

REVIEW

Management of hyperthyroidism during pregnancy and lactation

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Abstract

Introduction: Poorly treated or untreated maternal overt hyperthyroidism may affect pregnancy outcome. Fetal and neonatal hypo- or hyper-thyroidism and neonatal central hypothyroidism may complicate health issues during intrauterine and neonatal periods.

Aim: To review articles related to appropriate management of hyperthyroidism during pregnancy and lactation.

Methods: A literature review was performed using MEDLINE with the terms 'hyperthyroidism and pregnancy', 'antithyroid drugs and pregnancy', 'radioiodine and pregnancy', 'hyperthyroidism and lactation', and 'antithyroid drugs and lactation', both separately and in conjunction with the terms 'fetus' and 'maternal.'

Results: Antithyroid drugs are the main therapy for maternal hyperthyroidism. Both methimazole (MMI) and propylthiouracil (PTU) may be used during pregnancy; however, PTU is preferred in the first trimester and should be replaced by MMI after this trimester. Choanal and esophageal atresia of fetus in MMI-treated and maternal hepatotoxicity in PTU-treated pregnancies are of utmost concern. Maintaining free thyroxine concentration in the upper one-third of each trimester-specific reference interval denotes success of therapy. MMI is the mainstay of the treatment of *post partum* hyperthyroidism, in particular during lactation.

Conclusion: Management of hyperthyroidism during pregnancy and lactation requires special considerations and should be carefully implemented to avoid any adverse effects on the mother, fetus, and neonate.

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Introduction

Hyperthyroidism during pregnancy is uncommon and has been reported as occurring in 0.05–3.0% of pregnancies (1, 2). The clinical diagnosis of hyperthyroidism may be difficult in pregnant women, as symptoms and signs of nervousness, sweating, and dyspnea; tachycardia and cardiac systolic murmur are seen in most normal pregnancies. More specific findings such as weight loss, goiter, and ophthalmopathy may suggest Graves' hyperthyroidism (3, 4). In addition, the occurrence of transient hyperthyroidism of hyperemesis gravidarum may complicate the diagnosis (5, 6). The diagnosis of hyperthyroidism should always be confirmed by the measurement of circulating free thyroxine (FT₄) and TSH. Serum T₄ concentration (both total and free) varies during normal pregnancy and normal range values of total and FT₄ and free tri-iodothyronine (T₃) as well as TSH concentrations must be developed for each specific trimester of pregnancy (4, 7).

Overt hyperthyroidism has well-documented adverse impacts on pregnancy outcomes (8–10). Therefore, despite its rarity, recognition and proper management of

hyperthyroidism during pregnancy is of utmost importance. Medical therapy is preferred by most authorities, as radioiodine is contra-indicated and thyroidectomy requires pre-treatment with antithyroid drugs and may be complicated by surgical adverse effects. However, there is no consensus regarding the best method of therapy for hyperthyroidism during pregnancy. The objective of this study is to review specific considerations in the management of hyperthyroidism during pregnancy and the *post partum* period.

Methods

Data source

The terms 'hyperthyroidism and pregnancy', 'antithyroid drug and pregnancy', 'radioiodine and pregnancy', 'hyperthyroidism and lactation', 'antithyroid drug and lactation', both separately and in conjunction with the terms 'fetus' and 'maternal' were used to search MEDLINE for articles published between 1980 and June 2010. All abstracts were reviewed; studies

published in English were included if appropriately designed. The articles of abstracts meeting criteria were then reviewed to identify details of materials related to pregnancy complicated by hyperthyroidism, breastfeeding, and antithyroid drugs. The strategy used to search for articles was developed with the assistance of a research librarian at the Research Institute for Endocrine Sciences of Shahid Beheshti University of Medical Sciences.

Study selection

The following criteria were considered essential for an article to qualify for inclusion in this review:

- i) Proper study design of survey, case-control and cohort studies, and clinical trials.
- ii) Review articles by prominent scholars if the authors had at least four articles of their own in the list of references of review papers.

Reviewers were not blinded to the study authors' names. This resulted from the fact that we wanted to include all pertinent studies, and it was an exposure to the articles and the study authors. A deliberate strategy to limit bias was, therefore, developed. All articles were initially potential candidates for inclusion; an article was excluded if it lacked appropriate study design.

Results

What are the changes in thyroid function during normal pregnancy?

As pregnancy is a high estrogenic state, serum thyroxin binding globulin (TBG) increases and results in high serum total T_4 and T_3 concentrations. During the first trimester, the serum hCG level rises continuously and peaks near the end of the first trimester. The stimulating effect of hCG on the TSH receptor causes a fall in serum TSH levels in the first trimester of pregnancy (11, 12). Being aware of the changes regarding serum FT_4 , TSH and hCG levels throughout pregnancy would be helpful for interpretation of thyroid function test in hyperthyroid mothers (Fig. 1) (11).

