

# What you need to know about thyroid disorders in pregnancy

Managing overt disorders is straightforward, but even subclinical disease warrants heightened scrutiny

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Until recently, thyroid dysfunction was thought to have little influence on pregnancy as long as it was treated, and management was straightforward. That was before case-control studies in prominent journals suggested an association between even subclinical hypothyroidism and impaired neonatal neurodevelopment.<sup>1-4</sup>

The risk associated with hyperthyroidism in pregnancy is less clear. Currently, it is believed to cause no adverse effects; the low thyroid-stimulating hormone (TSH) resolves in most women within 4 to 12 weeks.

As for the nonpregnant state, there is no agreement between the American College of Physicians and its British counterpart as to whether isolated, subclinical hyperthyroidism leads to morbidity or mortality, although some investigators have found an excess risk of atrial fibrillation and possibly increased bone loss in postmenopausal women. Treatment of hyperthyroidism in nonpregnant women is recommended only if low TSH persists after 4 to 12 weeks and the level is less than 0.1 mIU/L.<sup>5</sup>

This article discusses the detection and management of thyroid disease in pregnancy, concentrating on 2 representative cases. (See **TABLE 1**, page 28, for a list of the full spectrum of thyroid disorders.)

## CASE 1 History of Graves' disease

S.H., 32, is 6 weeks' pregnant with her first child. She has a history of Graves' disease, and underwent radioactive iodine treatment 10 years ago. She then became hypothyroid and has been on levothyroxine replacement for the past 9 years. She visits her endocrinologist annually and reports good control on 125 µg daily of oral levothyroxine sodium.

How should her pregnancy be managed?

When the mother has a history of Graves' disease, regardless of her current thyroid state, 1% to 5% of newborns develop hyperthyroidism due to transplacental passage of thyroid-stimulating immunoglobulins (TSI). Fetal or neonatal hyperthyroidism is associated with fetal tachycardia (heart rate >160 bpm), poor growth, goiter, craniosynostosis, and advanced bone age. Therefore, fetal growth and heart rate should be monitored throughout pregnancy in these women. Investigators have published monograms on fetal thyroid measurement,<sup>6</sup> and even argued that Doppler ultrasonography can differentiate between fetal hypo- and hyperthyroidism caused by drugs or disease processes.<sup>7</sup> However, measurement of TSI levels (poor predictive value) and ultrasonography for fetal goiter (low yield) are controversial.

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**TABLE 1**

**The spectrum of thyroid disorders is wide**

**Hypothyroidism**

- Hashimoto's or subacute thyroiditis
- Subclinical hypothyroidism
- Subclinical hypothyroxemia
- Postpartum thyroiditis
- Secondary hypothyroidism
  - Hypothalamic dysfunction
  - Radioactive iodine therapy
  - Thyroidectomy
  - Iodine deficiency
  - TSH receptor resistance/mutation

**Hyperthyroidism**

- Grave's disease
- Subclinical hyperthyroidism
- Thyroid storm
- Secondary hyperthyroidism
  - TSH-producing pituitary adenoma
  - Toxic multinodular goiter
  - Toxic adenoma
  - Subacute thyroiditis
  - Metastatic follicular thyroid cancer
  - Iodine excess
  - Factitious/iatrogenic
  - Thyroid hormone resistance syndrome
  - Struma ovarii
  - Gestational trophoblastic neoplasia
  - Hyperemesis gravidarum

**FAST TRACK**

**Levothyroxine should be ingested at least 4 hours before or after the prenatal vitamin**

Another important consideration: The requirement for thyroxine hormone increases by approximately 30% in women on thyroid supplementation during pregnancy.<sup>8</sup> This has been demonstrated in more than 9 studies, with athyrotic women experiencing greater increases than women with autoimmune hypothyroidism.<sup>9</sup> The need for thyroxine increases as early as 5 weeks' gestation and plateaus by 16 weeks.

