Thyroid dysfunction in pregnancy

JUAN CARLOS GALOFRE a,b AND TERRY F. DAVIES b

b Department of Medicine. Mount Sinai School of Medicine. The Mount Sinai Hospital and the James J. Peters VA Medical Center. New York. New York. USA.

Pregnancy induces complex hormonal and immunological changes that modify normal thyroid physiology. Therefore, evaluation of thyroid function during pregnancy should be interpreted according to these changes. In our opinion, the high prevalence of pregnancy-related thyroid disorders and their important consequences for both mother and fetus indicate the need for routine thyroid function screening both before and during pregnancy. Once thyroid dysfunction is diagnosed, the management of the disorder requires frequent monitoring to adjust treatment accurately. The goal of treating hyperthyroidism with thionamide drugs is to maintain serum thyroxin (T4) in the upper normal range (free T4, 2-2.5 ng/dl; total T4, 12.0-18.0 µg/dl) using the lowest possible dose of the drug, while in hypothyroidism the goal is to return serum thyrotropin to the range between 0.5 and 2.5 mU/l.


INTRODUCTION

Pregnancy is a unique situation in which the physician is faced with at least two interactive patients. Any medical action or inaction may have positive or negative consequences for both the mother and the fetus.

Maternal physiological changes during pregnancy

The physiological changes that occur in normal pregnancy have important repercussions for the thyroid gland1,2. Usually thyroid gland volume enlarges and thyroid hormone production increases approximately 50% above the preconception baseline. These changes are secondary to a variety of factors.

Human chorionic gonadotropin. Rising plasma levels of placental human chorionic gonadotropin (hCG), which has a weak thyrotropin (TSH) agonist action due to the structural homology...
between both hormones, have a major thyroid stimulatory influence. hCG increases during the first trimester and plateaus from midgestation to shortly after delivery. The result of this hCG activity is an elevation in serum thyroxine (T4) and triiodothyronine (T3) concentrations and suppression of serum TSH, providing new normal ranges unique to pregnancy (fig. 1).

**Thyroid binding globulin.** Plasma oestrogen levels rise in pregnancy and induce an elevation of up to 100% in serum thyroid binding globulin (TBG). This occurs mainly during the first 20 weeks and is secondary to an extended half-life because of changes in TBG glycosylation. As a result, by approximately week 10 of pregnancy the total serum T4 (TT4) is elevated by up to 50%, remaining constant at this level until delivery. This large increase in TBG opens many T4 binding sites, which have to be filled to maintain free T4 equilibrium and, therefore, constitute another cause of increased thyroid hormone secretion. These ongoing changes in TBG have made assessment of free thyroid hormone levels in pregnancy a technical challenge, resulting in a polluted literature in which cross-sectional studies have suggested that free T4 (fT4) levels during the first trimester may be higher, lower or the same as those before conception (fig. 2).

**Other important factors influencing thyroid function.** During pregnancy, other physiological adjustments take place in maternal thyroid homeostasis which, together, may lead to incremental increases in thyroid hormone synthesis. The maternal glomerular filtration rate is also elevated secondary to increased cardiac output, resulting in high renal clearance and iodide excretion. Therefore, iodine intake needs to be increased to accommodate the continuing thyroid hormone synthesis. In addition, transplacental passage of T4 may also stimulate the maternal thyroid by depleting maternal circulating T4.

**Immune changes.** Pregnancy is a time of placenta-induced immune suppression secondary to placental cytokine and hormone secretion resulting in enhanced regulatory T cell function. This particular situation can be extremely important to autoimmune reactions and most autoimmune diseases, including thyroid disorders, tend to improve during gestation.

Maternal thyroid function is totally reset to normal activity by 6 months after delivery unless thyroid dysfunction develops.
Fetal thyroid physiology

The fetal thyroid starts producing sufficient hormones for the fetus by the end of the first trimester. Before this time, the fetus is dependent on a supply of maternal thyroid hormones, which is metabolically controlled by the placental deiodinase enzymes. The placenta expresses all three deiodinases D1, D2 and D3. D2 converts the pro-hormone T4 into the biologically active T3, whereas D3 inactivates T3. The role of D1 is less important. D3 is by far the most prevalent isofrom in the placenta and consequently fetal T3 plasma concentrations are low until the 30th week of gestation.

