Hyperthyroidism during pregnancy: Treatment

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gestetinal trasient thyrotoxicosisは治療の必要はない
潜在性やmildも治療の必要はない、１か月毎のモニタリング
Free T4が明らかに増加、又はTotal T4,T3が上限の1.5倍以上の時、治療
治療の原則はfree T4が上限が目標で薬は最小量、βーブロッカーは禁忌
　total T4は18mcg/dl(50%増）が目標
　TSHは妊娠を通じてlowかundetective
　結局、プロパジールは100m分2、メルカゾールは2.5m分１が目標
奇形の発生率（Japan)
メルカゾール；4.1%　プロパジール；1.9%　コントロール；2.1%
肝障害
　メルカゾールは閉塞性
　プロパジールは肝細胞性で突然発症、常に患者教育が必要
中期に入ったら、プロパジールはメルカゾールに変更（1/20～1/30)
　変更後は２～３週毎にモニター
　もし発疹が出現の場合はプロパジールに再度、変更
後期では３人に１人は薬が不要（TRabが低値になるから）
授乳はメルカゾールは心配ないが、授乳後に服用も一法
新生児の甲状腺機能亢進症は1～5%
　妊娠２０週でTRabかTBIIを測定、３倍以上で新生児のモニタリングが必要
出産後の再炎は殆どが出産後の４～８か月後に出現
　出産後は84%、一般的には５６％

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hCG-me e treatment.
Similarly nt because it is
mild and subsides as hCG production falls (typically by 14 to 18 weeks gestation). Women with severe hyperemesis, however, require treatment of dehydration with intravenous fluids. (See "Treatment and outcome of nausea and vomiting of pregnancy".)

Pregnant women with subclinical (low TSH, normal free T4) and mild asymptomatic overt hyperthyroidism due to Graves' disease may be followed with no treatment. This includes women with a low TSH and minimal elevation in total T4 and/or total T3 ([<1.5 times the upper limit of the nonpregnant normal] or minimal elevation in trimester-specific free T4). In women who are being monitored without therapy, we measure TSH, free T4 (if there is a trimester-specific reference range), and/or total T4 or total T3 every four to six weeks.

Women with symptomatic moderate to severe overt hyperthyroidism due to Graves' disease or gestational trophoblastic disease require treatment of hyperthyroidism. This includes women with total T4 and/or total T3 >1.5 times the upper limit of the nonpregnant normal, or women with marked elevation in trimester-specific free T4 levels. Although hyperthyroidism due to gestational trophoblastic disease resolves with treatment of the underlying gestational trophoblastic disease and subsequent normalization of hCG levels, symptomatic women require treatment prior to surgery. (See "Nonthyroid surgery in the patient with thyroid disease", section on 'Preoperative preparation for urgent surgery'.)

Therapeutic options — The therapeutic options for hyperthyroid women are limited because of the potential adverse fetal effects of the available treatments.

Thionamides are the primary treatment of hyperthyroidism due to Graves' or gestational trophoblastic disease. They are actively transported into the thyroid gland where they inhibit both the organification of iodine to tyrosine residues in thyroglobulin and the coupling of iodotyrosines. In addition, beta blockers, such as atenolol or propranolol, can be used to treat tachycardia and tremor. However, long-term treatment with beta blockers (longer than two to six weeks) should be avoided because of concerns regarding fetal growth retardation and hypoglycemia [4-6].

Radioiodine is absolutely contraindicated during pregnancy [7]. Fetal thyroid tissue is present by 10 to 12 weeks and therefore can be ablated by radioiodine. Many experienced clinicians, however, have encountered one or two women

inadvertently treated with radioiodine during early pregnancy; the anecdotal impression is that radioiodine given before about 8 to 10 weeks of pregnancy does not cause fetal hypothyroidism or birth defects. In one systematic review, the risks to the fetus were dependent upon the timing of exposure during pregnancy [8]. Spontaneous miscarriage was more likely when exposure (100 mGy) occurred during the first two weeks (prior to implantation). Exposure during organogenesis (from two weeks gestation) may result in birth defects. After fetal thyroid has developed the capacity to capture iodine (12 to 14 weeks), there is a risk of fetal thyroid ablation and the attendant effects on neurocognitive development. If treatment is given during pregnancy, there needs to be full disclosure. Depending on the couple's wishes, termination of pregnancy might be considered.

