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MINIREVIEWS

Thyroid disease in pregnancy: A review of diagnosis, complications and management

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Abstract

Malfunction of the thyroid gland is the second most common endocrine disorder encountered during pregnancy. It is well known that overt disease of the thyroid gland, either hyper or hypo can adversely affect pregnancy outcome. There is also an ongoing debate surrounding the issue of subclinical hypothyroidism and its effect on the cognitive development of the unborn child. The goal of this paper is to present a systematic review of the literature and the current recommendations for diagnosis and treatment of thyroid disease in pregnancy and postpartum.

Key words: Pregnancy; Hypothyroidism in pregnancy; Hyperthyroidism in pregnancy; Thyroid; Thyroid cancer in pregnancy; Subclinical hypothyroidism in pregnancy

Core tip: Uncontrolled thyroid disease in pregnancy is associated with significant morbidity and mortality for both mother and fetus. Timely diagnosis and adequate treatment ameliorates the risk of complications. Treatment of subclinical hypothyroidism in pregnancy with the goal of improving the cognitive outcome for the fetus has not been shown to be useful and is not currently recommended.

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INTRODUCTION

The thyroid gland produces three hormones: Triiodothyroxine (T3), tetraiodothyroxine (T4), also known as thyroxine, and calcitonin. The amount of hormone production is controlled by thyroid stimulating hormone (TSH) which is secreted by the pituitary gland. Production of TSH is in turn regulated by a negative feedback loop to the hypothalamus which produces thyroid releasing hormone. The thyroid gland uses iodine, a trace element which is not produced in the body and must be ingested, and tyrosine to manufacture

Table 1 Recommended values of thyroid stimulating hormone for each trimester

First trimester	0.1-2.5 mIU/L
Second trimester	0.2-3.0 mIU/L
Third trimester	0.3-3.0 mIU/L

T3 and T4. The majority of production is T4 which is converted in target tissues to the active form T3. The majority of circulating hormone is bound to thyroid binding globulin (TBG) proteins. Only the unbound free hormone is active.

During pregnancy the size of the thyroid gland increases by 10%-40%. The upper end of this range is seen in iodine deficient areas. Production of T3 and T4 increases by 50% with a concomitant increase in iodine requirement. The hypothalamic-pituitary-thyroid feedback systems function normally during pregnancy. However there is a significant change in protein binding of T3 and T4. Additionally the hormone of pregnancy, human chorionic gonadotropin (HCG), acts like TSH on thyroid receptors. Due to the increase in TBG's during pregnancy total and bound levels of T3 and T4 will be increased but free T3 (FT3) and free T4 (FT4) are unchanged. TSH is typically low when HCG is high during the first 10 wk and will increase after 10-12 wk when the level of HCG falls. Serum FT4 is highest when HCG is high and falls when HCG levels decrease[1].

Screening

There is controversy regarding universal screening for thyroid disease in pregnancy. In 2005 a joint statement from the American Thyroid Association, The Endocrine Society and the American Association of Clinical Endocrinologists supported universal screening in pregnancy to detect subclinical hypothyroidism (SCH) which at the time had been linked to poor neurocognitive outcomes in offspring[2]. In 2011, the American Thyroid Association issued a guideline which did not address screening but recommended that pregnant women with SCH and thyroid peroxidase antibodies should be treated with levothyroxine[3]. In 2015 the American College of Obstetricians and Gynecologists advised against universal screening because treatment of SCH has not been shown to improve neonatal outcomes[4].

Serum TSH is considered the most accurate method of evaluating thyroid function during pregnancy[3,5]. If no gestational age specific values are available for local laboratories, the American Thyroid Association makes the following recommendations for TSH: In the first trimester 0.1-2.5 mIU/L; in the second trimester 0.2-3.0 mIU/L; and in the third trimester 0.2-3.0 mIU/L[3] (Table 1).

Women with a history of hypothyroidism, women currently on medication for hypothyroidism, women with a history of Graves disease, and women currently on medication for Graves disease should be evaluated with a serum TSH at the first prenatal visit.

Anti-thyroid antibodies

There are three types of TSH receptor antibodies (TRAb); TSH stimulating antibodies (TSI), inhibitory antibodies known as TSH binding inhibitory immunoglobulins (TBII) and neutral antibodies.

TSH stimulating immunoglobulins are IgG antibodies that bind the TSH receptors in the thyroid causing increased production of T4 and T3. TSI antibodies cross the placenta and may cause neonatal thyrotoxicosis. TSI antibodies are not routinely used for the diagnosis of Graves disease but should be evaluated in pregnancy because of the risk to the fetus[6]. TSH binding inhibitory immunoglobulins competitively inhibit TSH receptors. TBII may cause hypothyroidism and paradoxically are often present in patients with Graves disease. The clinical relevance of neutral TSH receptor antibodies is unknown.