Maternal thyroid function, especially in the first trimester, is, therefore, extremely important to adequate fetal central nervous system (CNS) development. Recent studies have shown that there are specific thyroid hormone transporters in the fetal CNS that play an important role in fetal CNS development, but their consideration is beyond the scope of this review.

**ASSESSMENT OF THYROID FUNCTION DURING PREGNANCY**

Gestation is a prime time for the diagnosis of thyroid diseases, insofar as gravid women usually seek regular medical care. Indeed, thyroid diseases are the most common group of pre-gestational endocrine diseases that persist during pregnancy. Although thyroid dysfunction is an important barrier to pregnancy, significant thyroid dysfunction still occurs in 1-2% of pregnant women and mild forms of thyroid disease are even more prevalent. The presence of either hypothyroidism or hyperthyroidism as evidence of autoimmune thyroid disease (AITD) leads to adverse reproductive outcomes and may severely affect pregnancy and offspring.

Screening programs

The controversy. Surprisingly, the need for routine thyroid evaluation in early pregnancy is far from being unanimously supported; possibly because these opinions are expressed by men. Since thyroid disease is common in the female population, checking thyroid function before or at the time of pregnancy diagnosis would appear to be essential. Certainly, thyroid testing is routine in fertility assessment and, because normal thyroid function is essential for normal intellectual development, screening for thyroid dysfunction is an important part of careful medical assessment. Only recently has the American Association of Clinical Endocrinologists recommended thyroid function screening in all women seeking to become pregnant and/or during the first trimester of pregnancy. This screening should include determination of thyroid antibodies, which also represent important consequences for pregnancy outcome. The recommendation for aggressive case finding in women with increased risk for thyroid disease is nonsense in light of the high frequency of these disorders.

Choosing screening tests. Selecting only a single test for thyroid dysfunction screening in pregnancy may be inadequate. This is because of the controversy over the claim that serum TSH and T4 levels may not always be coincident. Half of so-called “hypothyroid” pregnant women display low T4 serum levels without high TSH and an equal number have high TSH serum concentrations with little change in serum T4. Indeed, very few women show both low T4 and high TSH levels. Usually, an abnormally high TSH concentration is of autoimmune origin and is associated with thyroid autoantibodies (TAbS). The cause of the reported low T4 group remains speculative but may be related to iodine deficiency with T3 levels maintaining normal TSH or to unreliable testing assays. To avoid misinterpretation, it should be borne in mind that low TSH serum levels can also be a physiological response during the first trimester (see above).

While there is consensus on the utility of TSH determination, different opinions persist on whether serum TT4 or FT4 measurement should be the complementary test of choice (table 1). We prefer to use a T4 index with an appropriate binding assessment such as TBG or a T3 resin binding assay, since these indices give results in pregnancy similar to those in non-pregnant women.

Ultrasound. Although scintigraphy scans are contraindicated in pregnancy, routine ultrasound may be considered when nodular disease is suggested by history and examination. This procedure is useful not

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**TABLE 1. Routine recommendations for normal pregnancy**

<table>
<thead>
<tr>
<th>Recommendation</th>
<th>Procedure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid function</td>
<td>TSH and T4*. Interpretation should be trimester-specific</td>
</tr>
<tr>
<td>Presence of AITD Ultrasound</td>
<td>Anti-TPO and anti-Tg Recommended, especially when nodular disease is suggested by history and examination 250 µg/day (range, 200-300 µg/day)</td>
</tr>
<tr>
<td>Iodine supplement</td>
<td></td>
</tr>
</tbody>
</table>

AITD: autoimmune thyroid disease; anti-Tg: anti-thyroglobulin antibodies; anti-TPO: anti-thyroperoxidase antibodies; T4: thyroxin; TSH: thyrotropin.

*See text: Once the diagnosis of pregnancy is confirmed, or preferably, before pregnancy occurs, iodine supplements should be started and screening for thyroid disease performed.
only to characterize nodules and evaluate their growth characteristics but can also help establish a clinical diagnosis of Graves’ disease (GD) (by excluding nodules) or Hashimoto’s thyroiditis (based on typical heterogeneous patterning).

