Treatment for Graves' disease is determined according to the patient's condition, the priority of the patient, and the resources available. Treatments include oral anti-thyroid drugs (ATDs), radioactive iodine, and surgical procedures. Among the oral prophylactic drugs, Propylthiouracil is used during lactation. Radioactive iodine is not used during pregnancy or lactation. Thyroidectomy is better to be used in the third trimester of pregnancy.

Conclusion: The treatment of Graves' disease is very important; if not treated, this disease causes many complications with the fetus. After delivery, the mother and the baby should be monitored for thyroid problems. Pre- and postpartum planning and the effective management of Graves' disease in women of childbearing age are necessary to prevent the pathogenesis of Graves' disease during pregnancy.

Keywords: Graves' Disease, Pregnancy, Therapeutics

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Introduction

Graves' disease is an autoimmune disease involving the thyroid gland. It is specifically detected by the presence of autoantibodies in the blood that are attached to and stimulate thyroid hormone receptors.[1] The highest incidence of Graves' disease is seen in people within the age range of 30 to 50 years, but it can occur at any age. The risk of incidence is 3% in women and 0.5% in men.[2] Women are more likely to be at risk for autoimmune thyroid disease than men. The prevalence of Graves' disease is associated with age, and it has a high incidence among smokers.[3] Orgiazzi reported the incidence of hyperthyroidism as 65 per 100 000 women annually.[4]

Although the main cause of Graves' disease has still not been identified, it is believed that this disease is caused by a complex interaction between genetic and environmental factors.[1] Demographic studies have shown that different members of a family are at risk for Graves' disease. Family risk factors are especially high among twins, individuals with an infected brother or sister, and individuals whose parents or siblings were infected at younger ages. This indicates the genetic basis of this disease. Other investigations have shown that environmental factors also have an effect on the spouses of an individual afflicted with Graves' disease, which indicates that environment as well as genetics influence the incidence of disease.[5]

Hyperthyroidism in women at childbearing age is mainly caused by Graves' disease. Changes in the immune system during pregnancy can affect the onset of disease. In a study conducted by Mestman, the cause of hyperthyroidism in a large number of pregnant women was found to be Graves' disease.[6]

Women with Graves' disease appear to be older during pregnancy, and most of them are smokers. The incidence of hyperthyroidism varies considerably during pregnancy. It is very high in the first trimester and very low in the last trimester of pregnancy; the highest incidence is 9 months after childbirth.[4]

The thyroid gland is enlarged and the production of

hormones is increased during normal pregnancy. Thus, the expression of thyroid function during pregnancy needs to be adjusted. Important physiological changes occur during pregnancy. At this time, the mother's thyroid hormones (THs) play an important role in the development and function of the placenta and the fetus. The thyroid gland usually increases in size during pregnancy, and the synthesis of TH is increased to about 50% higher than previous amounts. These changes are in response to numerous factors.[7] During pregnancy, the normal thyroid-stimulating hormone (TSH) level is slightly lower due to the high level of the Human chorionic gonadotropin (hCG) hormone which reacts mutually with the receptor TSH.

There is a significant increase in the production of hCG in the placenta. Both hormones hCG and TSH consist of alpha and beta subsets, and the alpha subset is the same for both hormones. This biochemical similarity will lead to some mutual interactions of hCG bonding to TSH receptors. The activity of TSH, like the hormone hCG, leads to a slight increase in free T4 and reduces serum TSH levels in pregnant women. Moreover, increasing estrogen production during pregnancy significantly increases TBG and subsequently increases the level of Total T4. This phenomenon should be considered by monitoring the replacement of the thyroid hormone during pregnancy and/or making a diagnosis of hyperthyroidism.[8]

Adequate THs are very important for a successful pregnancy.[9] Hyperthyroidism is diagnosed based on clinical features and biochemical abnormalities.[2] Thyroid tests during pregnancy should be done in symptomatic women and in individuals with a history of thyroid disease.[10]

Measuring TSH is generally the best test for diagnosing and monitoring treatment in patients with thyroid disease. Although there are some diseases and situations in which the level of TSH cannot be used as a guide for diagnosis,[8] some complications make it difficult to diagnose thyroid disorders during pregnancy, including the effects of abnormal conditions such as gestational trophoblastic disease and vomiting during pregnancy which can affect thyroid function test results. Although nausea is common in early pregnancy, the incidence of severe vomiting with weight loss during pregnancy may indicate hyperthyroidism. Thyroid tests can be useful in these situations. Otherwise, routine tests are not recommended in patients with gestational vomiting.[10]