Thyroidectomy during pregnancy is rarely necessary but is an option for women who cannot tolerate thionamides because of allergy or agranulocytosis (see 'Surgery' below). Plasmapheresis has also been used to rapidly control hyperthyroidism in women with trophoblastic disease and severe hyperthyroidism [9,10].

A good fetal and maternal outcome depends upon controlling the mother's hyperthyroidism. The goal of treatment is to maintain the mother's serum free T4 concentration at or just above the trimester-specific normal range for pregnancy using the lowest possible dose. If a trimester-specific reference range is not available, free T4 should be maintained in the high-normal range for nonpregnant women using the lowest drug dose [11]. This requires assessment of thyroid function frequently (ie, at four-week intervals) with appropriate adjustment of medication.

Beta blockers — Beta blockers may be given to ameliorate the symptoms of moderate to severe hyperthyroidism in pregnant women. We typically start with atenolol 25 to 50 mg daily. Propranolol, 20 mg every six to eight hours, is an alternative option. The dose can be increased as needed to control symptoms. However, if possible, beta blockers should be weaned as soon as the hyperthyroidism is controlled by thionamides because occasional cases of neonatal growth restriction, hypoglycemia, respiratory depression, and bradycardia have been reported after maternal administration [4,5,12]. There are no data directly comparing the effect of atenolol versus propranolol on birth weight. In a retrospective analysis, women with chronic hypertension who used atenolol in early (15 weeks gestation) compared with late (30 weeks gestation) pregnancy had significantly smaller babies [4]. There has been one report suggesting a higher rate of spontaneous abortion for hyperthyroid women treated with both a thionamide and propranolol compared with a thionamide alone [13]. In most patients, beta blockers can and should be tapered and discontinued within two to six weeks. (See "Beta blockers in the treatment of hyperthyroidism" and "Treatment of Graves' hyperthyroidism", section on 'Beta blockers'.)

Thionamides — Thionamides are recommended for treatment of moderate to severe hyperthyroidism complicating pregnancy. Available thionamides include propylthiouracil (PTU), methimazole (MMI), and carbimazole (CBZ), which is completely metabolized to MMI.

Both methimazole (MMI) and propylthiouracil (PTU) probably cross the placenta with equal transfer kinetics [14] and have similar effects on the fetus [15,16]. In one report of 77 newborns of euthyroid mothers treated with PTU or MMI, there were no significant differences in TSH concentrations measured in cord blood at birth [16]. However, mean cord TSH levels were higher in neonates exposed to PTU, but not methimazole, compared with control neonates who were not exposed in utero to thionamides.

Low thyroid function at birth is found in approximately one-half of neonates whose mothers received PTU or MMI during pregnancy and who had serum T4 concentrations within the normal (nonpregnant) range [17]. In spite of these observations, two studies reported that the IQ scores of children who were exposed to thionamides in utero (but were euthyroid at birth) were normal [18,19].

Possible teratogenicity — Methimazole and carbimazole have been associated with possible teratogenic effects including case reports of aplasia cutis, a scalp defect, in newborns of mothers treated with (or exposed to) MMI [20-22]. (See "Vesiculobullous and pustular lesions in the newborn", section on 'Aplasia cutis congenita'.) More serious congenital malformations, such as tracheoesophageal fistulas, patent vitellointestinal duct, choanal atresia, omphalocele, and omphalomesenteric duct anomaly, have been observed with maternal MMI and carbimazole, but not PTU use [22-32].

The following illustrates the range of observations:

- In the UK, spontaneous reporting of adverse drug reactions over a 47-year period found 57 cases with 97 anomalies for carbimazole, and only six cases with 11 anomalies for PTU; however, the relative use of these two drugs in pregnant women is unknown [30].
- In a population-based study from Taiwan, there was no increased risk of congenital anomalies among babies of hyperthyroid women treated with either PTU (n = 630 women) or methimazole (n = 73 women) [33]. The small number of methimazole-treated women may have made this study underpowered to detect a teratogenic effect.

- In a Japanese study of pregnant women with Graves' disease, 50 of 1231 patients (4.1 percent) treated with methimazole, 12 of 1399 (1.9 percent) treated with PTU, and 40 of 1906 (2.1 percent) who did not receive antithyroid drugs had congenital malformations [31].