**Diagnosis of suspected disease**

**Choice of tests.** There is a similar controversy to that discussed above when choosing tests for the established pregnant patient under consideration. Once again, the most useful tests are determination of serum TSH, even though normal values are pregnancy-specific with an upper limit of < 2.5 mU/l (fig. 1) and simultaneous TT4 (which is expected to be a maximum of 1.5 µg/dl above the normal range of non-pregnant women because of the increased TBG levels). A common practice in pregnancy has been determination of plasma FT4 to bypass the changes in TBG plasma levels. However, FT4 determination using commercial assays may be insensitive to the increase in serum transport proteins, which occurs during gestation, leading to false readings in the presence of high TBG. Moreover, there is no absolute value of FT4 that defines hyperthyroxisma. In contrast, changes in TT4 during pregnancy are predictable and the assays do not depend on the problem of elevated TBG concentrations. A rough higher reference range for TT4 during pregnancy can be calculated by multiplying the reference value of non-pregnant women by 1.5. Again, as mentioned earlier, in other centers, common practice is to use the relation between TBG and TT4 to calculate the free T4 fraction or T4 index (fig. 2).

**Normal ranges.** Interpretation of thyroid functions tests should be trimester-specific (fig. 1) or FT4. Although locally generated trimester-specific reference levels should be applied when available, notably, the upper 95% confidence limit for serum TSH in the first trimester has been reported to be 2.5 mU/l. TSH is known to decrease by 60-80% by week 10 and to recover slowly thereafter, but may not reach the normal range until gestation ends.

**Diagnosis of hyperthyroidism**

Diagnosis of hyperthyroidism may be supported biochemically when very low TSH serum levels are found (< 0.1 mU/l) in the presence of concurrently elevated T4 concentrations. However, 10-20% of pregnant women may have low plasma TSH levels without concurrent thyrotoxic symptoms. Half of these women may detectable but subnormal serum TSH serum levels, whereas the other half has fully suppressed concentrations. When TSH is low, a trend in the T4 serum concentration can be helpful to differentiate transient physiological states from thyrotoxic conditions. Hence, more than just biochemistry is required for full confidence in the diagnosis. TSH receptor antibodies, eye disease, family history, goiter, weight loss, arrhythmias, and other factors need to contribute to the diagnosis.

**Diagnosis of hypothyroidism**

Evidence of an elevated serum TSH concentration makes the diagnosis of primary hypothyroidism straightforward. The presence of thyroid antibodies is a useful confirmatory finding. According to some studies, serum TSH above 2.5 mU/l in non-pregnant women should be used as a guide for thyroid dysfunction. Similarly, > 2.5 mU/l is too high for the first trimester and when serum TSH is > 4 mU/l irrespective of the presence (or absence) of thyroid antibodies, there is no doubt about the presence of thyroid dysfunction. To confirm the diagnosis and severity, TT4 or FT4 must be measured. Normal pregnancy TT4 may be increased by 4-5 µg/dl (50-60 nmol/l) whereas FT4 should remain normal. Therefore, in early pregnancy any T4 levels below the normal range are suggestive of hypothyroidism, whereas in late pregnancy a FT4 value reduction of around 20-30% from pre-pregnancy values may be physiological.

**AUTOIMMUNITY AND PREGNANCY**

**The immunology of pregnancy**

Many changes in immune function develop during pregnancy, mostly initiated at the trophoblastic-uterine interface. For example, placental steroids and cytokines enhance the function of regulatory B cells and contribute directly to the modulation of immune reactivity in pregnancy. T cell function and antibody (Ab) secretion are both depressed during normal pregnancy, as reflected in the measurement of a wide variety of pathologic antibodies and quiescence of many autoimmune diseases.

**Thyroid autoantibodies**

TAbs are present at birth in normal individuals but are suppressed by the normal immune system. However, almost 15% of the so-called normal population have easily detectable antibodies to thyroglobulin (Tg) and/or thyroid peroxidase (TPO)47 indicating that such suppression is faulty in a large number of people. Furthermore, post-mortem studies have shown that the presence of serum thyroid antibodies is indicative of coincidental thyroiditis47. Thyroid antibody levels fall significantly during pregnancy and then rebound in the postpartum once the suppression of pregnancy is lost.