Thyroid peroxidase is an enzyme that oxidizes iodide to iodine which is then added to tyrosine for production of T3 and T4. Antibodies to thyroid peroxidase (TPO-Ab) indicate autoimmune mediated thyroid disease (*i.e.*, Hashimoto's). Greater than 80% of patients with overt hypothyroidism and approximately 50% of women with SCH have circulating TPO-Ab antibodies.

Hypothyroidism

Approximately 2%-3% of pregnancies are complicated by hypothyroidism[1]. Overt hypothyroidism is defined as an elevated serum TSH (> 2.5 mIU/L) with a low serum FT4, or TSH ⩾ 10 mIU/L regardless of the amount of FT4. Hypothyroidism is associated with two-fold increased risk of ovulatory dysfunction. In pregnancy there is an increased risk of fetal demise, miscarriage, abruption and decreased fetal growth[3-5]. Symptoms may be missed because they are often nonspecific and mimic common complaints of pregnancy such as fatigue, dry skin, constipation and hair loss.

All pregnant women with hypothyroidism should receive hormone replacement in the form of Levothyroxine with the goal of keeping the TSH in the normal to high normal range. No available data supports the addition of T3 or thyroid preparations other than levoT4 (levothyroxine). Treatment has been shown to decrease the risk of adverse pregnancy outcomes[1,3]. Women who enter pregnancy on levothyroxine will need to increase their dosage. The average increase in dose during pregnancy has been reported between 45%-50%. The increased requirement is mediated by an increase in Thyroxin-binding globulin, increased maternal circulating volume and placental destruction of T4.

A starting dose of levothyroxine can be calculated as 1-2 μg/kg per day or 100 μg/d. Serial determinations of TSH should be followed every 4-6 wk and the dose of levothyroxine should be adjusted in 25-50 mcg increments until TSH is within the desired range. After

Table 2 Studies of subclinical hypothyroidism in pregnancy

Ref.	Design	Method	Result	Conclusion
Pop *et al*[23], 1999	Cohort study	220 children were evaluated at 10 mo of age. Maternal TSH, FT4 and TPO antibodies were measured at 12 and 32 wk of pregnancy	Children of women with FT4 levels less than the 5th and 10th centiles at 12 wk had lower scores on the Bayley Psychomotor Development Index at 10 mo. No differences were found at 32 wk	FT4 < 10% ile at 12 wk is a risk factor for impaired psychomotor development in offspring
Haddow *et al*[7], 1999	Retrospective	62 women with high TSH	Children of these women did less well on 15 tests of intelligence. Average decrease in IQ was 4 points	Undiagnosed hypothyroidism adversely affects the fetal neurodevelopment
Henrichs *et al*[8], 2010	Population based cohort	Women with normal TSH and FT4 < 5th and 10th centile. Expressive vocabulary of children was evaluated by mother at 18 and 30 mo	Maternal TSH not related to outcome. Both mild and severe low FT4 associated with higher risk of expressive language delay at all ages. Severe had higher risk of nonverbal cognitive delay	Maternal low FT4 is a risk factor for early childhood cognitive delay
Lazarus *et al*[11], 2012	Randomized prospective	Women in screening group were tested and treated Women in the control group had stored samples which were tested after delivery and received no treatment during pregnancy	No difference in cognitive function between the two groups at 3 yr of age	Screening and treatment for hypothyroidism did not improve neurodevelopmental outcomes in the offspring
Ghassabian *et al*[24], 2014	Cohort	3727 mother-child pairs with prenatal thyroid fxn tests before 18 wk. FT4 < 5% of normal. MRI of childrens brains and IQ test at age 6 yr	Children of mothers with low FT4 scored 4.3 points lower on nonverbal IQ test. No morphologic difference by MRI	Maternal hypothyroxinemia has adverse effect on children's non-verbal IQ at school age
Chen *et al*[13], 2015	Prospective	106 babies born to mothers with SCH and 106 babies born to euthyroid mothers	Babies from both groups had similar scores on the Gesell development test	No neurodevelopmental deficit detected up to 24 mo in babies of mothers with SCH

TSH: Thyroid stimulating hormone; TPO: Thyroid peroxidase; FT4: Free T4; SCH: Subclinical hypothyroidism; MRI: Magnetic resonance imaging; IQ: Intelligence quotient.

delivery, the dosage can immediately be returned to the pre-pregnancy amount and TSH should be checked at the 6 wk postpartum visit.