- In a registry-based cohort study from Denmark (817,093 live-born infants, 1820 exposed to antithyroid drugs), the prevalence of birth defects was significantly higher in children exposed to any antithyroid drug (8.0, 9.1, 10.1, and 5.4 percent for PTU, methimazole/carbimazole [MMI/CMZ], both PTU and MMI/CMZ, and no ATD use in early pregnancy, respectively) [32]. MMI/CMZ and PTU were associated with urinary system malformation, and PTU with malformations in the face and neck region. Choanal atresia, esophageal atresia, omphalocele, omphalomesenteric duct anomalies, and aplasia cutis were common in MMI/CMZ-exposed children.

Choice of drug — In the past, PTU was considered the drug of choice throughout pregnancy for women with hyperthyroidism, because of concerns about the possible teratogenic effects of MMI [34].

However, reports of severe PTU-related liver failure have now raised concerns about the routine use of PTU, including the use of PTU in pregnancy [35]. Methimazole has also been associated with liver disease, but it is typically due to cholestatic dysfunction, not hepatocellular inflammation.

We agree with the change in recommendations for antithyroid drugs as outlined by the American Thyroid Association, the Endocrine Society, and the US Food and Drug Administration [1,3,35,36]:

- We recommend that PTU **not** be used as a first-line drug in children or adults [35,36]. (See "Pharmacology and toxicity of thionamides", section on 'Hepatotoxicity'.)

- For pregnant women with hyperthyroidism, we suggest that PTU use be limited to the first trimester only. Although the teratogenic effects of MMI are not well proven, they are potentially serious and are likely confined to the first trimester during organogenesis. After the first trimester, the potential risk of PTU-associated hepatotoxicity, although extremely rare, is thought to outweigh any potential risks of MMI. Women who are taking MMI and learn they are pregnant should be switched to PTU at the time of the positive pregnancy test.

- In the second trimester, we suggest switching from PTU to an equivalent dose of MMI. Although the ratio of potencies of PTU and MMI is uncertain, clinical experience suggests that methimazole is 20 to 30 times as potent on a milligram to milligram basis. Therefore, 300 mg of PTU would be roughly equivalent to 10 or 15 mg of MMI. Thyroid function testing should be performed two to four weeks after switching to methimazole to be sure that a euthyroid state has been maintained.

- Subsequent monitoring of thyroid function should be performed every four weeks. Extra caution is necessary after switching from PTU to MMI to avoid maternal overtreatment and fetal hypothyroidism. (See 'Dose and monitoring' below.)

PTU-associated liver failure, which can occur at any time during the course of treatment, has a sudden onset and a rapidly progressive course. Therefore, routine monitoring of liver function is not currently suggested by the ATA and FDA. Patients should be advised to stop their medication and contact their clinician if they develop weakness, malaise, nausea and vomiting, jaundice, dark urine or light-colored stools.

Some clinicians and their patients prefer to monitor liver function every four weeks when blood is being drawn to assess thyroid function. If this approach is chosen, PTU should be discontinued if serum transaminases are greater than three times the upper limit of normal. This approach has not been shown to reduce the risk of PTU-associated liver failure. Once the drug is discontinued, the patient should be followed closely with frequent transaminase measurements to be sure that they are returning to normal. If they progressively rise, immediate referral to a clinician with expertise in liver disease is recommended.

- If the patient develops a rash when switched to MMI, the drug should be stopped and PTU resumed.

- Autoimmune thyroid disease frequently ameliorates in the third trimester. Whenever possible, based on assessment of thyrotropin antibody measurements and thyroid function tests, thionamides should be tapered and potentially discontinued during the third trimester.

Dose and monitoring — To minimize the risk of hypothyroidism in the fetus, we give the lowest dose of thionamide (PTU 50 mg two to three times daily, MMI 5 to 10 mg daily, or carbimazole 5 to 15 mg daily) necessary to control thyroid function. However, in patients with severe hyperthyroidism, full initial doses may be required (PTU 100 mg three times per day) or MMI (10 to 30 mg daily) to control hyperthyroidism.

Thyroid function tests (TSH and free T4 or total T4 if a trimester specific reference range is not available for free T4) should

be obtained every four weeks and more frequently immediately after switching antithyroid drugs. Our goal is to maintain persistent but minimal mild hyperthyroidism in the mother in an attempt to prevent fetal hypothyroidism [17]. Transient central hypothyroidism may be seen in infants whose mothers had poorly controlled hyperthyroidism during pregnancy, presumably due to suppression of the fetal pituitary-thyroid axis [37]. On the other hand, overtreatment of maternal hyperthyroidism can cause fetal hypothyroidism and goiter.