**Consequences of thyroid autoantibodies in pregnancy**

The presence of TAbs in women of childbearing age has four main adverse consequences (table 2).

1. In euthyroid women, the presence of TAbs has been correlated with early unexplained pregnancy
loss\textsuperscript{30}, probably related to a more generalized immune instability.

2. Women with TAbs before conception have an increased risk of developing hypothyroidism during pregnancy because of their reduced thyroid reserve consequent to their thyroiditis, which may negatively affect the development of the fetal CNS.

3. Irrespective of maternal thyroid function, the presence of TAbs is associated with higher rates of obstetric complications\textsuperscript{42}.

4. The presence of TAbs is directly related to the development of the postpartum thyroid syndromes\textsuperscript{43}.

The first reports of an association between an increase in early abortions and the presence of thyroid autoimmunity were published more than 15 years ago\textsuperscript{30}. The presence of TAbs in euthyroid women during the first trimester is now well known to be associated with a 2- to 4-fold increase in the abortion rate. A recent study found that pregnant women with positive antithyroglobulin Ab (anti-Tg), but without anti-thyroperoxidase Ab (anti-TPO), also had an increased risk of very premature delivery\textsuperscript{44} in the absence of a significant association with TSH.

As mentioned earlier, there are several possible explanations for the association between TAbs and fertility-related adverse effects. Some authors have suggested that the presence of TAbs signals an autoimmune reproductive diathesis. TAbs may also indicate subtle thyroid dysfunction that negatively affects outcome.

TABLE 2. Effects of thyroid auto-antibodies (TAbs) in pregnancy

<table>
<thead>
<tr>
<th>Consequences of positive TAbs</th>
<th>Possible explanations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Delays in conception and consequently women are older when they conceive</td>
<td>Autoimmune reproductive diathesis</td>
</tr>
<tr>
<td>Early pregnancy loss</td>
<td>Generalized immune instability</td>
</tr>
<tr>
<td>Increased risk of developing hypothyroidism during pregnancy</td>
<td>Reduced thyroid reserve consequent to thyroiditis</td>
</tr>
<tr>
<td>Higher rates of obstetric complications</td>
<td>TAbs may be a marker of a generalized autoimmune imbalance. TAbs may also indicate subtle thyroid dysfunction that negatively affects outcome</td>
</tr>
<tr>
<td>Increased prevalence of postpartum thyroid syndromes</td>
<td>Predisposition to autoimmune diseases</td>
</tr>
</tbody>
</table>

Fig. 3. Thyroid autoantibody titer expressed as the mean at each time point of a study of a group of 33 euthyroid pregnant women who did not develop postpartum thyroiditis (group A) and a group of 33 euthyroid women who developed postpartum thyroiditis (group B). On average, Ab titers were two-fold higher in group B than in women who did not develop the disease (group A). The measurements were performed during each trimester and 3 and 6 months after delivery. Tg: thyroglobulin, TPO: thyroperoxidase. Modified from Stagnaro-Green et al\textsuperscript{38}.
of conception and women become older when they conceive. It is also known that the higher women’s age, the greater the presence of TAbs. These observations can be linked to the observed older age of women with poor obstetric outcomes. Lastly, women with TAbs may have higher plasma TSH levels, reflecting subtle thyroid dysfunction. While some authors have found that levothyroxine (LT4) treatment did not prevent miscarriage in women with TAbs, others have reported prevention of pregnancy loss.

These data suggest that starting treatment with LT4 at the time of pregnancy may be appropriate to reduce the risk of miscarriage and prematurity in euthyroid anti-TPO-positive women.

The presence of anti-TPO in early gestation is also a useful marker for predicting the development of postpartum thyroid disease. Anti-TPO can usually be detected in 10% of euthyroid pregnant women at 14 weeks of gestation. After delivery, thyroid dysfunction (postpartum thyroiditis) occurs in 5-10% of all women. However, 30-50% of anti-TPO-positive women will develop postpartum thyroid dysfunction. Maternal anti-TPO has also been related to intellectual impairment even when thyroid function was apparently normal, although once again thyroid deficiency may have been extremely subtle. These data require confirmation.

