Thyroid Disorders in Pregnancy

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ABSTRACT

Thyroid disorders are the second most common endocrine disorders affecting women of reproductive age. Disorders of thyroid hormone product affect fertility, pregnancy outcome, fetal growth and development.

Key words: Serum thyroxine binding globulin, free thyroxine, thyroid stimulating hormone, thyroid storm

Thyroid disorders are the second most common endocrine disorders affecting women of reproductive age, and obstetricians often care for patients who have been previously diagnosed with alterations in the thyroid gland function. Disorders of thyroid hormone production can affect fertility, fetal growth and development. The physiological changes during pregnancy such as increase in cardiac output, oxygen consumption and heat production may mimic mild thyrotoxicosis, may exacerbate or improve underlying thyroid disorder.

Thyroid Physiology During Pregnancy

It is imperative for physicians to be aware of changes that occur in thyroid physiology during pregnancy. In addition to changes in maternal thyroid elaboration, one also needs to keep in mind the fetal milieu (Table 1).

Maternal

- Serum thyroxine binding globulin (TBG) levels rise in pregnancy due to estrogen mediated increases in hepatic synthesis and greater sialation, with consequent decreased hepatic clearance of TBG.[1]
- High levels of deiodinases types II and III are found in the placental tissue, such that in pregnancy there is, proportionally, greater production of biologically inactive reverse tri-iodothyronine (rT3) than in non-pregnant state.[2]
- Normal pregnancy is associated with increased glomerular filtration rate, such that the renal clearance of iodides increases. This may be sufficient to decompensate women with marginal iodine deficiency, leading to goiter.[3,4]
- Serum free thyroxine (fT3) and thyroxine stimulating hormone (TSH) are considered as the most reliable indicators of thyroid function during pregnancy.[5]

Table 1. Changes in Thyroid Physiology in Pregnancy

- Serum TBG increases
- Total T_4 and T_3 rise
- Increased clearance of iodide
- Free T_3 and TSH are the best indicators of thyroid function

Fetal

The developing pituitary-thyroid axis is sufficiently mature to function, towards the end of the first trimester, with fetal derived T_4 detectable in blood from around 10 week's gestation.[2]

- Fetal serum levels of TSH, TBG, fT_4 and fT_3 increase throughout gestation, reaching mean adult levels at approximately 36 weeks of gestation.
- Placental transfer of thyroid occurs, which is explained by the fact that significant concentrations of T_4 and T_3 are detectable in blood of neonates unable to synthesize thyroid hormones due to congenital organification defects.[4]

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Physiological changes during pregnancy in the thyroid gland bring in alterations in the thyroid function tests (Table 2).[6] As already pointed out, there is 2- to 3-fold increase in TBG concentrations, 30-100% increase in total tri-iodothyronine and thyroxine concentrations, increased serum thyroglobulin and increased renal iodide clearance. Furthermore, hCG has mild thyroid stimulating activity.

Assessment of thyroid function during pregnancy should be done with a careful clinical evaluation of the patient's symptoms as well as measurement of TSH and free, not total, thyroid hormones[7] (Figs. 1 and 2).

Table 2. Changes in Thyroid Physiology in Pregnancy

Physiologic change	Resulting change in thyroid activity
↑ serum estrogen	↑ serum TBG
↑ serum TBG	↑ demand for T_4 and T_3
	↑ total T_4 and T_3
↑ hCG	↓ THS, ↑ fT_4
	↑ in dietary requirement of iodides
↑ iodine clearance	↓ hormone production in iodide deficient areas
	↑ goiter in iodide-deficient areas
↑ type III deiodinases	↑ T_3 and T_4 degradation, demand for T_3 and T_4
↑ demand for T_3 and T_4	↑ serum thyroglobulin
	↑ thyroid volume
	↑ goiter in iodide deficient areas

Hyperthyroidism in Pregnancy

The incidence of hyperthyroidism in pregnant women has been estimated at 0.2%.[8] The causes of hyperthyroidism during pregnancy are the same as those seen in general population and in addition, one should also consider pregnancy-specific conditions such as hyperemesis gravidarum and hydatidiform mole (Table 3). The most common cause of hyperthyroidism in pregnancy is Graves' disease, which accounts for 85-90% of all cases.[8,9]

Clinical features of hyperthyroidism include nervousness, tremors, tachycardia, frequent stools, excessive sweating, heat intolerance, weight loss, goiter, insomnia, palpitations and hypertension. The distinctive signs of Graves' disease are lid lag and lid retraction indicating ophthalmopathy, and localized or pretibial myxedema which suggests dermopathy.