SCH defined as a normal FT4 with an elevated TSH has been the subject of much debate. In 1999, the *New England Journal of Medicine* published a study that evaluated the children of 62 women with high thyrotropin (TSH) and low thyroxine (T4) levels compared to the children of 124 controls with normal values[7]. Children in the study group had lower IQ scores (average 4 points lower) and performed less well on fifteen standard tests of attention, language, visual-motor performance and reading ability. They concluded that SCH had an adverse effect on the neurologic well-being of the fetus and that routine screening for thyroid disorders should be performed during pregnancy. After that initial publication, multiple observational studies reported a possible association between SCH and decreased intelligence in offspring[8-10].

In 2012 the Controlled Antenatal thyroid screening study was published which randomized pregnant women with SCH to treatment *vs* no treatment[11]. The primary outcome of interest was offspring IQ at age 3. The study found no difference in IQ between the two groups. The protocol for the second wave of the Controlled Antenatal Thyroid screening (CATS Ⅱ) study was published in 2014 and will assess the cognitive function of the same group of children between ages 7 and 10 years[12].

Chen *et al*[13] reported on a prospective study of 106 infants of mothers with SCH compared to 106 infants of euthyroid mothers. They reported no differences in neurodevelopment up to 24 mo between the two groups.

In 2013 the European Thyroid Association published a guideline on the management of SCH. They defined two categories of SCH based on the level of elevation of serum TSH; mild (4.0-10.0 mU/L) and severe (> 10 mU/L)[14]. They did not address SCH in pregnancy but recommended treatment for patients < 65 years of age with TSH in the severe range. They suggested a trial of treatment in patients with symptoms and mild elevations of TSH. Table 2 displays relevant studies addressing SCH in pregnancy.

Neither Screening for SCH, nor treatment of SCH in pregnancy with the goal of improving neurocognitive outcomes in offspring is supported by current evidence.

Fetal surveillance

No studies have addressed the frequency of growth scans or the need for antenatal surveillance in patients with hypothyroidism. In cases of overt disease, particularly those patients on medication, monthly growth scans may be a reasonable consideration.

Table 3 Diagnosis and treatment of thyroid disease in pregnancy

	TSH	FT4	FT3	Rx	Goal of treatment
Hypothyroid	↑	↓	↓	Levothyroxine starting dose 1-2 mcg/kg daily	Keep TSH normal range
Hyperthyroid	↓	↑	↑	PTU 50-150 mg TID in first trimester methimazole 10-40 mg BID or TID after first trimester	Keep FT4 high normal "watch for agranulocytosis"

TSH: Thyroid stimulating hormone; FT3: Free T3; FT4: Free T3; BID: Twice daily; TID: Three times daily; PTU: Propylthiouracil.

Breastfeeding

Thyroxine is a normal component of breast milk. Levothyroxine is considered safe during breastfeeding. Thyroid hormones are necessary for lactation and overt hypothyroidism is associated with a low milk supply. Thyroid hormone replacement has been shown to improve the milk supply in hypothyroid patients[15].

HYPERTHYROIDISM

Hyperthyroidism complicates up to 0.4% of pregnancies. Hyperthyroidism is defined as a suppressed TSH with elevated FT4. Left untreated in pregnancy there is an increased risk of miscarriage, stillbirth, low birth weight, and preterm delivery. Maternal complications include thyroid storm and a 5-fold increase in the risk of preeclampsia and congestive heart failure.

During pregnancy, it is important to differentiate Graves disease from gestational hyperthyroidism due to the effect of HCG on the maternal thyroid. Signs of overt hyperthyroidism include tremor, nervousness, heat intolerance, irritability and weight loss, and typically will not occur in patients with gestational hyperthyroidism. Absence of a goiter or ophthalmopathy also favors gestational disease. If there is doubt, thyroid receptor antibodies and T3 can also be obtained. If antibodies are present the diagnosis is more likely Graves disease.

Anti-thyroid mediation should not be used in patients with gestational hyperthyroidism. The serum T4 will normalize between 14-18 wk.