**HYPERTHYROIDISM AND PREGNANCY**

**Epidemiology and etiology**

Hyperthyroidism during gestation is uncommon, secondary to the low fertility state, increased pregnancy loss, and the immunological changes that occur during pregnancy. The overall prevalence rate is about 0.1-0.4% of pregnant women, with GD accounting for 85-90% of all cases. In addition, gestational transient thyrotoxicosis (GTT) occurs even more frequently but is not a disease.

**Clinical features**

The presentation of thyroid hyperactivity during pregnancy may not be obvious because the symptoms may resemble gestational manifestations such as palpitations, excessive perspiration, dyspnea, and nervousness. Some signs, such as inadequate weight gain for gestational age, onycholysis, lid lag, muscle weakness, and heart rate greater than 100 beats per minute (that does not decrease with the Valsalva maneuver), may help differentiate between thyrotoxicosis and the hypermetabolic state attributable to pregnancy.

**Risks**

Hyperthyroidism affects pregnancy outcome, and serious complications may be associated. For the mother the risks include congestive heart failure, thyroid storm, preterm labour, pre-eclampsia and even death, while the fetus may be stillborn, small-for-gestational age, or have congenital malformations. Studies of pregnant women with the rare condition of thyroid hormone resistance syndrome demonstrated that their increased thyroid hormone levels, which are typical of this syndrome, were harmful to the normal fetus and caused a high miscarriage rate. From these studies, the potential for fetal loss in mild (subclinical) hyperthyroidism can be deduced. In addition, it can be inferred that expectant women may also be at risk if they have inadequately treated hyperthyroidism.

Only isolated case reports of Graves’ associated ophthalmopathy and pregnancy have been published, since this complication rarely appears or worsens during pregnancy. In severe cases, surgical decompression may be warranted.

**Gestational transient thyrotoxicosis**

GTT consists of biochemical hyperthyroidism in women with an otherwise normal pregnancy secondary to the thyrotoxic effects of hCG. The prevalence of GTT depends on which ranges are used as normal for TSH and serum thyroid hormones but this disorder is clearly identified in approximately 2-3% of all pregnancies. In its most marked state, GTT is associated with morning nausea but improves spontaneously as pregnancy progresses. In the most severe form, high serum concentrations of hCG occur along with hyperemesis gravidarum – defined by severe nausea and vomiting leading to a 5% loss of body weight – dehydration and ketosis. Characteristically, whether symptomatic or not, GTT usually resolves spontaneously by 20 weeks’ gestation as hCG declines. This disorder is, therefore, more frequent in multiple pregnancies, in which hCG levels tend to be higher. A tendency to reappear in subsequent pregnancies has also been observed.

GTT must be differentiated from GD because the course, fetal risk, management and follow-up are different. GTT does not usually require specific treatment.

**Management**

Significant hyperthyroidism during pregnancy, whatever its cause (GD or nodules), must be treated. The most important issue to consider is that at least two patients are always involved (table 3).

**Antithyroid drugs.** In general, the treatment of choice in pregnancy is antithyroid drugs (ATD). Many physicians recommend the use of propylthiouracil (PTU) rather than methimazole (MMI) or carbimazole because of the widespread belief that this drug causes fewer side effects in the fetus. Very rare cases of aplasia cutis have been associated only with MMI and carbimazole. However, if allergy or intolerance appears, it is still recommended that MMI be substituted. However, in Spain there are only two available ATDs, i.e., carbimazole or its metabolite MMI. Hence, PTU

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TABLE 3. Management of hyperthyroidism in pregnancy