Table 3. Causes of Hyperthyroidism in Pregnancy

Graves's disease (85-90% of all cases)
Subacute thyroiditis
Toxic multinodular goiter
Toxic adenoma
TSH-dependent thyrotoxicosis
Exogenous T_3 or T_4
Iodine-induced hyperthyroidism
Pregnancy-associated associations
• Hyperemesis gravidarum
• Hydatidiform mole

Source: Mestman, et al[8] and Bishnoi and Sachmechi.[9]

Diagnosis of Graves' disease can be very difficult because women with no thyroid dysfunction may also exhibit tachycardia, palpitations, mild heat intolerance, emotional lability and warm moist skin. It is necessary to diagnose hyperthyroidism, if present, during pregnancy because untreated or poorly-treated hyperthyroidism can lead to adverse obstetrical outcomes. Clinical suspicion with relevant laboratory testing and their informed interpretation assume importance.

Laboratory testing should include the measurement of serum TSH. It should be remembered that values for total T_3 and T_4 will be increased in healthy pregnant women, and instead assessment of free hormone values be carried out. Routine laboratory tests in hyperthyroid patients may show mild leucopenia, hypocalcemia (in <10% of patients), increased alkaline phosphatase, and occasionally mild-to-moderate elevation in other liver enzymes.[8]

Inadequately treated hyperthyroidism is associated with an increase in preterm deliveries, low birth weight babies and fetal losses. Inadequately treated maternal thyrotoxicosis is associated with a greater risk of preterm delivery, severe pre-eclampsia and heart failure than in treated and controlled maternal thyrotoxicosis[10,11] (Table 4).

Treatment

The goal of treatment of hyperthyroidism during pregnancy is to keep the patient euthyroid with the fT_4 in the upper limit of normal range so as not to cause