The thionamide dose should be adjusted monthly to maintain serum free T4 concentrations at or just above the upper limit of normal, using a trimester-specific reference range. If trimester–specific normal ranges are not available, free T4 should be maintained in the high-normal range for nonpregnant women, or total T4 up to 18 mcg/dL (50 percent above the upper limit of normal for nonpregnant women), and serum TSH concentrations in the low-normal or suppressed range. Serum TSH levels may remain low or undetectable throughout pregnancy.

Ultimately, low doses of PTU or MMI (eg, 50 mg twice daily or less for PTU; 2.5 to 5 mg a day for MMI) may be all that is required [38]. It is possible to discontinue the thionamide during the third trimester in at least one-third of women [38]; the amelioration of hyperthyroidism as pregnancy progresses is due to a fall in serum TSH receptor-stimulating antibody concentrations or, rarely, a rise in TSH receptor-blocking antibodies [39,40]. However, Graves' hyperthyroidism can worsen postpartum. (See 'Postpartum issues' below.)

Monitoring throughout pregnancy is important because maternal hyperthyroidism in the third trimester may increase the risk of low birth weight (independent of the risk of neonatal Graves' disease). As an example, in a study of 181 women with a current or past history of hyperthyroidism, the risk of low birth weight was increased fourfold in the 35 women who had clinical and biochemical evidence of hyperthyroidism in the third trimester [41].

Nursing — PTU is less soluble than MMI and is more bound to plasma proteins, whereas MMI is free in serum, so that relatively more MMI reaches the infant via breast milk [42]. However, the doses of MMI are lower, so the actual milk levels are not that different. Nonetheless, there is little difference in serum thyroid hormone concentrations or thyroid function in infants of mothers given moderate doses of either drug. As an example, in a study of 139 mothers taking up to 20 mg MMI daily, thyroid function, growth, and development of their breast-fed infants were normal [43]. Similar results were seen in a study of mothers taking PTU [44].

There has yet to be a report of agranulocytosis in an infant who was nursed by a woman taking PTU or MMI.

Both methimazole and PTU have been rated as safe for nursing mothers by the American Academy of Pediatrics [45]. However, given the concerns about potential PTU-associated hepatotoxicity, we suggest methimazole rather than PTU for nursing mothers. Methimazole should be administered following a feeding in divided doses. When the maternal dose of MMI is >20 mg daily, infants should have thyroid function tests assessed after one and three months.

T4 administration — We do not recommend the use of T4 with thionamide therapy during pregnancy. Little T4 crosses the placenta, making it more difficult to determine the minimal dose of thionamide needed to control hyperthyroidism in the mother.

Iodine — We do not generally recommend the use of pharmacologic doses of iodine in pregnant women, but its short-term use could be considered in patients being prepared for thyroidectomy when thionamides are contraindicated. One study of 35 women with mild to moderate Graves' hyperthyroidism suggested that low doses of iodine are safe during pregnancy [46]. Prolonged high-dose iodine therapy, however, can cause fetal goiter [47].

Surgery — Thyroidectomy during pregnancy may be necessary in women with Graves' disease who cannot tolerate thionamides because of allergy or agranulocytosis. The indications for surgery are similar to those in nonpregnant women and men. Surgery during pregnancy, however, is associated with an increased risk of spontaneous abortion or premature delivery [48] and significantly higher rates of surgical complications than nonpregnant women [49]. These risks are minimized by operating during the second trimester. (See "Management of the pregnant patient undergoing nonobstetric surgery", section on 'Timing'.)

Prior to thyroidectomy, pregnant women with intolerance to thionamides should be pretreated with beta-blockers (atenolol or propranolol) and a short course (ie, 7 to 10 days) of potassium iodine solution (35 to 50 mg iodine per drop, 1 to 3 drops daily). Iodine lowers serum thyroid hormone concentrations acutely and, in addition, decreases thyroid gland vascularity. (See "Surgery in the treatment of hyperthyroidism: Indications, preoperative preparation, and postoperative follow-up", section on 'Preoperative preparation'.)

FETAL HYPERTHYROIDISM — Approximately 1 to 5 percent of mothers with hyperthyroidism caused by Graves' disease (active or treated) have neonates (or fetuses) with hyperthyroidism [50]. Although rare, it can be severe, even life threatening, and have deleterious effects on neural development.