Methods

In this study, texts were reviewed, and internet searches and library studies were conducted during the time period 2007 to 2016. Databases such as Science Direct, Google Scholar, Ovid, and MEDLINE, which index the vast majority of published journals and studies, were searched using the keywords Graves' disease, pregnancy, and therapeutics. Inclusion criteria was English language articles and quantitative studies. The search uncovered 65 articles, 25 of which were excluded based on the exclusion criteria, and 19 of which were used for content.

Results

Pregnancy affects the thyroid gland by changing the size and amount of secretion hormones. Graves' disease is complicated during pregnancy. The goal of treatment during pregnancy is to normalize the level of thyroid hormones and prevent the injury to the fetus (Table 1).

Discussion

Thyroid-stimulating immunoglobulins prompt the excessive production of THs by stimulating the thyrotropin receptor. Therefore, the role of normal regulation of thyrotropin is eliminated. Moreover, the secretion of immune cells such as B cells, T cells, and antigen-presenting cells causes the interleukin production of B1, 6, 12, interferon Y, alpha tumor necrosis factor, ligand CD40, and other cytokines.

These cytokines, in turn, stimulate and strengthen inflammation and change the behavior of thyroid epithelial cells. Anti-thyroid drugs (ATDs) can weaken the production of THs and the emergence of thyroid cytokines, thus adjusting the safety process.[2]

The pathogenic cause of Graves' disease during pregnancy is an immune disorder of the receptor TSH, and hyperthyroidism is caused by the antibodies that bind to these receptors and activate them. Of these patients, 90% show manifestations of Grave's disease.[9]

The symptoms of Graves' disease include weight loss, rapid heartbeat, shortness of breath, tremor, hyperkinesia and increased reflexes, muscle weakness and fatigue, heat intolerance, increased sweating, irritability, increased frequency of bowel movements, anxiety, insomnia, anger, increased activity, itching, increased appetite, thirst, polyuria, changes in the menstrual cycle in women, decreased libido, hair loss, and heart failure.[2,11]

The clinical features of hyperthyroidism can easily be confused with the symptoms of pregnancy. Some of these symptoms include anger, heat intolerance, rapid heartbeat, enlarged thyroid gland or goiter, and weight loss.[10]

The presence of anti-thyroid antibodies, ATD, and mother's thyroid function determine the factor of changes in the thyroid functions of the embryo and neonate. Although a small number of infants of mothers with Graves' disease have thyroid dysfunction, the mother's hyperthyroidism refers to the risk of a wide range of thyroid abnormalities in infants.[12] Pregnant women with hyperthyroidism face a significant risk of low fetal growth, low birth weight, and premature births.[13]

Thyroid diseases that can affect the newborn infants of mothers with Graves' disease include (1) hyperthyroidism in the infants caused by the passage of stimulant antibodies from the placenta; (2) initial hypothyroidism; (*a*) transient hypothyroidism passed through anti-thyroid medications prescribed to the mother from the placenta or the passage of blocking antibodies from the placenta; (*b*) permanent hypothyroidism caused by thyroid disorders; and (3) hypothyroidism of hypothalamic pituitary caused by the increasing passage from the placenta of THs to the fetus which interferes with the development of the thyroid and changes the pituitary feedback that regulates thyrotropin secretion.[12]