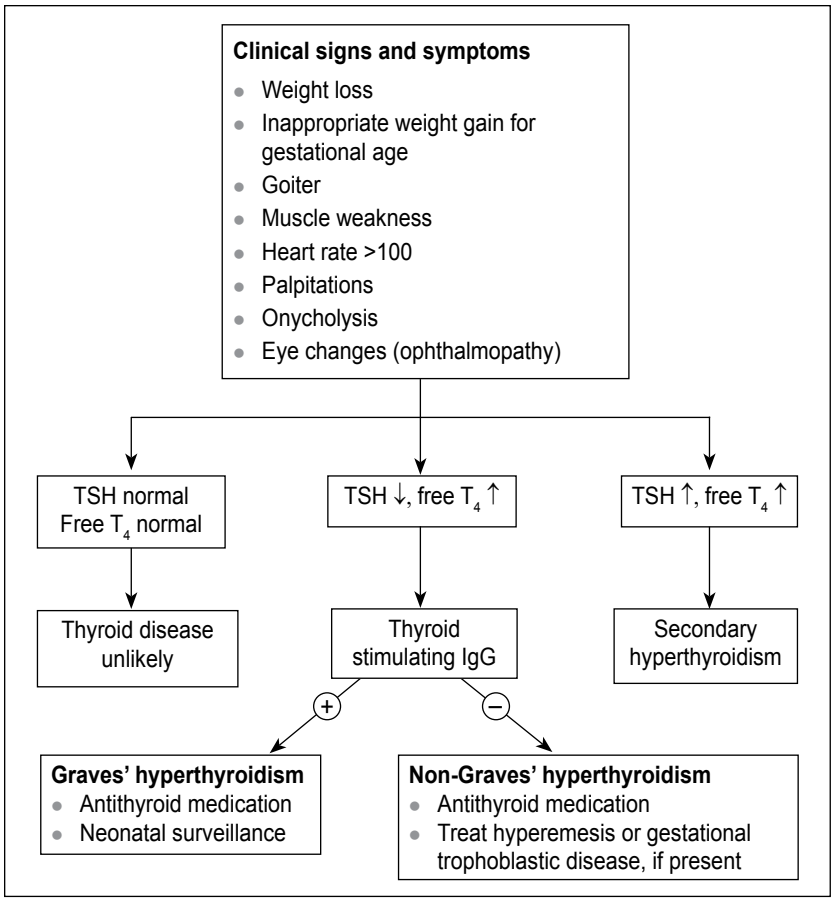

Figure 1. Algorithm for the evaluation of hyperthyroidism during pregnancy.
Source: Fantz, et al 7

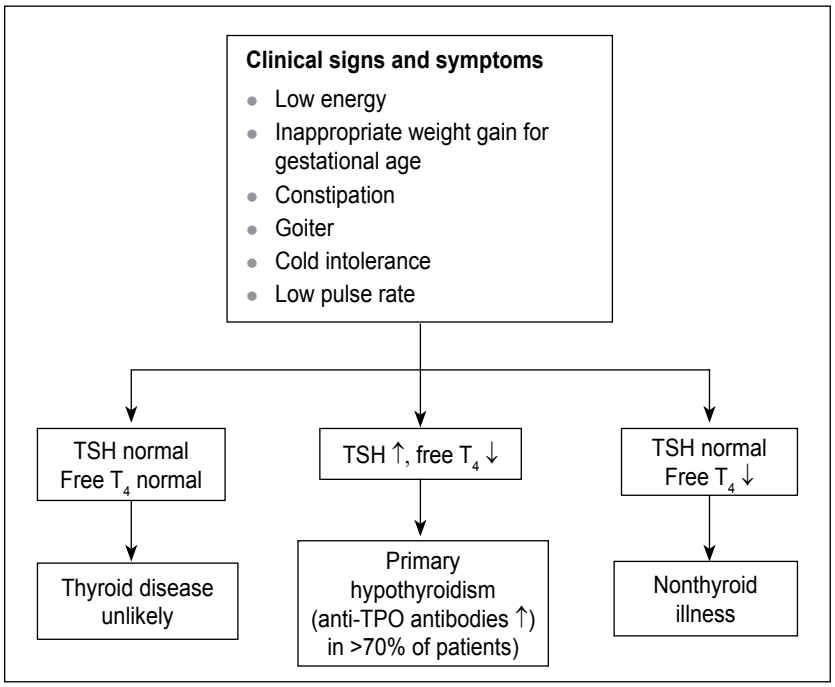

Figure 2. Algorithm for the evaluation of hypothyroidism during pregnancy.
Source: Fantz, et al 7.

fetal or neonatal hypothyroidism.[12] Medical management[13] of hyperthyroidism in pregnancy can include:

Thioamides

Thioamides specifically propylthiouracil (PTU) given 100-150 mg every 8 hours not exceeding 450 mg a day depending upon the severity of the disease is given. Methimazole (15-30 mg/day, as a single dose) can also be used. These drugs decrease thyroid hormone synthesis by blocking the organification of iodide. The described side effects are agranulocytosis, rash (5%), pruritus, hepatitis, lupus-like syndrome, drug fever, bronchospasm and aplasia cutis. Choanal atresia/esophageal atresia could be a manifestation of methimazole embryopathy

β-blockers

β-blockers to control adrenergic symptoms. Propranolol (20-40 mg, two or three times a day) or atenolol (50-100 mg daily) may be used if necessary.[12] Prolonged therapy has been associated with fetal growth restriction, fetal bradycardia and hypoglycemia.

Iodides

Iodides such as potassium iodide, 5-10 drops, twice daily, along with thioamides and β-blockers are used to treat thyroid storm. Iodides readily cross the placenta and may cause fetal goiter, therefore, their use should be minimized for only short-term (<2 weeks).

Thyroidectomy

Thyroidectomy should be reserved for women in whom treatment with thioamides is unsuccessful. It is best performed in the second trimester.