Because hypothyroxemia or hypothyroidism (clinical or subclinical) may be associated with adverse neurodevelopment in the newborn, I recommend increasing the dosage of levothyroxine at the first encounter with this patient to 150 µg/day (<25% dosage increase). I also suggest measuring the baseline

TSH level, if no reading is available from the past 3 months. If baseline TSH is less than 2.5 mIU/L, the dosage increase is probably adequate. If the TSH exceeds 2.5 mIU/L, however, I would ask the patient to take 1 extra pill (125 µg) on 2 days of the week (>30% dosage increase) and measure TSH again 4 to 6 weeks later (thyroxine takes 5 weeks to equilibrate after a change in dosage). Once the dosage has been adequately adjusted, I would monitor TSH every 6 to 8 weeks until delivery. At that time, the dosage should be reduced to the prepregnancy level, with TSH measured again in 4 to 6 weeks to confirm that the dosage is adequate.

Levothyroxine absorption is hampered by ferrous sulfate, aluminum hydroxide antacids, proton-pump inhibitors, and cholestyramine. Levothyroxine should be ingested at least 4 hours before or after the prenatal vitamin. The metabolism of levothyroxine is altered by phenytoin, carbamazepine, and rifampin.

**Subclinical hypothyroidism can progress to overt disease**

The majority of women with hypothyroidism are asymptomatic, with only 20% to 30% having any complaints, usually nonspecific (TABLE 2, page 31). Women with 1 or 2 symptoms are no more likely to have abnormal thyroid function tests than are asymptomatic women.

Overt hypothyroidism is primarily diagnosed with laboratory tests—specifically, low free thyroxine (FT<sub>4</sub>) or free triiodothyronine (FT<sub>3</sub>), or both, resulting in elevated TSH levels.

If untreated, overt hypothyroidism is associated with significant morbidity in both the nonpregnant and pregnant states (TABLE 3, page 32). Levothyroxine is easily administered and well tolerated, with no to few adverse effects with appropriate follow-up.<sup>10</sup>

In women with subclinical hypothyroidism, only 1 of the thyroid function tests is elevated—either elevated TSH

with normal free thyroid hormone levels (mild thyroid failure) or normal TSH with low FT<sub>4</sub> levels (hypothyroxemia). Most cases of mild thyroid failure are thought to be related to thyroid dysfunction, whereas hypothyroxemia is usually associated with a deficiency of iodine.

Subclinical hypothyroidism can occur in women with a history of thyroid disease, after surgery or radioactive iodine therapy for toxic goiter, or as the result of an inadequate dosage of thyroid medication. It can also occur in women with no history of thyroid dysfunction, detected in routine testing in women with no symptoms or with nonspecific complaints that could be related to thyroid disease. Experts agree that women with secondary subclinical disease should be treated to achieve a euthyroid state because approximately 5% per year will develop overt disease. Considerable controversy clouds management of women with primary subclinical hypothyroidism.

Subclinical hypothyroidism is more common among white women (~67%) than among black women.

### Subclinical hyperthyroidism is more elusive

Overt hyperthyroidism can be detected through symptom-based screening (TABLE 2).

Subclinical hyperthyroidism is defined as low TSH with normal thyroid hormone levels. The pituitary appears to be more sensitive to the presence of thyroid hormones than to their absence. Subclinical hyperthyroidism is most common in black women and smokers. Approximately 50% of women with subclinical disease will have normal TSH levels several weeks to 1 year later.

Because subclinical hyperthyroidism can occur in up to 20% of women on thyroid replacement therapy, the dosage should be adjusted to achieve a euthyroid state.