High fetal heart rate (>160 beats/minute), fetal goiter, advanced bone age, poor growth, and craniosynostosis are manifestations of fetal hyperthyroidism. Cardiac failure and hydrops may occur with severe disease.

Measurement of maternal antibodies — Measurement of maternal serum TSH receptor antibodies (TRAb) during the third trimester (24 to 28 weeks) helps to predict which infants are at higher risk for development of fetal and neonatal Graves' hyperthyroidism [51,52]. The most readily available (and least expensive) assays are measurements of TSH-binding inhibitory antibodies in receptor assays (thyrotropin binding inhibitory immunoglobulin [TBII]). Although TBII assays do not indicate biologic activity, women with Graves' disease usually have stimulatory antibodies and the fetus or infant is more likely to have Graves' hyperthyroidism when the maternal value is more than three to five times the upper limit of normal. TRAb can also be detected by the thyroid stimulating immunoglobulin (TSI) assay, which measures biologic activity through generation of cyclic AMP.

In pregnant women with a past or present history of Graves' disease, we routinely check serum TRAb at 20 to 24 weeks gestation. If TRAb levels are over three times the upper limit of normal, fetal monitoring is necessary.

Monitoring — All fetuses of women with Graves' disease should be monitored for signs of fetal thyrotoxicosis by determination of fetal heart rate and assessment of fetal growth [11]. Fetal ultrasound monitoring should be performed in pregnant women with active Graves' hyperthyroidism and/or women with serum TRAb levels greater than two to three times the upper limit of normal [51]. In one report, half of the goiters associated with fetal hyperthyroidism had central color flow Doppler versus none of the goiters associated with fetal hypothyroidism [53].

Fetal blood sampling — Fetal blood for thyroid function tests can be obtained by percutaneous umbilical vein sampling after 20 weeks of gestation [54,55]; however, since this procedure is associated with a 1 to 2 percent risk of fetal loss it should **not** be done routinely in all pregnant women with Graves' disease.

Fetal blood sampling can provide useful clinical information when fetal thyroid function is uncertain. As an example, in one study of 24 pregnancies (26 fetuses) among 18 mothers with Graves' disease, fetal blood sampling was performed when maternal anti-TSH receptor antibody levels were high or there were sonographic signs of fetal thyroid disease [54]. Five fetuses were found to be either hypothyroid (n = 3) or hyperthyroid (n = 2).

In view of the risks of umbilical vein sampling, this procedure should be considered only when fetal goiter is present on ultrasound, and there is clinical uncertainty as to whether the fetus is hyperthyroid or hypothyroid because of maternal thionamide treatment.

In these situations, knowledge of fetal thyroid status and medical intervention can improve fetal/neonatal outcome and thus justify the risk of the procedure, which should only be performed by experienced obstetricians [54,55]. (See "Fetal blood sampling".)

Thionamides may be given to mothers, regardless of maternal thyroid status, to treat the hyperthyroid fetus.

Neonatal hyperthyroidism — The topic of neonatal hyperthyroidism is reviewed in detail separately. (See "Evaluation and management of neonatal Graves' disease" and "Thyroid physiology and screening in preterm infants".)

POSTPARTUM ISSUES — Postpartum hyperthyroidism may be due to postpartum thyroiditis or to an exacerbation of Graves' disease. (See "Overview of thyroid disease in pregnancy", section on 'Postpartum thyroid dysfunction' and "Postpartum thyroiditis".)

Women with Graves' disease who have been treated during pregnancy need careful monitoring during the postpartum period, as they may experience an exacerbation [56]. In addition, women with Graves' who have been in remission are at risk for having a relapse during this period. This was illustrated in a study of 150 women with Graves' disease in remission after antithyroid drug therapy [57]. Of the 25 women who had a subsequent pregnancy, 21 (84 percent) experienced a relapse, compared with 70 of 125 (56 percent) who did not have a pregnancy. The risk of relapse appeared to be related to the postpartum period rather than the pregnancy itself, as 20 of the 21 relapses occurred four to eight months postpartum.

INFORMATION FOR PATIENTS — UpToDate offers two types of patient education materials, "The Basics" and "Beyond the Basics." The Basics patient education pieces are written in plain language, at the 5th to 6th grade reading level, and they answer the four or five key questions a patient might have about a given condition. These articles are best for patients who want a general overview and who prefer short, easy-to-read materials. Beyond the Basics patient education pieces are longer, more sophisticated, and more detailed. These articles are written at the 10th to 12th grade reading level and are best for patients who want in-depth information and are comfortable with some medical jargon.