Table 4. Complications of Hyperthyroidism During Pregnancy

First-trimester spontaneous abortions
Preterm deliveries
Low brith weight infants
Still births and neonatal deaths
Fetal and neonatal hyperthyroidism
Fetal growth restriction

Source: Mestman, et al[8] and Bishnoi and Sachmechi.[9]

Two weeks of iodine therapy given along with PTU will reduce the size and vascularity before surgery.

Radioactive Iodine

Radioactive iodine (^{131}iodine [^{131}I]) is contraindicated in pregnant women because of the risk of fetal thyroid ablation; therefore, women should avoid pregnancy for at least four months after ^{131}I treatment. Counseling of women exposed to ^{131}I in pregnancy should focus on the gestational age of exposure. If the woman was <10 weeks of gestation at the time of exposure, then it is unlikely that the fetal thyroid is ablated. If the exposure occurred at or after 10 weeks of gestation, one must consider the risk of induced congenital hypothyroidism while deciding to continue pregnancy. Breastfeeding is better avoided[14] for at least 120 days after treatment with ^{131}I.

It may take 6-8 weeks to see a clinical change. In these patients fT_4 levels should be monitored monthly and after the mother is euthyroid, the dosage of the antithyroid drug be tapered to a minimum to prevent fetal hypothyroidism.

Thyroid Storm

Thyroid storm during pregnancy is a medical emergency characterized by an extreme hypermetabolic state. It is rare, seen in 1% of pregnant patients with hyperthyroidism, but has a high risk of maternal heart failure.[10] Clinical features of thyroid storm are tachycardia out of proportion to fever, vomiting, diarrhea and cardiac arrhythmias. There will be restlessness, confusion and at times may manifest with seizures.

When thyroid storm is suspected, serum fT_3, fT_4 and TSH levels should be evaluated to confirm the diagnosis, but therapy should not be withheld pending the results.[15] Treatment of thyroid storm in pregnant women include thioamides, any of the iodine solutions or lithium carbonate, dexamethasone and β-blockers (Table 5).[16,17] Thioamides, as already described, block the additional synthesis of thyroid hormone from the gland, and PTU also blocks the peripheral conversion of T_4 to T_3. Saturated solution of potassium iodide and sodium iodide block the release of thyroid hormone from the gland. Dexamethasone decreases thyroid hormone release and peripheral conversion of T_4 to T_3, and propranolol inhibits the adrenergic effects of excessive thyroid hormone. Phenobarbital can be used to reduce extreme agitation or restlessness and may increase the catabolism of thyroid hormones.[17] Maternal supportive measures in the form of oxygen, intravenous fluids, electrolyte replacement and antipyretics may be needed. Fetal status should be assessed with ultrasound, biophysical profile or non-stress test, depending upon the gestational age. Delivery should be reserved for fetal indications that outweigh the risks to the woman. These patients should be cared for in labor and delivery in intensive care unit.

Fetal and Neonatal Thyrotoxicosis

Fetal and neonatal thyrotoxicosis is seen in approximately 1% of infants who are born to mothers with Graves'

Table 5. Treatment of Thyroid Storm During Pregnancy

Propylthiouracil (PTU): 600-800 mg orally, stat, then 150-200 mg orally every 4-6 hourly. If oral administration is not possible, use methimazole rectal suppositories
Starting 1-2 hours after PTU administration
• Saturated solution of potassium iodide (SSKI), 2-5 drops orally every 8 hours or
• Sodium iodide, 0.5-1.0 g IV every 8 hours *or*
• Lugol's solution, 8 drops every 6 hours, *or* • Lithium carbonate, 300 mg orally every 6 hours
Dexamethasone, 2 mg IV or IM every 6 hours for 4 doses
Propranolol: 20-80 mg orally every 4-6 hours or 1-2 mg IV every 5 minutes for a total of 6 mg, then 1-10 mg IV every 4 hours
If the patient has a history of severe bronchospasm: Reserpine 1-5 mg IM every 4-6 hours; guanethidine 1 mg/kg orally every 12 hours; diltiazem 60 mg orally every 6-8 hours
Phenobarbital 30-60 mg orally every 6-8 hours as needed for extreme restlessness.