**TABLE 2**

### Know these signs and symptoms of thyroid dysfunction

HYPOTHYROIDISM	HYPERTHYROIDISM
Fatigue	Resting tremors
Constipation	Hyperdefecation
Somnolence	Insomnia
Cold intolerance	Heat intolerance
Hair loss	Diaphoresis
Depression	Nervousness
Decreased libido	Palpitations
Menstrual irregularities	
Weight gain despite poor appetite	Weight loss
Dry skin	Warm, moist skin
Deafness	Ophthalmopathy
Hoarseness	Sinus tachycardia
Paresthesia	
Carpal tunnel syndrome	
Periorbital puffiness	
Slow cerebration or movement	
Slowing ankle jerk	Hyperreflexia
Goiter	Thyromegaly

### CASE 2 Diabetes, with a family history of hypothyroidism

M.H., 30, is 12 weeks' pregnant with her second child and reports a 12-year history of diabetes. Before she became pregnant, she was taking insulin, with HbA<sub>1c</sub> = 8.5%. Her history includes a mother with hypothyroidism.

How should she be managed?

Besides the obvious need for good diabetes control, this case merits screening for thyroid dysfunction, as the patient has 2 risk factors (TABLE 4, page 37).

One prominent controversy of the 21st century is whether all pregnant women should undergo routine screening for hypothyroidism. The contro-

### FAST TRACK

Approximately 5% of women with secondary subclinical hypothyroidism develop overt disease each year

**TABLE 3**

<b>Consequences of untreated thyroid dysfunction are significant</b>	
<b>HYPOTHYROIDISM</b>	<b>HYPERTHYROIDISM</b>
<b>Nonpregnant state</b>	
Hyperlipidemia	Atrial fibrillation
Atherosclerosis	Congestive heart failure
Osteoporosis	
Neuropsychiatric disorders	Neuropsychiatric disorders with or without dementia/Alzheimer's disease
Reduced functional status and quality of life	Reduced functional status and quality of life
<b>Pregnancy</b>	
Spontaneous abortion	Spontaneous abortion
Preterm delivery <32 weeks	Preterm labor
Low birth weight	Low birth weight
Perinatal morbidity and mortality	Stillbirth
Preeclampsia/gestational hypertension	Preeclampsia
Anovulation	
Cesarean delivery	
Postpartum hemorrhage	
Placental abruption	
Nonreassuring fetal heart rate tracing	
Impaired neurodevelopment	
<b>Subclinical disease</b>	
Risk factor for overt disease	Risk factor for overt disease

versy extends to screening all women of childbearing age.

**\$64,000 question: Should all women be screened?**

Screening would involve testing thyroid function in women with no history and few or no signs and symptoms of thyroid dysfunction. Such screening could be population-based (using special methods to recruit, contact, and follow patients) or case-finding (performed on patients who present for unrelated reasons). The decision to screen a woman who is preg-

nant or planning to conceive should be based on many factors, most notably whether treatment prevents impaired neonatal neurodevelopment and preterm delivery.

**A mother's elevated TSH level can have lasting effects in the child**

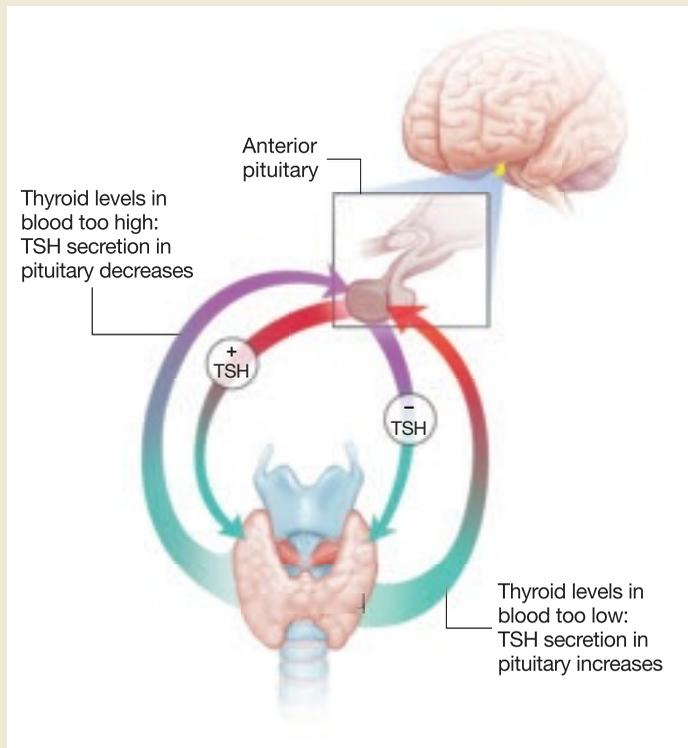
Haddow and colleagues<sup>1</sup> measured the IQ of 47 children, ages 7 to 9 years, whose mothers had had an elevated serum TSH concentration in the second trimester, 15 children whose mothers had high serum TSH values in combination with low thyroxine levels in the second trimester, and 124 children whose mothers had normal TSH values. None of these children had hypothyroidism at birth. The children of the women with an elevated TSH concentration had lower IQs. Interestingly, the group with hypothyroxemia was not evaluated at the time, and the mean FT<sub>4</sub> level was low in the entire group, suggesting overt hypothyroidism rather than subclinical disease.