Table 1. Graves' Disease in Pregnancy

Author	Year	Country	Journal Name	Results
Elston et al[15]	2014	New Zealand	Aust N Z J Obstet Gynaecol	This retrospective study examined 29 women who were treated for hyper-thyroidism with surgery and radioactive iodine before pregnancy and had at least one pregnancy. From the total 49 pregnancies, 22 were in women who had surgery, and 29 were treated with radioactive iodine. A large number of women in both groups had hypothyroidism during pregnancy. The difference was that more individuals who underwent surgery had been euthyroid during pregnancy.
Papendieck et al[12]	2009	Brazil	J Pediatr Endocrinol Metab	In this retrospective study, 28 infants were selected. The infants who were born of mothers with untreated hypothyroidism were all clinically diagnosed with hyperthyroidism and had low weight, tachycardia, irritability, goiter, and exophthalmia. In contrast, the infants who were born of mothers being treated with ATDs were all asymptomatic, and most of them had transient hypothyroidism, which is caused by the passage of antithyroid drugs prescribed to the mother through the placenta.
Rotondi et al[18]	2008	Italy	J Clin Endocrinol Metab	In this retrospective study, 150 women with Graves' disease were selected and divided into groups of pregnant and non-pregnant women. A significant increase in the recurrence of hyperthyroidism after discontinuation of antithyroid drugs in pregnant patients compared with those who were not pregnant was observed. None of these patients had a recurrence of hyperthyroidism in the first trimester of pregnancy. In contrast, 95% of them became infected after childbirth.
Levy-Shraga et al[19]	2014	Israel	Thyroid	In this retrospective study, 96 infants of mothers with Graves' disease were selected, of whom 4% had overt hyperthyroidism FT4 levels higher than normal between the fifth and twelfth days. All FT4 measurements returned to normal levels from the fourteenth day onwards, but TSH levels remained low until the third month.

In treating hyperthyroidism during pregnancy, it should be noted that both the mother and the fetus are being treated. Treatment should be done based on the balance in one without communication to the other.[14]

The treatment for Graves' disease is determined based on socio-clinical factors, patient priority, and the available resources.[15] In the treatment of Graves' disease during pregnancy, the complex mutual effects of biochemical, immunological, and pharmaceutical factors on the mother and infant should be taken into consideration. Planning before and during childbirth and the effective management of Graves' disease in women at the age of fertility are necessary to prevent pathogenicity caused by Graves' disease during pregnancy. Recent treatments have been limited to controlling the secretion of hormones, and more effective reductive treatments resulted in different immunological and biochemical conditions.[16]

The treatment of Graves' disease according to the guidelines of the Endocrine Association of America includes the following methods: iodine therapy and treatment with anti-thyroid and thyroidectomy drugs.[17]

Oral medications for the treatment of hyperthyroidism:

- Beta blockers: Beta blockers competitively block beta-adrenergic receptors. Propranolol can inhibit the conversion of thyroxine to tryidotroline. Specific beta blockers of the heart should be used in patients with chronic obstructive pulmonary disease (COPD). Calcium blockers can be replaced with beta blockers in these patients.
- ATDs: These include methimazole, carbimazole, and Propylthiouracil (thioamide drugs). These drugs inhibit the thyroid peroxidase enzyme and reduce the synthesis of THs. Propylthiouracil can convert thyroxine to tryidiothrinine.[2] Propylthiouracil is used more in America due to the possibility of teratogenic effects with methimazole. Emerging evidence suggests that the use of propylthiouracil in early pregnancy causes embryonic anomalies often in the urinary tract and neck and facial lesions. Okosieme et al. have stated that carbimazole and methimazole are associated with low risk of embryonic anomalies including esophageal atresia and omphalocele.[16]
- Recent prospective studies have shown the effects of the combination of levothyroxine and antithyroid drugs used in treatment during pregnancy; this combination is currently the only standard for treatment with ATDs. Graves' disease should be treated with ATDs (propylthiouracil, if available). At the lowest possible dose, the serum levels of FT4 in pregnant mothers is normal or slightly higher than that of non-pregnant individuals, or the serum level of Total FT4 should be 1.5 times the normal level in non-pregnant individuals.

The serum level of total FT4 or FT4 in pregnant mothers should both be measured for up to four weeks for the titration of ATDs.[14]

Frequent recurrence is one of the disadvantages of ATDs, and several tests are needed to achieve treatment. In less than 5% of patients, mild side effects including rash, hives, arthralgia, fever, nausea, and smell and taste disorders have been observed. The most significant side effect in patients is agranulocytosis, which usually appears in the first trimester of pregnancy.[2] Transient leukopenia occurs in approximately 10% of pregnant women treated with thiamide, but usually does not require that treatment be stopped. Agranulocytosis is not dose-dependent in almost 0.2% of women, and the outpatient counting of leukocytes during treatment is not useful in preventing it, because the incidence is severe. For this reason, if patients treated with thiamide drugs see signs of fever or sore throat, the drug should be immediately stopped and discontinued until a thorough investigation of the agranulocytosis can be performed.[10] Further research is needed to understand the extent and severity of the risks of

