

Thyroid Disease in Pregnancy

The following section is entitled “**Thyroid Disease in Pregnancy**”. This section deals with some of the basic concepts important to the diagnosis, management and investigation of thyroid disease during pregnancy and the postpartum period. The section begins with a *learner handout* with space for the learner to make their own notes. The *learner handout* is followed by the *teaching script* for the educator. The section then concludes with several cases for discussion and a brief bibliography for this topic.

THYROID DISEASE IN PREGNANCY

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Physiologic Changes in Pregnancy

- Free thyroxine levels remain within the normal range during pregnancy (though total thyroxine levels are increased secondary to increased TBG).
- TSH decreases slightly in first trimester.
- The thyroid gland increases slightly in size during pregnancy.

Hypothyroidism

- Untreated patients with hypothyroidism rarely conceive and carry a pregnancy.
- Treated hypothyroidism usually has no associated pregnancy complications.

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Hypothyroidism

- Some patients will require increased levothyroxine doses during their pregnancies.
- Monitor thyroid function tests each trimester and at other clinically indicated times.
- Prenatal vitamins can decrease the absorption of levothyroxine.

Hyperthyroidism

- 95% of hyperthyroidism in pregnancy is secondary to Graves' Disease.
- A good pregnancy outcome can be expected in patients with good control.

Hyperthyroidism

- Untreated hyperthyroidism is associated with decreased fertility, an increased rate of miscarriage, intrauterine growth retardation (IUGR), premature labor, and perinatal mortality.
- Poorly controlled thyrotoxicosis is associated with thyroid storm especially at labor and delivery.

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Hyperthyroidism

- Beta Blockers and PTU can be safely used in pregnancy and in nursing mothers.
- PTU crosses the placenta but does not usually cause fetal hypothyroidism and goiter unless used in high doses.
- Treatment goals favor mild hyperthyroidism over hypothyroidism.

Hyperthyroidism Graves' Disease

- Like other immune mediated diseases in pregnancy, Graves' Disease tends to improve in the third trimester.
- Exacerbations may occur in the first trimester and postpartum.

Hyperthyroidism Graves' Disease

- Neonatal and fetal thyrotoxicosis may occur because of transplacental passage of thyroid stimulating antibodies.

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Postpartum Thyroiditis

- Postpartum thyroiditis is a destructive autoimmune thyroiditis that begins with a period of hyperthyroidism followed by a period of hypothyroidism. The gland is often enlarged.
- There is usually complete recovery but a chance of recurrence in subsequent pregnancies exists.

Postpartum Thyroiditis

- 80-85% of patients will have positive antithyroid antibodies.
- A radioactive iodine uptake scan can differentiate postpartum thyroiditis from an exacerbation of Graves' Disease.

Postpartum Thyroiditis

- **POSTPARTUM THYROIDITIS IS AN IMPORTANT CONSIDERATION IN WOMEN WITH POSTPARTUM DEPRESSION.**

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Hyperemesis Gravidarum

- **Hyperemesis is associated with abnormal thyroid function tests in a significant number of cases.**
- *Hyperthyroidism may be the cause of hyperemesis or hyperemesis may be the cause of the hyperthyroidism.*

Thyroid Nodules

New thyroid nodules should be aggressively investigated during pregnancy because of a high incidence of malignancy.

Thyroid Investigations

- **Radioactive iodine is contraindicated in pregnancy.**
- **Nursing mothers who have radioactive iodine uptake scans should pump and discard their milk for 48-72 hours after the test.**

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Teaching Script

Physiologic Changes in Pregnancy

Thyroid disease is often seen in women of reproductive age so it is not uncommon for it to occur in pregnant women. There are several normal physiologic changes in pregnancy which are important to understand in caring for these women. Before the routine availability of free thyroxine levels, interpretations of tests such as total T4 and THRU were complicated by the fact that thyroid binding globulin increases in pregnancy. However, free T4 levels are now available and while it does remain within the normal range, levels decrease later in pregnancy. TSH does decrease slightly in the first trimester. This corresponds with increased beta HCG levels. The changes in TSH levels may be explained by the fact that beta HCG is not only structurally quite similar to TSH, but it also has thyrotropic activity. It should also be noted that the thyroid gland itself may increase slightly in size during pregnancy. However, in areas of adequate iodine intake, the finding of a goiter should be considered significant and appropriately investigated.

Hypothyroidism

Significant hypothyroidism is unusual in pregnancy as untreated hypothyroid patients rarely conceive and carry a pregnancy. The few patients who do become pregnant and remain untreated have an increased risk for miscarriage, fetal loss, preeclampsia and low birth weight. Treated hypothyroidism generally does not confer an increased risk for pregnancy complications. Some patients will require increased doses of thyroxine during their pregnancy and whether this represents a true need for increased doses or whether these patients were inadequately

supplemented to begin with is somewhat unclear. It is our practice to check thyroid function tests once per trimester. If this frequency of testing shows that a patient requires an increase in thyroxine replacement, we then consider checking the patient's thyroid function more frequently. Although most patients will *not* need an adjustment in their dose of thyroxine during pregnancy, there are individuals who will require dose increases up to as high as 200 micrograms of levothyroxine per day. Patients should also be instructed not to take their thyroid supplement at the same time as their prenatal vitamins since iron can decrease its absorption.