In a study from the Netherlands, Pop and associates<sup>2</sup> found impaired psychomotor function in 22 infants (age 10 months) whose mothers had had FT<sub>4</sub> below the 10th percentile at 12 weeks of gestation, compared with 194 infants whose mothers had normal readings. When these children were re-evaluated at 2 years, no neurodevelopmental delay was found in the infants whose mothers had a spontaneously increased free thyroxine level after the first trimester.

There is much speculation about precisely when thyroid hormone is critical for fetal brain development. The study by Pop and associates<sup>2</sup> would suggest it is important after the first trimester. That study also recommends exogenous thyroxine for FT<sub>4</sub> values below 0.96 ng/mL (12 pmol/L).

In Italy, Vermiglio and coworkers<sup>11</sup> conducted behavioral and neuropsychological testing in 27 children at ages 18 to 36 months and again at 8 to 10

## How common?



Thyroid disorders affect approximately 5% of the general population, two thirds of them women.<sup>17</sup> Subclinical hypothyroidism occurs in an additional 4.3%, and subclinical hyperthyroidism in 0.7%.

In pregnancy, subclinical disease is present in 3.6% of women; overt hypothyroidism, in 2.5%; and overt hyperthyroidism, in 0.2%. In addition, thyroid disease affects 5% to 9% of postpartum women.<sup>14</sup>

years. Mothers of 16 of these children were from a moderately iodine-deficient area (group A), and the mothers of 11 children were from a marginally iodine-sufficient area and were monitored with thyroid function tests in the first trimester (group B). Attention-deficit and hyperactivity disorders were more prevalent in group A.

Two studies published in 2006 also suggest that maternal free thyroxine levels in the first trimester of pregnancy correlate with impaired neonatal behavior at 3 months, and impaired mental development at ages 6, 9, and 12 months.<sup>3,4</sup>

## No consensus on whom to test or what test is best

There is no clear agreement about which population should be targeted for screening or what test to use. Most medical societies do not recommend routine screening, including the American College of Obstetricians and Gynecologists, which recommends TSH testing only in women with a history of thyroid disease and in women with “symptoms” (but does not specify which symptoms or how many symptoms warrant testing). A majority of organizations agree that all high-risk women should be tested when pregnancy is planned or as soon as pregnancy is confirmed (TABLE 5, page 38).

Proponents of routine screening argue that it may limit health risks to children and save money in the long run, and they point out that thyroid disease is easy to treat with pills. Opponents note that no cost-benefit analysis has been performed, the benefits of treating mild disease are unclear, and screening a large population could be a significant expense (\$40–100 per person) and would necessitate a lifelong commitment to daily medication in asymptomatic patients.

As a diagnostic test, the TSH immunoassay has 98% sensitivity and 92% specificity, and the current third-generation test lacks biases between methods and does not require method-specific reference ranges. However, it has low predictive value as a screening test (7–25%), possibly because of multiple confounding variables (TABLE 6, page 41). Despite being the “gold standard,” it can lead to falsely positive results.