The goal of treatment is to keep FT4 levels in the high normal range with the minimum required dose of anti-thyroid medication. Two medications are commonly used in pregnancy: Methimazole and propylthiouracil (PTU). A third medication carbimazole is metabolized to methimazole. Both drugs cross the placenta and may suppress the fetal thyroid. Methimazole embryopathy has been identified in patients who took the drug during the first trimester and consists of choanal or esophageal atresia, cutis aplasia, minor dysmorphic features and developmental delay. Propylthiouracil has been associated with liver damage. The Food and Drug administration of the United States and the American Thyroid Association recommend PTU in the first trimester with a switch to methimazole in the second trimester. This avoids the teratogenic effect of methimazole in the first trimester and decreases the risk of hepatotoxicity from long term use of PTU[4]. The dose of PTU is 50-150 mg TID. The dose of methimazole is 10-40 mg 2 to 3 times a day.

Approximately 10% of women on antithyroid medication develop a transient leukopenia which does not require medication cessation. Agranulocytosis is a decrease in granulocytes (neutrophils, eosinophils and basophils) which can result in life-threatening infections. Agranulocytosis occurs in 1% of patients on medication; may develop suddenly and is an indication for medication discontinuation. Patients should be warned of this complication and instructed to discontinue medication if a fever or sore throat develops and to have a complete blood count for evaluation.

FT4 should be checked every four weeks during pregnancy. This is to ensure that target values are achieved and maintained. This information is summarized in Table 3.

Thyroid storm

Thyroid storm or crisis is a rare life threatening complication of uncontrolled hyperthyroidism. Thyroid storm is characterized by fever (> 103 F), tachycardia, hypertension and impaired thinking. Evaluation of TSH and FT4 will show suppressed TSH with elevated FT4 though the amount of FT4 does not correlate with symptom severity. Due to the life threatening nature of thyroid storm for both the mother and fetus, aggressive management is indicated. Admit to an intensive care unit with Ⅳ fluids and maintenance of electrolytes. Give Tylenol for hyperpyrexia. Antithyroid medication should be given immediately either 30 mg of methimazole or 300 mg of PTU every 6 h. An alternate dosing schedule recommended by the American Congress of Obstetricians and Gynecologists is a loading dose of 1000 mg of oral PTU followed by 200 mg orally every 6 h. The thioamides will block the synthesis of T3 and T4. One hour after starting medication give iodine either orally as 10 drops of Lugol's solution every 8 h or 1 g of sodium iodide Ⅳ every 8-12 h. Hydrocortisone 50-80 mg every 8 h for 3 doses or Dexamethasone 2 mg Ⅳ every 6 h for four doses should be given to block the peripheral conversion of T4 to T3. To control the tachycardia consider a beta blocker; esmolol, propranolol and labetolol are all equally efficacious (Table 4).

Radioactive iodine is commonly used to ablate the thyroid in cases of Graves thyrotoxicosis. This technique should not be used during pregnancy. The fetal thyroid begins to concentrate iodine at approximately 14 wk and is dependent on maternal sources. Radioactive

Table 4 Six steps for treatment of thyroid storm

1 Admit to intensive care unit	IV fluids and watch electrolytes
2 Tylenol 650 mg q6 h	For hyperpyrexia
3 Loading dose of 1000 mg PTU orally then 200 mg orally q6 h; alternate dosing 300 mg PTU q6 h	Will block synthesis of T3 and T4
4 Iodine supplementation 10 drops of Lugol's solution q8 h OR 1 g sodium Iodide IV q8-12 h Iodine allergy use lithium carbonate 300 mg PO q6 h	Blocks release of hormone from the thyroid gland
5 Hydrocortisone 50-80 mg q8 h for 3 doses OR Dexamethasone 2 mg IV q6 h for 4 doses	To block peripheral conversion of T4 to T3
6 Beta blocker Labetolol 300 mg TID may increase to a max dose of 800 mg TID but watch blood pressure	To control the tachycardia – use cautiously in heart failure

PTU: Propylthiouracil; TID: Three times a day.

iodine will destroy the fetal thyroid resulting in congenital hypothyroidism. However treatment prior to 12 wk is not associated with damage to the fetus.

If thyroidectomy is required during pregnancy, it is ideally performed in the second trimester due to a perhaps unjustified concern for teratogenesis of anesthetics in the first trimester, and possible onset of labor resulting in extreme prematurity during the third trimester. There is also less risk of supine hypotension from an enlarged uterus in mid trimester.

During an acute thyroid crisis, the fetal status will not be reassuring and fetal death is a significant risk. Nonetheless, delivery should not be undertaken until the maternal status is stable.