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indications</th>
<th>Recommendations</th>
<th>Comments</th>
<th>ATD: anti-thyroid drugs; FT4: free thyroxin; MMI: methimazole; PTU: propylthiouracil; T4: thyroxin; TSH: thyrotropin; TT4: total thyroxin.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antithyroid drug</td>
<td>Drug of choice: PTU (100-150 mg/8 h)</td>
<td>Monthly monitoring:</td>
<td>Maternal hormone target levels:</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Clinical: mother and foetus.</td>
<td>TT4: 12-18 µg/dl or</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Ultrasonic: foetus.</td>
<td>FT4: 2-2.5 µg/dl</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Biochemical: TSH and T4*; mother</td>
<td>TSH: 0.1-0.4 mU/l (in late</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>gestation)</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>Uncontrolled maternal hyperthyroidism with high doses of ATD (over 300 mg of PTU or 40 mg/day MMI)</td>
<td>Second trimester</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beta-adrenergic blockers</td>
<td>Preparation for surgery</td>
<td>Should be temporarily used</td>
<td>Side effects: increased risk of</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>(no more than 4 weeks)</td>
<td>abortion or small-for-date infants</td>
<td></td>
</tr>
<tr>
<td>Radioactive iodine therapy</td>
<td>Contraindicated</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>Possible teratogenic effects</td>
<td></td>
</tr>
</tbody>
</table>

The median time to normalization of maternal T4 should be 7-8 weeks. Monitoring by TSH is more useful in late gestation when the disease is controlled. The block and replacement approach (T4 plus ATD) should be avoided in pregnancy because of the difficulty of monitoring fetal thyroid function and the increased risk of producing goiter and hypothyroidism.

When maternal hyperthyroidism is not controlled with high doses of ATD (over 300 mg of PTU or 40 mg/day MMI), surgery is often recommended in the second trimester. However, this happens rarely since the disease tends to improve as pregnancy progresses.

Managing the fetus. The management of the fetus requires serial ultrasound assessment for tachycardia, goiter, growth and hydromic changes. Fetal thyroid echo-Doppler may also be useful to evaluate gland function by a vascularization pattern. Goiter can usually be detected (when or if it is present) after week 32 but should be completely avoidable with appropriate disease management.

Beta-adrenergic blockers. Beta-blockers should be avoided in pregnancy, or used temporarily for no more than 4 weeks until the ATD becomes effective in severe hyperthyroidism, or as preparation for surgery. Data in the literature have associated propranolol use in the first trimester with an increased risk of abortion and other effects such as small-for-date infants.

Iodide. Information on use of large doses of iodides in pregnancy to control hyperthyroidism is scarce. Anecdotal data consists of case reports. Low-dose iodide (6-40 mg/day of potassium iodide) has been used, leading to improvement in maternal thyroid function and normal neonatal outcome. Because of the risk of fetal goiter, iodide use is not recommended except perhaps to prepare for surgery.

Surgery. Subtotal or total thyroidectomy is indicated when, for any reason, ATDs fail to control the hyperthyroid disease. The appropriate time is the 2nd trimester. Ideally, surgery requires previous pharmacological treatment to normalize thyroid function but this may not be possible except with the use of beta-blockers and iodide.

Radioactive iodine therapy. During pregnancy 131I is contraindicated because of the possible teratogenic effects of radiation. However, the consequences of inadvertent administration of 5-10 mCi of 131I to pregnant women show that hypothyroidism occurs in only 3% of the fetuses.

Special considerations in Graves’ disease

In general, the management of GD follows the same recommendations as those for any cause of hyperthyroidism. can only be prescribed as a foreign medication through a correspondent document.

The initial dose of ATD depends on the severity of the disease. PTU is usually initiated at 100-150 mg/8 h guided by maternal T4 levels. The therapeutic aim is to maintain the “two patients” in a euthyroid state but fetal hypothyroidism must be avoided at all costs. ATDs pass through the placental barrier. Therefore, to avoid fetal hypothyroidism, the lowest dose possible to keep maternal T4 in the high normal range should be used. With this double objective in mind, once ATDs are started, “the patients” should be monitored every 4 weeks during gestation and the dose adjusted accordingly. Monitoring consists of assessing maternal pulse, weight gain, thyroid size and measurements of TT4 (or FT4), TSH with the recommended therapeutic target being TT4: 12-18 µg/dl (or FT4, 2-2.5 ng/dl) and other effects such as small-for-date infants.

Beta-blockers. Beta-blockers should be avoided in pregnancy, or used temporarily for no more than 4 weeks until the ATD becomes effective in severe hyperthyroidism, or as preparation for surgery. Data in the literature have associated propranolol use in the first trimester with an increased risk of abortion and other effects such as small-for-date infants.