Here are the patient education articles that are relevant to this topic. We encourage you to print or e-mail these topics to your patients. (You can also locate patient education articles on a variety of subjects by searching on "patient info" and the

keyword(s) of interest.)

- Basics topics (see "Patient information: Hyperthyroidism (overactive thyroid) (The Basics)" and "Patient information: Hyperthyroidism (overactive thyroid) and pregnancy (The Basics)")
- Beyond the Basics topics (see "Patient information: Hyperthyroidism (overactive thyroid) (Beyond the Basics)" and "Patient information: Antithyroid drugs (Beyond the Basics)")

SUMMARY AND RECOMMENDATIONS

Treatment

- Women with symptomatic and/or moderate to severe overt hyperthyroidism due to Graves' or gestational trophoblastic disease require therapy for the treatment of hyperthyroidism. Pregnant women with subclinical (low TSH, normal free T4) and asymptomatic and/or mild overt hyperthyroidism may be followed with no treatment. In women who are being monitored without therapy, we measure TSH and free T4 every four to six weeks. (See 'Indications' above.)
- Assuming there are no contraindications to its use, we suggest using a beta blocker for pregnant women with moderate to severe hyperthyroidism and hyperadrenergic symptoms (**Grade 2B**). (See 'Beta blockers' above and "Beta blockers in the treatment of hyperthyroidism".)

  However, they should be given only to women who have many symptoms because occasional cases of fetal growth restriction, hypoglycemia, respiratory depression, and bradycardia have been reported after maternal administration.

  We typically start with atenolol 25 to 50 mg daily or propranolol 20 mg three to four times daily.
- For women with moderate to severe hyperthyroidism complicating pregnancy, we suggest a thionamide as our first choice of treatment (**Grade 2B**). (See 'Thionamides' above.)

  We suggest using PTU rather than methimazole in the first trimester (**Grade 2C**) and switching to methimazole at the start of the second trimester (**Grade 2C**). (See 'Choice of drug' above.)

  Thyroid function should be monitored monthly to maintain serum free T4 concentrations in the high-normal range and serum TSH concentrations in the low-normal or suppressed range. We try to limit the dose of PTU to 50 mg twice daily or less and MMI to doses of 5 to 10 mg per day or less; higher doses (eg, doses in excess of 200 mg/day) can result in fetal goiter and hypothyroidism. (See 'Dose and monitoring' above.)
- We suggest thyroidectomy in hyperthyroid women during pregnancy only when thionamides are not tolerated because of allergy or agranulocytosis (**Grade 2C**). (See 'Surgery' above.) Such women should be treated with a short course (7 to 10 days) of beta blockers and iodine in preparation for thyroidectomy.
- We suggest not administering pharmacologic doses of iodine for long-term use because chronic use can cause fetal goiter (**Grade 2C**). (See 'Iodine' above.)
- Radioiodine therapy for pregnant women with hyperthyroidism is absolutely contraindicated. (See 'Treatment' above.)

Fetal monitoring

- All fetuses of women with Graves' disease should be monitored for signs of fetal thyrotoxicosis by determination of fetal heart rate and assessment of fetal growth. (See 'Fetal hyperthyroidism' above.)
- If fetal thyrotoxicosis is suspected, we suggest prenatal sonography to rule out fetal goiter. (See 'Monitoring' above.)
- Because of the potential risk of fetal loss with fetal blood sampling, we suggest **not** performing this procedure routinely in pregnant women with Graves' disease. Specific indications for fetal blood sampling are outlined above. (See 'Fetal blood sampling' above.)

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Disclosures

Disclosures: **Douglas S Ross, MD** Grant/Research/Clinical Trial Support: Genzyme [thyroid cancer (rhTSH)]. **David S Cooper, MD** Nothing to disclose. **Charles J Lockwood, MD, MHCM** Nothing to disclose. **Jean E Mulder, MD** Employee of UpToDate, Inc.

Contributor disclosures are reviewed for conflicts of interest by the editorial group. When found, these are addressed by vetting through a multi-level review process, and through requirements for references to be provided to support the content. Appropriately referenced content is required of all authors and must conform to UpToDate standards of evidence.

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