Hyperthyroidism

The signs and symptoms of hyperthyroidism in pregnancy are the same as they are for the nonpregnant individual but the clinical diagnosis is made more difficult by normal changes in pregnancy which mimic hyperthyroidism. These include increased heart rate, heat intolerance, warm skin, and systolic flow murmurs. Findings more suggestive of hyperthyroidism, however, are tremor, weight loss, hyper defecation, thyroid bruit, and eye findings consistent with Graves' Disease.

Thyrotoxicosis in pregnancy is caused by Graves' Disease 95% of the time. Other potential etiologies include a toxic solitary nodule, toxic multinodular goiter, Hashimoto's thyroiditis, as well as trophoblastic disease. Patients with good control are likely to have a good pregnancy outcome. In contrast, patients with untreated hyperthyroidism have decreased fertility and an increased risk of miscarriage, intrauterine growth retardation (IUGR), premature labor, and perinatal mortality. Thyroid storm can also occur in patients with poorly controlled thyrotoxicosis especially at labor and delivery. Thus the appropriate treatment of hyperthyroidism in pregnancy is very important for both maternal and fetal health. This usually involves the use of beta blockers and propylthiouracil (PTU). (Methimazole can be used but is less favored because of reports of associated aplasia cutis). Although PTU does cross the placenta, it appears not to significantly affect the fetal thyroid unless the mother is taking high doses. To minimize fetal exposure to PTU and its associated risk of fetal hypothyroidism and

fetal goiter, treatment favors use of lower doses of medication which allow the patient to be mildly hyperthyroid. Further, Graves' disease often goes into remission in the third trimester so that decreasing doses are often required as pregnancy progresses and sometimes these medications can be stopped entirely. Despite improvement antepartum, Graves' Disease often relapses after delivery and, if needed, both beta blockers and PTU can be used in nursing mothers.

Graves' Disease is an immune mediated disease and as such has some interesting features in pregnancy. Other immune mediated diseases, such as Rheumatoid Arthritis, have been noted to improve later in pregnancy and develop exacerbations postpartum. As previously noted, this occurs in Graves' Disease as well. While this frequently observed phenomena is attributed to the immune changes in pregnancy, the details of how it occurs are poorly understood. Also related to the immune aspect of Graves' Disease, there is transplacental passage of thyroid stimulating antibodies such that neonatal and fetal thyrotoxicosis may occur. Since this is an antibody related entity, it may occur even in women who have previously had their thyroid ablated but still have circulating antibody.

Postpartum Thyroiditis

An interesting entity known as postpartum thyroiditis exists which resembles a lymphocytic thyroiditis and is the most common case of postpartum hyperthyroidism. It frequently begins approximately 4 months postpartum and usually starts with a period of acute inflammation that manifests itself as a non-tender goiter associated with hyperthyroidism. Over the course of time, the hyperthyroidism is often followed by many months of hypothyroidism. This hypothyroidism usually resolves within a year following delivery. Antithyroid antibodies are positive in 85% of the cases. At times it may become important to distinguish postpartum thyroiditis from a postpartum exacerbation of Graves' disease. A radioactive iodine uptake scan can easily make the distinction as there will be little uptake in postpartum thyroiditis. Although there is usually complete recovery in postpartum thyroiditis, a risk of recurrence does exist with subsequent pregnancies. ***Postpartum thyroiditis may masquerade as postpartum depression so it is essential to consider it in any woman presenting with depressive symptoms in the year after delivery.***

Hyperemesis Gravidarum

Although not traditionally felt to be an endocrine disorder, hyperemesis gravidarum is associated with abnormal thyroid function tests in a significant number of cases. In the majority of cases, it is felt that the hyperthyroidism is caused by the hyperemesis itself. Beta HCG, the placental hormone which is believed to be partially responsible for the nausea and vomiting of hyperemesis, is only one amino acid different from Thyroid Stimulating Hormone (TSH). It is therefore believed that in some cases of hyperemesis, the high levels of Beta HCG may stimulate the thyroid. Hyperthyroidism associated with hyperemesis usually resolves at the end of the first trimester when the beta HCG levels start to decline and the symptoms of hyperemesis tend to resolve. However, it is believed that some individuals manifest hyperemesis because they have underlying hyperthyroidism. Deciding which is the “primary” illness in an individual patient with hyperemesis and hyperthyroidism can be quite difficult. Further complicating this is the fact that some patients who have severe hyperemesis will manifest sick euthyroid syndrome. Therefore, in the interpretation of thyroid function tests in the setting of hyperemesis and hyperthyroidism the patient’s clinical thyroid status should be used as an important guide in management decisions.