Why is the fetus of hyperthyroid mother at risk?

TSH receptor stimulating autoantibodies are the culprits of pathogenesis of hyperthyroidism in fetus (13). The likelihood of developing fetal hyperthyroidism requiring treatment is related to the level of maternal stimulating TRAb levels, medical treatment of maternal disease. A study showed that the transplacental passage of stimulating maternal TRAb caused hyperthyroidism or Graves' disease in 1–5% of neonates who were

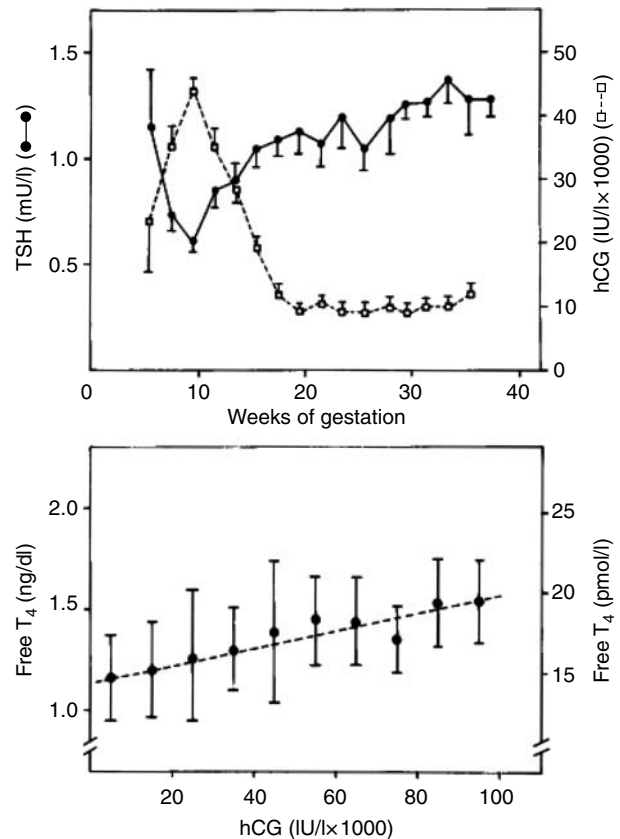


Figure 1 Alteration in serum concentration of hCG, TSH, and FT_4 during pregnancy. Reproduced with permission from Glinöer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocrine Reviews* 1997 18 404–433. Copyright 1997, The Endocrine Society.

born to mothers with Graves' disease (14). The incidence was low because of the balance of stimulatory and inhibitory antibodies and thionamide treatment of the mothers (13). It passes the placenta and stimulates fetal thyroid and may cause fetal hyperthyroidism that manifests with fetal tachycardia (heart rate >160 beats/min), goiter, prematurity, heart failure, and hydrops (1–3). It occurs in 5% of neonates of mothers with Graves' disease.

What are the consequences of untreated hyperthyroidism during pregnancy?

Low birth weight (odds ratio (OR)=9.2, 95% confidence interval (CI) 5.5–16), prematurity (OR=16.5, 95% CI 2.1–130), eclampsia (OR=4.7, 95% CI 1.1–19.7), and risk of miscarriage are more common in untreated hyperthyroid mother than in those who are euthyroid (9, 14, 15). The frequency of small-for-gestational age infants may increase in those who remain hyperthyroid (26.7 vs 7.7%) compared with those who were euthyroid throughout pregnancy (16). Whether the untreated Graves' disease is associated

with congenital anomaly is a matter of debate. Some studies reported more birth defects in hyperthyroid in comparison to euthyroid women (16, 17).

What is the best choice of treatment in pregnant patients with hyperthyroidism?

Antithyroid drugs are the treatment of choice for hyperthyroidism during pregnancy (18). They inhibit thyroid hormone synthesis by reducing iodine organification and coupling of MIT and DIT. Methimazole (MMI), propylthiouracil (PTU), and carbimazole have been used for the treatment of hyperthyroidism during pregnancy. The pharmacokinetics of MMI is not altered in pregnancy; it has been reported that serum PTU concentrations may be lower in the third than in the first and second trimesters of gestation (19). Use of PTU should be restricted to first trimester of pregnancy, after which change to MMI is recommended (20).

Although adrenergic β -blocking agents may be used for the management of hyper-metabolic symptoms, their use should be limited to a few weeks because of possible intrauterine growth retardation (21) and, if used in late pregnancy, they may be associated with transient neonatal hypoglycemia, apnea, and bradycardia.

What is the amount of placenta passage of MMI and PTU?

All antithyroid drugs cross the placenta and may potentially affect fetal thyroid function (22).