disease secondary to transplacental transfer of maternal thyroid stimulating immunoglobulins (TSIs).[18] These antibodies can be present even after surgery or ^{131}I treatment and can activate the fetal thyroid. This unusual situation does not necessarily correlate with the presence of active disease in the mother. The earliest sign of fetal thyrotoxicosis is a tachycardia >160 bpm; other features being growth retardation and craniosynostosis. Occasionally, fetal hydrops and death can occur. Maternal TSI in excess of 300% of control values are predictive of fetal hyperthyroidism.

Neonatal features include hyperkinesis, poor weight gain, vomiting, arrhythmias, exophthalmos, hepatosplenomegaly, craniosynostosis and heart failure. Affected neonates are treated with β-blockers, PTU and iodine, and digoxin as needed.

Hypothyroidism During Pregnancy

The incidence of hypothyroidism in pregnant women has been estimated to be 0.3-0.7%.[19] There is a well-known association between hypothyroidism and decreased fertility.[20] Causes of hypothyroidism during pregnancy could be iodine deficiency, infiltrative diseases like sarcoid or amyloidosis, primary atrophic or TSH dependent hypothyroidism. Autoimmune thyroid disease (Hashimoto thyroiditis) and post-thyroid ablation are the most common causes of hypothyroidism.[8]

The complications associated with hypothyroidism in pregnancy are pre-eclampsia, placental abruption, post partum hemorrhage and increased frequency of low birth weight infants.[8]

Clinical Recommendations

The American College of Obstetricians and Gynecologists (ACOG) has recommended the following guidelines.[15]

- **Level A** (recommendations are based on good and consistent scientific evidence)
  - Levels of TSH or fT_3, fTI (free thyroid index) should be monitored to manage thyroid disease in pregnancy
- **Level B** (recommendations are based on limited or inconsistent scientific evidence)
  - Either PTU or methimazole can be used to treat pregnant women with hyperthyroidism
  - Thyroid function tests are not indicated in asymptomatic pregnant women with slightly enlarged thyroid glands
- **Level C** (recommendations are based primarily on consensus and expert opinion)
  - Thyroid nodules should be investigated during pregnancy to rule out malignancy
  - Indicated testing of thyroid function may be performed in women with a personal history of thyroid disease or symptoms of thyroid disease
  - Pediatrician should be present at the time of delivery of woman with thyroid disease.

Key Practice Points

- TSH and fT_3 are useful investigations in the management of thyroid disorders during pregnancy and not total T_3 or T_4.
- Graves' disease is the commonest cause of hyperthyroidism in pregnancy.
- Thioamides (PTU or methimazole) are the first-line drugs in the management of hyperthyroidism during pregnancy.
- Radioactive ^{131}I therapy is contraindicated in the management of hyperthyroidism during pregnancy.
- Thyroid storm is a medical emergency which needs to be anticipated and treated aggressively during pregnancy.
- Hashimoto thyroiditis is the most common cause of hypothyroidism in pregnancy.
- Thyroxine, in the initial dose of 0.1-0.15 mg is the drug of choice during pregnancy.
- Dosage of thyroxine is adjusted every four weeks to keep the TSH levels at the lower limit of normal.
- Ferrous sulfate and thyroxine dosages should be spaced 4 hours apart.
- Thyroid nodule needs to be evaluated during pregnancy.