ATDs on the health of the fetus.[16]

Radioactive Iodine

Hyperthyroidism is usually treated with ATDs, but the use of radioactive iodine or surgery is recommended in patients who have had a recurrence after consuming a series of ATDs.[1] Radioactive iodine damages thyroid cells, causes their death, and can reduce the size of a goiter. This drug should not be used in patients with active thyroid ophthalmopathy, in pregnant women, or in lactating women up to six weeks after breastfeeding.

Thyroidectomy

In surgery, either a large part or all of the thyroid tissue is removed, and rapid euthyroidism is one of the benefits of this method. Thyroidectomy should be performed during the second trimester of pregnancy. The complications of this method include surgical complications.[2] This method has had the highest improvement rate over other treatments, and that rate of disease recurrence in patients with Graves' disease is negligible.[17]

Surgery is not considered the first line of treatment because of maternal and fetal risks, but it may be done if it is needed for maternal health. The conditions recommended for consideration before surgery include the need to consume higher doses of antithyroid drugs (more than 450 mg of propylthiouracil or more than 300 mg of methimazole), no dysphagia or airway obstruction by the goiter, and the lack of treatment or severe reaction to drug therapy.[14]

One study investigated and compared the effects of treatment for Graves' disease on pregnancy in patients treated with thyroidectomy and those treated with radioactive iodine. A large number of patients in both groups had been affected by hypothyroidism during pregnancy; however, those who underwent surgery had eutroids during pregnancy, and fewer patients needed to be referred to an endocrinologist.[15]

Papendieck et al studied infants of mothers with Graves' disease. They determined that those infants born of mothers with untreated hyperthyroidism were all clinically diagnosed with hyperthyroidism and had low weight, tachycardia, irritability, goiter, and exophthalmia. In contrast, those infants born of mothers under treatment with ATDs were all asymptomatic. Most of these infants had transient hypothyroidism, possibly due to the passage of ATDs prescribed to the mother through the placenta.[12]

Another study investigated the rate of recurrence of Graves' disease during pregnancy. In this study, women who regained normal thyroid status with antithyroid drugs were divided into 2 groups: pregnant and non-pregnant women. A significant increase was observed in the recurrence of hyperthyroidism in pregnant patients after discontinuation of antithyroid drugs compared to those who were not pregnant. It should be noted that none of these patients had a recurrence of hyperthyroidism in the first trimester of pregnancy. In contrast, more than 95% of the women who became pregnant after discontinuing drug therapy and experienced a recurrence of Graves' disease sustained the spread of disease after childbirth.

According to this study, Rotondi et al recommend that patients with Graves' disease who are in the silent period after treatment with ATDs be investigated for thyroid function in the third and sixth months after childbirth.[18]

In a study on infants of mothers with Graves' disease, only 2% of the infants had overt hyperthyroidism with increased rates of FT4 and reduced TSH. The main symptoms seen in these infants were tachycardia and weight loss. Average FT4 levels were higher than normal between the fifth and twelfth days. All FT4 measurements returned to normal levels from the fourteenth day onwards, but the TSH measurement remained low until the third month. In this study, it was recommended that infants born of mothers with Graves' disease should be carefully evaluated and investigated after birth, including blood tests for thyroid function. Infants with higher than normal levels of FT4 should be investigated for symptoms such as irritability, tachycardia, and low weight. Treatment should be done based on the thyroid test results. It seems that no further review is needed for asymptomatic infants with normal FT4 levels on the fourteenth day, but they should be supervised by a doctor.[19]

Conclusion

According to the studies reviewed, the treatment of patients with Graves' disease is very important, and in the absence of treatment in pregnant patients, its implications will affect the fetus as well as the mother. Among the therapeutic methods, it seems that thyroidectomy has fewer complications and fewer implications on the fetus. It should be noted that both mother and infant should be monitored for thyroid problems.

Authors' Contributions

All authors contributed equally to this study.

Conflict of Interest Disclosures

The authors declare they have no conflicts of interest.

Ethical Approval

Not applicable.

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