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Special considerations in Graves’ disease

In general, the management of GD follows the same recommendations as those for any cause of hyperthyroidism.
Thyroid dysfunction in pregnancy

In contrast with toxic multinodular goiter, GD usually improves as pregnancy progresses for several reasons. Pregnancy-associated immunosuppression promotes a reduction in TSHR-Ab titers. Some authors speculate that the balance between TSHR-Ab blocking and stimulating activities may be modified in favor of blocking Abs but other authors disagree. Whatever the case, a fluctuating clinical course can be expected with exacerbation during the first trimester and improvement during the latter half. Consequently, ATD dosage is normally adjusted downward after the first trimester and many women are able to discontinue therapy in the final weeks of pregnancy. Attempts have been made to adjust medication dose guided by umbilical blood samples to control fetal thyroid function but this is not normally necessary.

Importantly, the clinical situation and the corresponding treatment approach vary according to when GD is diagnosed. Different clinical conditions can be summarized in the following four situations (table 4).

1. **First, a woman with active GD becomes pregnant.** In this situation, continuing with an ATD is recommended. To determine whether the fetus is at risk, TSHR-Ab titers should be assessed in the third trimester (preferably by bioassay) to confirm they are of the stimulating variety.

2. **A second situation, although rare, is new onset of GD early in pregnancy.** Treatment should be started with an ATD as soon as the diagnosis is made.

3. **The third scenario consists of a relapse during early pregnancy in a woman with a past history of GD who was cured after a course of ATD.** In this event, medication should be restarted. When evaluating these patients, the normal physiological increase in T4 plasma concentrations during the first trimester should be borne in mind.

4. **Finally, a different scenario is pregnancy after a previous ablative treatment (surgery or radioiodine).** In these cases, reassessment of TSHR-Ab levels at the beginning of pregnancy is recommended to determine the chance of fetal or postnatal hyper- or hypothyroidism, as maternal thyroid function is normal on T4 replacement therapy. When positive TSHR-stimulating Ab (TSD) are found, several precautionary measures should be initiated, as a hyperthyroid fetus in a euthyroid mother is possible. In this condition the fetal pulse must be monitored and should not be tachycardic (>160 bpm). If tachycardia is detected, it is reasonable to initiate PTU 100-200 mg/8 h (to control fetal hyperthyroidism), as well as to continue LT4 supplementation to maintain maternal euthyroidism. This situation resembles the block and replacement approach as previously stated.

As previously stated, measurement of TSHR-Ab at 26-28 weeks' gestation is recommended to evaluate the likelihood of neonatal hyperthyroidism. Fortunately, the prevalence of neonatal hyperthyroidism (because of the passage of the antibodies) is not common (about 0.6-9.5% of cases) and can be predicted on the basis of high stimulating TSHR-Ab titers. In any event, neonatal GD is self-limiting and resolves in 5-10 months.

As pregnancy progresses, the immune-privileged state disappears and a relapse, exacerbation or new onset of GD may occur between 4-12 months after delivery.

### TABLE 4. Specific recommendations for Graves’ disease

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendations for the mother</th>
<th>Recommendations for the fetus</th>
<th>Treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pregnancy in active GD</td>
<td>Monitoring TFT every month, and adjusting treatment accordingly. Assessment of TSHR-Ab titers (3rd trimester) to observe if the fetus is at risk.</td>
<td>Monitoring fetal pulse, which should not be tachycardic (&gt;160 bpm). If maternal TSHR-Ab titers are positive, neonatal thyroid function should be investigated after delivery.</td>
<td>Mother should continue with ATD.</td>
</tr>
<tr>
<td>New diagnosis of GD during pregnancy</td>
<td>Medication should be restarted.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Relapse during early pregnancy</td>
<td>Maternal hyperthyroidism is impossible. Reassessment of TSHR-Ab levels at the beginning of pregnancy to determine the probability of fetal or postnatal hyperthyroidism.</td>
<td>If fetal tachycardia is detected in a fetus with maternal positive TSHR-Ab, initiating treatment with PTU 100-200 mg/8 h is recommended, as well as continuing LT4 supplementation to the mother to maintain maternal euthyroidism.</td>
<td></td>
</tr>
</tbody>
</table>

ATD: anti-thyroid drugs; PTU: propylthiouracil; TFT: thyroid function tests.