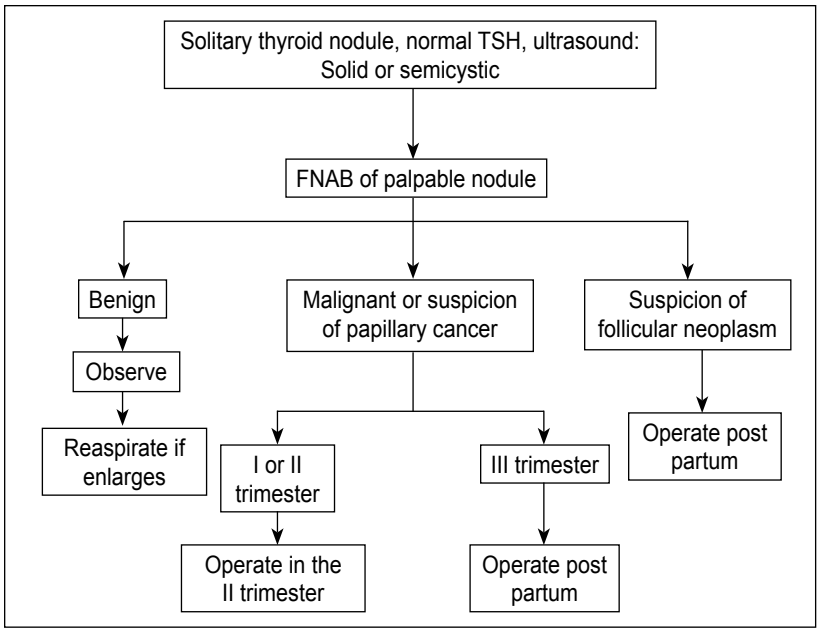

Figure 3. Showing the algorithm of evaluation of thyroid nodule in pregnancy.
Source: Tan GH, et al 24.

Laboratory evaluation of hypothyroidism includes measurement of TSH and an assessment of free hormone values. Total T_4 and T_3 measurements are considered unreliable due to the increase in the TBG concentrations. In hypothyroidism, TSH can be elevated with or without suppressed levels of fT_4. Anti-TPO antibodies and anti-thyroglobulin antibodies are increased in most patients with Hashimoto thyroiditis and therefore may be useful in establishing this diagnosis. Other laboratory abnormalities include elevated creatinine phosphokinase, cholesterol and liver function tests.

Treatment

Treatment should begin as soon as the diagnosis of hypothyroidism[21] is made. Replacement of thyroxin should begin with 0.1 mg/day to 0.15 mg/day. The dosage is adjusted every four weeks to keep the TSH at the lower end of the normal. TSH and fT_3 levels are to be monitored every eight weeks. T_4 requirements most likely will increase as the pregnancy progresses, which is secondary to the increased demand for T_4 during pregnancy and probably the inadequate intestinal absorption that is caused by ferrous sulfate. During pregnancy, ferrous sulfate and thyroxine dosages should be spaced at least 4 hours apart.[12]

Thyroid Nodules, Malignant Tumors, Non-toxic Goiter

Most thyroid nodules are benign hyperplasic (or colloid) nodules. However, between 5-20% are true neoplasms, benign adenomas or carcinomas.[22] The incidence of thyroid cancer in pregnancy is 1/1,000.[23] Any thyroid nodule discovered during pregnancy should be evaluated (Fig. 3),[24] because malignancy will be found in upto 40% of these nodules.[14] Fine needle aspiration biopsy (FNAB) is safe in pregnancy and can be performed at any stage. It should be performed on solitary and dominant thyroid nodule. Benign lesions are best left to be kept under observation. Suspicion of or malignant lesions diagnosed in early pregnancy can be operated in second trimester and for those diagnosed late any intervention can wait till delivery.

References

1. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine binding globulin (TBG) with increased sialation; a mechanism for estrogen induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65:689-96.
2. Burrow GN. Maternal and fetal thyroid function. N Engl J Med 1994;331:1072-7.
3. Nelson M, Wickus GG, Caplan RH, Begui EA. Thyroid gland size in pregnancy: An ultrasound and clinical study. J Reprod Med 1987;32:888-90.
4. Vulsma T, Gons MH, de Vijlder JM. Maternal–fetal transfer of thyroxine in congenital hypothyroidism due to total organification defect of thyroid agenesis. N Engl J Med 1989;321:13-6.
5. Drake WM, Wood DF. Thyroid disease in pregnancy. Postgrad Med J 1998;74:583-6.
6. Brent GA. Maternal thyroid function: interpretation of thyroid tests in pregnancy. Clin Obstet Gynecol 1997;40:3-15.
7. Fantz CR, Jack SD, Ladenson JH, Gronowski AM. Thyroid function during pregnancy. Clin Chem 1999;45:2250-8.
8. Mestman J, Goodwin TM, Montoro MM. Thyroid disorders of pregnancy. Endocrinol Metab Clin N Am 1995;24:41-71.