Although PTU is more extensively bound to serum albumin than MMI and hypothetically less of it might be transferred through placenta than MMI, it has been shown that placental passage of PTU and MMI is similar. A study showed that transfer rates across the placenta were independent of the perfusate protein concentration, and this might be due to highly efficient placental extraction of the unbound drug (23). Cord PTU levels were higher than maternal concentrations in hyperthyroid pregnant patients treated with PTU until term (24). In addition, there were no differences in thyroid hormone and TSH concentrations in cord blood at birth between the MMI- and the PTU-treated newborn (25).

What are the side effects and complications of MMI and/or PTU in mothers and which one should be used in maternal hyperthyroidism?

The side effects of these drugs occur in a small number of patients taking thionamide drugs. Mostly, minor complications such as skin reactions, arthralgias, and gastrointestinal discomfort occur; however, major and sometimes life-threatening or even lethal side effects, including agranulocytosis, polyarthritis, vasculitis, and immunoallergic hepatitis, may be seen (26).

Agranulocytosis was seen in 0.35–0.4% of patients using both antithyroid drugs. Vasculitis was seen more commonly with PTU and antineutrophil cytoplasmic antibody positivity was 40 times more frequent with PTU than with MMI (27). Immunoallergic hepatitis occurs only with PTU, its frequency ranging between 0.1 and 0.2% (28). PTU-related liver failure is seen in one in every 10 000 adults and one in 2000 children and on average; it occurs 3 months after initiation of PTU therapy (29), although this complication may occur at any time during PTU treatment. In severe cases, up to 25–50% fatality has been reported and liver transplantation may be required (30). Therefore, it has been advised that PTU should not be prescribed as the first-line agent in children or adults. However, due to the probability of association of fetal teratogenicity with MMI, PTU is still recommended as the drug of choice during the first trimester of pregnancy (31). Only two cases of liver failure have so far been reported with PTU in pregnancy (32, 33).

What are the associated complications with antithyroid drugs in the fetus?

Three types of side effects of antithyroid drugs should be considered.

Teratogenicity There are two distinct teratogenicity patterns, aplasia cutis and choanal/esophageal atresia, reported with MMI use during pregnancy, but the data are controversial. Although multiple case reports of animal studies have been published associating aplasia cutis with MMI therapy in pregnant mothers (34), no case of aplasia cutis was seen in a series of 243 pregnant women treated with MMI (35), and the occurrence of aplasia cutis with MMI did not exceed baseline rate of one in 30 000 births in normal pregnancies (36). Choanal and esophageal atresia may have a higher incidence than that expected in fetuses exposed to MMI during the first trimester of gestation, OR may be as high as 18 (37–39). However, the mother's disease might be the causal factor rather than MMI treatment (40). A prospective cohort study did not show any significant difference in incidence of major anomalies or spontaneous abortions between MMI treatment and controls during pregnancy (37).

Effects on the fetal thyroid There is a lack of correlation between fetal thyroid function and maternal dosage of antithyroid drugs (23, 41, 42). Decreased serum-FT₄ in 36% of neonates is seen when the maternal serum-FT₄ is in the lower two-thirds of the normal non-pregnant reference range. Maternal thyroid status is the most reliable marker, and in pregnant mothers with serum-FT₄ levels in upper third of the normal range, serum-FT₄ concentrations of over 90% of their neonates are within normal range (17, 23, 42).

Overtreatment of pregnant ladies with antithyroid drugs resulting in decreasing maternal serum-FT₄ is usually accompanied by fetal hypothyroidism.

Effect on pediatric physical and mental growth No differences in thyroid function or physical and psychomotor development has been found between children born to MMI- or PTU-treated hyperthyroid mothers during pregnancy and those born to euthyroid mothers (43, 44).

Which tests should be performed during treatment with ATD and what levels should be achieved?

Methimazole in doses of 10–20 mg or PTU 100–200 mg daily should be started, and after 1 month, it is desirable to adjust the doses in order to maintain maternal FT₄I in the upper one-third of each trimester-specific reference interval (41) (Fig. 2). FT₄I and TSH should be monitored at monthly intervals during pregnancy. Serum TSH levels of 0.1–2.0 mU/l are appropriate, but TSH <0.1 is also acceptable if the patient is doing well clinically and serum FT₄ is in the appropriate range.

What are the indications and timing of subtotal thyroidectomy in the management of pregnancy and hyperthyroidism?

Surgery in pregnancy carries more risks than medical therapy and is complicated by hyperthyroidism. It is associated with an increased risk of spontaneous abortion or premature delivery (45). Thyroidectomy in maternal hyperthyroidism is rarely indicated, and subtotal thyroidectomy is indicated in patients with

major or severe adverse reactions to antithyroid drugs, and if hyperthyroidism is uncontrolled because of lack of compliance, high doses of antithyroid drugs are required to control the disease (46) and large goiter that may require high doses of antithyroid drugs (ATD). The optimal timing for surgery is in the second trimester when organogenesis is complete, the uterus is relatively resistant to stimulating events, and the rate of spontaneous miscarriage is reduced.