As for the value of FT<sub>4</sub> alone as a screening test, we lack sufficient data on its utility. Another problem is that equilibrium dialysis, the most accurate and reliable laboratory method to measure FT<sub>4</sub>, is too technically complex and expensive for routine use. The most widely used 2-step radioimmunoassay is automated, but different methods are used by different commercial laboratories, cutoffs vary for every laboratory, and

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**TABLE 4**

### Risk factors for hypothyroidism include other autoimmune disorders

Family history of thyroid disease
More than 3 symptoms
History of postpartum thyroid disease
Type 1 diabetes mellitus
Recurrent spontaneous abortions
Unexplained intrauterine fetal demise
Other autoimmune disorders
• Vitiligo
• Addison's disease
• Pernicious anemia
• Multiple sclerosis
• Rheumatoid arthritis
• Sjögren's disease

the results are sensitive to abnormal binding-protein states such as pregnancy in a method-specific manner. Tandem mass spectrometry is as reliable as equilibrium dialysis, but is not yet readily available.<sup>12</sup>

Another consideration: The physiologic changes in pregnancy render the cutoffs for the nonpregnant state inapplicable. TSH is lower in pregnancy, whereas the FT<sub>4</sub> level is probably slightly increased or unchanged (TT<sub>4</sub> is 1.5 times the prepregnancy value).

The normal reference values in each trimester of pregnancy from iodine-sufficient, autoimmune thyroid antibody-negative women are becoming available for TSH,<sup>12</sup> as are nomograms that adjust for fetal number and gestational age.<sup>13</sup> The measurement of FT<sub>4</sub> still needs to be standardized across laboratories (method-specific, trimester-specific, and, possibly, population-specific reference ranges) for pregnancy.

### How to manage subclinical thyroid disorders

In the nonpregnant state, subclinical hyperthyroidism should be treated in the following groups if the abnormal thyroid levels persist beyond 4 to 12 weeks and

the TSH level is less than 0.1 mIU/L:

- High-risk women: postmenopausal or over age 60
- Low-risk women with cardiac disease, low bone density, or nodular thyroid disease.

If the TSH level is between 0.1 and 0.5 mIU/L, treatment is recommended for high-risk women with cardiac disease, low bone density, or nodular thyroid disease.

Subclinical hypothyroidism with a TSH level of 4.5 to 10 mIU/L need not be treated even in an elderly woman or a patient with a high antibody titer. Treatment of any woman is beneficial when the TSH level exceeds 10 mIU/L because it can ease symptoms, reduce low-density lipoprotein cholesterol, and prevent progression to overt disease. However, treatment may not lower morbidity and mortality and carries a roughly 20% risk of causing subclinical hyperthyroidism. It also involves a lifelong commitment to daily medication.

### How to treat subclinical hypothyroidism in pregnancy

It is clear that overt hypothyroidism warrants treatment in both the pregnant and nonpregnant states, but the management of subclinical disease remains controversial. No trials have assessed the benefits of thyroid hormone replacement on the neuropsychological development of the newborn. Expert opinion suggests that women be treated if they are planning a pregnancy, are already pregnant, or have high TSH or low FT<sub>4</sub>.

Until we have more data, pregnant women and those planning a pregnancy should be treated with levothyroxine (starting at 2 µg/kg/day) if they are found to have elevated TSH or low FT<sub>4</sub>.

### Two studies will answer questions about effects in pregnancy

The Controlled Antenatal Thyroid Screening (CATS) study will be completed in 2009, and the National Institute of Child Health and Human Development Ma-

### FAST TRACK

**Treat gravidas and women planning to conceive with levothyroxine (starting at 2 µg/kg/day) if they have an elevated TSH or low FT<sub>4</sub>**