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2. Adler JT, Meyer-Rochow GY, Chen H, Benn DE, Robinson BG, Sippel Rs, et al. Pheochromocytoma: current approaches and future directions. Oncologist 2008;13(7):779-93.
3. Luo A, Guo X, Ren H, Huang Y, Ye T. Clinical features and anesthetic management of multiple endocrine neoplasia associated with pheochromocytoma. Chin Med J (Engl) 2003;116(2):208-11.
4. Pacak K, Linehan WM, Eisenhofer G, Walther MM, Goldstein DS. Recent advances in genetics, diagnosis, localization, and treatment of pheochromocytoma. Ann Intern Med 2001;134(4):315-29.
5. Menger WM, Gifford RW Jr. Clinical and experimental pheochromocytoma. Cambridge, MA: Blackwell Science; 1996.
6. Sandur S, Dasgupta A, Shapiro JL, Arroliga AC, Mehta AC. Thoracic involvement with pheochromocytoma: a review. Chest 1999;115(2):511-21.
7. Whalen RK, Althausen AF, Daniels GH. Extra-adrenal pheochromocytoma. J Urol 1992;147(1):1-10.
8. Plouin PF, Chatellier G, Fofol I, Corvol P. Tumor recurrence and hypertension persistence after successful pheochromocytoma operation. Hypertension 1997;29: 1133-9.
9. Scott HW Jr, Halter SA. Oncologic aspects of pheochromocytoma: the importance of follow-up. Surgery 1984;96(6):1061-6.
10. d'Herbomez M, Gouze V, Huglo D, Nocaudie M, Pattou F, Proye C, et al. Chromogranin A assay and (131)I-MIBG scintigraphy for diagnosis and follow-up of pheochromocytoma. J Nucl Med 2001;42(7):993-7.

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9. Bishnoi A, Sachmechi I. Thyroid disease in pregnancy, Am Family Physician 1996;53:215-20.
10. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy Am J Obstet Gynecol 1989;160:63-70.
11. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH. Low birth weight and pre-eclampsia in pregnancies complicated by hyperthyroidism. Obstet Gynecol 1994;84:946-9.
12. Neale D, Burrow G. Thyroid disease in pregnancy. Obstet Gynecol Clin N Am 2004;31:893-905.
13. Gittoes NJ, Franklyn JA. Hyperthyroidism. Current treatment guidelines. Drugs 1998;55:543-53.
14. McClellan DR, Francis GL. Thyroid cancer in children, pregnant women and patients with Graves' disease. Endocrinol Metabol Clin North Am 1996;25:27-48.
15. ACOG practice bulletin. Thyroid disease in pregnancy No. 37. Int J Obstet Gynecol 200;79:171-80.
16. Ecker JL, Musci TJ. Thyroid function and disease in pregnancy. Curr Probl Obstet Gynecol Fertil 2000;23:109-22.
17. Molitch ME. Endocrine emergencies in pregnancy. Baillieres Clin Endocrinol Metabol 1992;6:167-91.
18. Weetman AP. Graves' disease. N Engl J Med 2000;343:1236-48.
19. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997;18:404-33.
20. Peterson M. Thyroid disease and fertility. Immunol Allergy 1994;14:725-38.
21. Mulder JE. Thyroid disease in women. Med Clin N Am 1998;82:103-25.
22. Nader S. Thyroid and other endocrine disorders during pregnancy. Obstet Gynecol Clin N Am 2004;31:257-85.
23. Moosa M, Mazzaferri EL. Outcome of differentiated thyroid cancer diagnosed in pregnant women. J Clin Endocrinol Metabol 1997;82:2862-66.
24. Tan GH, Gharib H, Goellner JR, VanHeerden JA, Bahn RS. Management of thyroid nodules in pregnancy. Arch Intern Med 1996;156:2317-20.