Should ATD therapy be discontinued in euthyroid pregnant women during the third trimester of gestation?

Some clinicians recommend discontinuation of antithyroid medications in the third trimester in 20–30% of pregnant women who have been euthyroid for several weeks on small doses and have low TRAb titers. A study has shown more recurrence of hyperthyroidism in the *post partum* period in those who had stopped antithyroid therapy compared with those who had continued such treatment throughout pregnancy and *post partum* (47).

What is the appropriate management of neonatal thyrotoxicosis?

Neonatal hyperthyroidism is due to transplacental transfer of maternal TRAb and occurs in 5% of neonates of mothers with Graves' disease (13). FT₄ and TSH should be measured in the cord blood of any infant delivered by women with a history of Graves' disease. If the woman was treated with ATD upto the end of pregnancy, clinical manifestations of neonatal hyperthyroidism may be only seen for the first time a few days after delivery, because the fetus was protected by the ATD received from the mother during the final weeks of gestation. Antithyroid treatment and propranolol should be initiated. Either MMI 0.5–1 mg/kg or PTU 5–10 mg/kg daily should be given to neonates with hyperthyroidism. Propranolol 2 mg/kg daily is helpful to slow down pulse rate and reduce hyperactivity in ill neonates. Lugol solution or potassium iodide and glucocorticoids may also be given in more severe cases (48).

What is the best management of hyperthyroidism in the post partum period?

Cases of thyrotoxicosis due to Graves' disease occur more frequently during the *post partum* period than at other times in women of childbearing age (49). In the months following delivery, exacerbation of immune reactivity occurs between 3 and 12 months *post partum* (50). Therefore, autoimmune thyroid disorders may begin to recur or exacerbate during this crucial period. Graves' disease and *post partum* thyroiditis are two major causes of thyrotoxicosis in the first year after delivery.

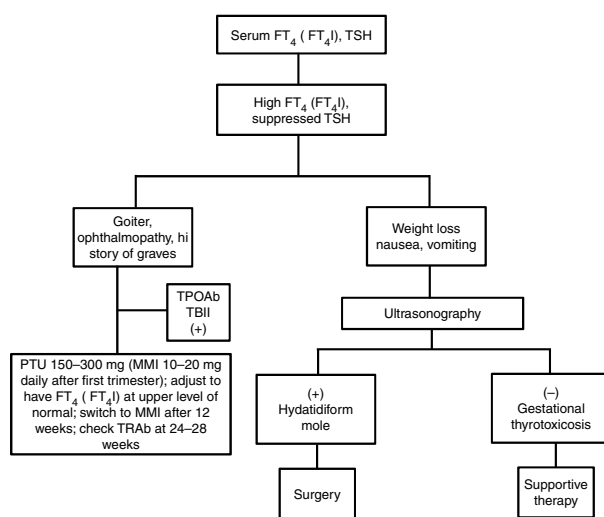


Figure 2 Algorithm for the systematic approach to hyperthyroidism suspected during pregnancy.

Thyrotoxicosis caused by *post partum* thyroiditis usually does not require treatment; therefore, it is of utmost importance to differentiate between Graves' disease and *post partum* thyroiditis, TSH receptor antibodies being positive in the former and negative in the latter (51). If a woman is not breastfeeding, radioiodine uptake may show low values in *post partum* thyroiditis and elevated or normal values in Graves' disease. Antithyroid drugs are the mainstay of treatment for thyrotoxicosis during *post partum* period (52). Neither PTU nor MMI causes any alterations in thyroid function and physical and mental development of infants breast-fed by lactating thyrotoxic mothers (53–55). Methimazole is the preferred drug, because of a risk of potential hepatotoxicity of PTU in either mother or child (56).

Conclusion

Management of hyperthyroidism during pregnancy and lactation requires special considerations and should be carefully implemented to prevent any adverse effects on the mother, fetus, or neonate. Taking into account the probability of association of fetal teratogenicity with MMI, PTU is recommended as the drug of choice during the first trimester of pregnancy, but due to its hepatotoxicity, it should be changed to MMI thereafter. Surgery is considered only if large doses of antithyroid drugs could not control hyperthyroidism or serious drug side effects have occurred. Radioiodine therapy is contraindicated during pregnancy and lactation. During the *post partum* period, all antithyroid drugs could be administered in nursing mothers, but MMI should be the drug of choice because of the risk of potential hepatotoxicity of PTU in either mother or child.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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