**TABLE 5**

<b>Comparison of screening recommendations highlights lack of consensus (and, in pregnancy, the absence of guidance)</b>			
<b>YEAR</b>	<b>ORGANIZATION</b>	<b>NONPREGNANT STATE</b>	<b>PREGNANCY</b>
1994	American Association of Clinical Endocrinologists (AACE) American Academy of Family Physicians	Periodic assessment via thyroid function tests in older women	No recommendation
1998	American College of Physicians	Office screening of women >50 years of age	No recommendation
2000	American Thyroid Association (ATA)	Measure TSH every 5 years in women age 35 and older (probably men also)	No recommendation
2002	American College of Obstetricians and Gynecologists	Measure TSH every 5 years in women age 65 and older	No screening recommended
2003	Institute of Medicine	Screening is not cost-effective in Medicare population	No recommendation
2004	United States Preventive Services Task Force	Routine screening of children and adults is not recommended	No recommendation
2004	AACE, ATA, the Endocrine Society Consensus Group	No population-based screening, but “aggressive case finding” in women at high risk and those over age 60	Do not support routine testing; recommend “aggressive case finding” and screening pregnant women at high risk

**FAST TRACK**

**Postpartum thyroid dysfunction affects 5% to 9% of women and usually involves psychiatric symptoms**

ternal-Fetal Medicine Units (NICHD-MFMU) study will conclude in 2014. The CATS study screened 22,000 pregnant women in the United Kingdom before 16 weeks’ gestation. Half these women were treated with levothyroxine in pregnancy if they had a TSH measurement above the 97.5th percentile or FT<sub>4</sub> below the 2.5th percentile, and half had their blood samples stored and tested only after delivery.<sup>14</sup> Cutoff values were derived from previously obtained antenatal sera from well-dated pregnancies, and were adjusted after every 2,000 to 3,000 samples.

The CATS study was conducted in an iodine-sufficient area with a median urinary iodine excretion of 100 µg/L (range: 11–240 µg/L). Each group contained 400 women with subclinical hypothyroidism (52% had low FT<sub>4</sub>, 45% had high TSH, and 3% had both). Anti-thyroid peroxidase antibodies were

present in 50% of women with elevated TSH but in only 10% of women with low FT<sub>4</sub>. Neuropsychological development in their children is being tested at 3 years of age.

The NICHD-MFMU study plans to screen 110,000 women at 14 centers over 2 years, and will randomize roughly 1,000 women to thyroxine treatment or placebo. They plan to assess intellectual development of the infants yearly for 5 years, and test the mothers for postpartum thyroid dysfunction and follow them at 1 and 5 years to detect the rate of progression to overt hypothyroidism.

**Postpartum dysfunction can be transient or permanent**

Postpartum thyroid dysfunction (PPTD) is an autoimmune disorder that occurs at 13 to 19 weeks postpartum, affects 1 in 12

women worldwide, and is usually associated with psychiatric symptomatology.<sup>15</sup>

PPTD also is strongly associated with antithyroid peroxidase antibodies (TPOAbs).<sup>16</sup> Premawardhana and colleagues found that 10% of women are TPOAbs-positive in the first trimester; of these, 50% develop PPTD. Of the women with PPTD, 20% to 30% develop permanent hypothyroidism, and an additional 30% to 40% develop it by 7 years. In contrast, only 5% of women without PPTD progress to overt disease by 7 years. These findings have generated considerable controversy about routine screening for PPTD. Proponents argue that PPTD is highly prevalent, linked to considerable morbidity, is easily diagnosed with relatively inexpensive tests, and is easy to treat effectively. Critics note the lack of consensus on the best screening test (thyroid function test versus TPOAbs), optimal timing of screening (early pregnancy or postpartum), and lack of high-quality, prospective cost-benefit analyses. The NICHD-MFMU hopes to resolve these controversies. ■

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**TABLE 6**

What makes a TSH measurement falsely high or low?	
ELEVATED TSH	LOW TSH
Recovery from nonthyroidal illness	Euthyroid sick syndrome
Late evening TSH surge	Recovery from normal pregnancy
Assay variability	
Adrenal insufficiency	
Drugs: metoclopramide, amiodarone, cholecystographic dye (sodium ipodate)	Drugs: glucocorticoids, dopamine

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#### FAST TRACK

**A late evening TSH surge can cause a falsely elevated TSH measurement**