Thyroid Nodules

It is very important to emphasize that although there is an unfortunate tendency among clinicians to avoid invasive investigations during pregnancy, new thyroid nodules always need to be aggressively investigated in the gravid woman. There appears to be a very high incidence of malignancy in new thyroid nodules appearing during pregnancy. Therefore, fine needle aspirations should never be delayed because a woman is pregnant. Despite the increased incidence of malignancy in thyroid nodules identified in pregnancy, pregnancy does not have an adverse effect on the course of the disease. Likewise, women with a history of thyroid carcinoma who become pregnant do not have a worsened prognosis overall.

Thyroid Investigations

A final note on thyroid investigations during pregnancy should be made. The fetal thyroid avidly binds iodine starting at 10-12 weeks gestation so that administering radioactive iodine to pregnant women results in doses to the fetus which are much greater than the exposure to the mother. It should be completely avoided in pregnancy. Nursing mothers who have radioactive iodine scans should be counseled to pump and discard their milk for 48-72 hours before resuming breastfeeding. If needed, thyroid ultrasounds and fine needle aspirations may be done safely in the pregnant woman.

THYROID DISEASE IN PREGNANCY

Case Discussion

Case #1

Adapted from ACP workshop syllabus

A 24-year old white primigravida presents at 12 weeks gestation with weight loss and palpitations. She was well prior to the pregnancy with no prior medical or surgical problems. The first trimester has been complicated by marked nausea and vomiting. She has also had some vaginal bleeding, but no abdominal cramping. Physical examination reveals a smooth non-tender 25 gm thyroid. Her pulse is 120 per minute and regular. Her uterus is large for dates. She has no eye signs of hyperthyroidism or pretibial myxedema.

What differential diagnosis should be considered in this case?

What investigations should be undertaken to confirm the diagnosis?

The investigations confirm Graves Disease. Thyroid function testing shows free thyroxine 3.9 mg/dL (NR 0.8-1.9 mg/dL) (SI 50 pmol/L NR 11-25 pmol/L); TSH <0.1 microU/mL (SI <0.1 mU/L) and strongly positive TSH-receptor autoantibodies (Thyroid stimulating immunoglobulins, TS1, TSAB).

What are the implications of Graves Disease in pregnancy for (a) mother and (b) fetus?

What is the optimal treatment for Graves Disease in pregnancy, and how should treatment be monitored?

The patient is concerned about the fetal effects of treatment. What do you tell her?

After your discussion, the patient agrees to begin PTU 100 mg tid and a beta blocker. Her symptoms improve and the beta blocker is stopped. Periodic testing reveals a minimally elevated free T4 until she is at 27 weeks gestation when the free T4 comes back in the midnormal range. The patient also mentions that the obstetrician has ordered an ultrasound to “check the baby’s neck” but says she’s been told the fetal heart rate has been normal.

What is the likely explanation for the change in her thyroid function tests and do you make any changes in her medication?

What concern does the obstetrician have?

The fetal ultrasound reveals no evidence of goiter. The patient is ultimately taken off the PTU by the end of the pregnancy. She delivers a healthy 6lb 8oz baby boy at 39 weeks gestation who has no evidence of neonatal hyperthyroidism. Several weeks postpartum the patient redevelops symptoms of hyperthyroidism. She is breastfeeding.

Are PTU and methimazole compatible with breastfeeding?

The patient is restarted on PTU but ultimately has definitive treatment with radioactive iodine. Several years later she presents 10 weeks pregnant. She is on levothyroxine 100mcg/day and has been on a stable dose for one year.

The patient is concerned about the effects of her hypothyroidism on this pregnancy and is wondering if she should stop her levothyroxine. What do you tell her?

Do you expect any changes in the dose of her medication through the pregnancy?

Are there any potential complications from her Graves' Disease even though the thyroid has been ablated?

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Case Discussion

Case #2

P.W. a 27-year old white woman G₂P₂ presents to her physician, ten weeks after a normal delivery at term. You note she has had significant weight loss and is tachycardic. Her pregnancy was totally uneventful, and no medical or obstetrical abnormalities were detected at her 6 week postpartum check.

Physical examination shows B.P. 140/65, pulse rate 104 regular, fine tremor of the hands and a smooth firm non-tender 30 gm thyroid. She is still breastfeeding.

What is the differential diagnosis?

What testing should be performed to confirm the diagnosis?

What treatment should be considered before test results are available? Can she breast feed?

After treatment her tachycardia settles and tremor improves. Four weeks later she returns for review and is now complaining of fatigue and depression. Her pulse rate is 62/min., BP 140/90 and her thyroid remains non-tender at 35 gm size.

What are the possible causes of this woman's symptomatology?

What further investigations, treatment and follow-up should be considered?

One year later she returns for pre-pregnancy counseling. She is now requiring Thyroxine replacement therapy, but is clinically and biochemically euthyroid. Thyroid size is 15 gm.

What are the possible maternal and fetal hazards associated with primary hypothyroidism?

How should this woman be monitored both during a subsequent pregnancy and the postpartum phase?

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