Thyrotoxic heart

Thyrotoxic heart failure is a direct result of the action of thyroid hormones on the heart. Common manifestations are left ventricular hypertrophy, abnormal rhythm usually sinus tachycardia or atrial fibrillation, pulmonary hypertension and diastolic dysfunction. Thyrotoxic heart is treated as thyroid storm with admission to the intensive care unit with cardiac monitoring, PTU to inhibit synthesis, and iodide to block release of hormone from the gland. Beta blockers should be used with caution with heart failure. Volume overload can be reversed with diuretics. The patient should be euthyroid before attempting cardioversion for atrial fibrillation because spontaneous resolution to sinus rhythm may occur and even if successfully cardioverted, atrial fibrillation is likely to recur if hyperthyroidism is the cause and has not been corrected[16].

Fetal surveillance

Titers of TSI antibodies should be measured by 24-28 wk in all women with a present or past history of Graves disease. Titers more than three times the upper normal limit are a significant risk to the fetus and warrant close follow-up. In the setting of high TSI titers the fetus should be followed with monthly growth scans for signs of hyperthyroidism which may include tachycardia, goiter, growth restriction and congestive heart failure. Weekly or twice weekly non-stress testing in the interval between growth scans can be considered.

In our practice we obtain monthly growth scans on all patients on anti-thyroid medication between 24-36 wk (Table 5).

Table 5 Frequency of antenatal surveillance

	Ultrasound	Antenatal testing (Nonstress test or Biophysical Profile)
Hyperthyroid	Monthly	Twice weekly if poorly controlled
Hypothyroid	No recommendation Consider monthly	No recommendation

Breastfeeding

Approximately 0.025% of the dose of PTU is excreted in breast milk. In contrast, the amount of methimazole excreted in breast milk is equal to maternal serum levels of the drug[17].

In a study of 42 breast fed infants of mother's on 30 mg of methimazole daily, all infants had normal thyroid function[18]. In a follow up study the authors looked at the same 42 children in comparison to breastfed infants of euthyroid mothers. They were followed up at 18 mo and at 86 mo of age. There was no difference in thyroid function or development between the two groups[19].

Breastfeeding is considered safe in women on doses of PTU less than 300 mg per day or methimazole 20-30 mg per day. It is recommended to take the medicine in divided doses immediately after feeding. Babies of mothers on these medications should be followed with thyroid function tests[3].

POSTPARTUM THYROIDITIS

Postpartum thyroiditis is an autoimmune mediated destructive thyroiditis occurring in the first year postpartum. It affects up to 21% of postpartum patients[20]. It is associated with the presence of anti-thyroid antibodies. The clinical course may vary but classically postpartum thyroiditis occurs in two phases. The first phase is a transient thyrotoxicosis occurring 2 to 6 mo postpartum, followed by a hypothyroid phase which may present between 3 mo up to one year postpartum. During the thyrotoxic phase actual symptoms are usually mild. The thioamides are not effective in treatment because the symptoms are due to autoimmune destruction of the gland. The goal of treatment is symptomatic relief usually with Beta Blockers. The thyrotoxic phase always resolves spontaneously. Patients may present with isolated hyperthyroidism (32%) or hypothyroidism (43%). It is estimated that 10% to 50% of women with postpartum thyroiditis remain hypothyroid at the end of the first postpartum year. Women who recover should

be screened annually for hypothyroidism[3].

THYROID CANCER IN PREGNANCY

The prevalence of thyroid cancer in pregnancy is estimated at 14.4/100000[3]. Thyroid nodules may be more common during pregnancy and the prevalence increases with parity. In the presence of a nodule, a serum TSH and FT4 should be drawn and an ultrasound of the thyroid and neck performed. If the ultrasound is suggestive of malignancy, fine needle aspiration should be performed. Thyroid function tests are usually normal in patients with thyroid cancer.

If the cytology is benign surgery is not indicated unless there is rapid growth that interferes with breathing or swallowing.

If cytology is suggestive of medullary, papillary, follicular or anaplastic carcinoma surgery should be offered. Women with well-differentiated thyroid carcinoma can be offered deferral of surgery until the postpartum period without concern that the delay will worsen the prognosis. If surgery is deferred ultrasound of the neck should be performed at least each trimester. Rapid tumor growth is a contraindication for surgery deferral[21].

Post-surgery, some patients require remnant ablation with radioactive iodine. As discussed previously, this should not be done during pregnancy. Women should not breastfeed while undergoing radioactive iodine treatment.

Thyroid hormone replacement should be initiated as soon as possible after surgery to maintain the TSH in normal range. Future pregnancies should be delayed 6 mo to one year to confirm remission of cancer and to achieve a stable dose of levothyroxine[21,22].

CONCLUSION

Diseases of the thyroid are common in pregnancy and knowledge of management is indispensable to anyone providing care to pregnant women. In this paper I have provided a brief review of diagnosis and management of thyroid disease during pregnancy and in the puerperium.

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