Management of Graves’ disease in pregnancy deserves particular consideration, bearing in mind the consequences of therapy on both mother and fetus. Stimulatory antibodies (TSHR-Ab) can stimulate both thyroids.
Hypothyroidism is associated with ovulatory dysfunction and consequently hypothyroid women have difficulty becoming pregnant. When hypothyroidism occurs, the signs and symptoms are similar to those in non-pregnant women, although only 20-30% of patients with overt hypothyroidism develop clear clinical features consistent with disease.

**Clinical features**

Hypothyroidism is associated with ovulatory dysfunction and consequently hypothyroid women have difficulty becoming pregnant. When hypothyroidism occurs, the signs and symptoms are similar to those in non-pregnant women, although only 20-30% of patients with overt hypothyroidism develop clear clinical features consistent with disease.

**Risks**

Hypothyroidism, even when mild, is classically associated with increased risks of anemia, gestational hypertension (pre-eclampsia or pregnancy-induced hypertension), fetal growth restriction, placental abruption, postpartum hemorrhage, cesarean section, perinatal mortality and neonatal morbidity. Preterm delivery (before week 32) is three times more common in pregnant women with high TSH levels. Hypothyroidism is also associated with an increase in spontaneous abortions. Gestational hypertension occurs more often in overtly hypothyroid patients (36%) than in those with subclinical disease (25%) or in the general population (8%).

**Danger to the future child**

Another worrying aspect associated with maternal hypothyroidism (especially when present in early gestation) is the adverse consequence to fetal mental development. Several studies have shown clear evidence of the adverse effect of maternal hypothyroxinemia on neurodevelopmental and intellectual development in early childhood.

**Hypothyroidism and Pregnancy**

**Epidemiology and etiology**

Overall, the prevalence of hypothyroidism during pregnancy is approximately 2.5%, including both overt and mild (subclinical) cases. However, transient high serum TSH levels in the first trimester can occur in two-thirds of women in certain populations, probably related to iodine deficiency. Notably, the percentage of pregnant women with increased serum TSH when they are TAb-positive is 40-60% compared with only 7-11% in matched non-pregnant Ab-positive women, revealing the stress placed on the thyroiditis-affected gland.

Determining the etiology of maternal hypothyroidism is important. The most common cause of hypothyroidism in women of reproductive age is the absence of iodine deficiency (AITD). A history of past total or subtotal thyroidectomy, radioidine ablation or transient thyroiditis accounts for most of the remaining cases of hypothyroidism.

If maternal hypothyroidism is present, then the first trimester is the most critical time for fetal development, but if both maternal and fetal hypothyroidism occur (for instance in cases of TSHR blocking Ab or iodine deficiency) then all trimesters, and especially the third trimester, are critical periods. However, the presence of TSHR blocking Ab is a rare cause of maternal hypothyroidism (1 in 180,000 live births). These antibodies may be transferred to the fetus and cause intrauterine or transient neonatal hypothyroidism.

**Clinical features**

Hypothyroidism is associated with ovulatory dysfunction and consequently hypothyroid women have difficulty becoming pregnant. When hypothyroidism occurs, the signs and symptoms are similar to those in non-pregnant women, although only 20-30% of patients with overt hypothyroidism develop clear clinical features consistent with disease.
with AITD (70%) rather than athyreotic women variation seems to occur more frequently in women requirements before and after pregnancy. This LT4 some women may present discordance in LT4 dosage usually return to pre-pregnancy levels. However, current diseases such as gastritis $\mu g/day$ for mild cases (i.e., TSH < 10 mU/l). Adjustments are made by increasing LT4 by 25-50 µg/day. Serum TSH and TT4 (FT4 according to some authors) should always be evaluated 3 to 4 weeks after every change of dosage. Kaplan has proposed LT4 dosage increments according to the initial TSH levels. For those with serum TSH concentrations < 10 mU/l, the average increase may be about 50 $\mu g$/day; for those with concentrations between 10-20 mU/l, 75 $\mu g$/day; and for those with concentrations > 20 mU/l/day, 100 $\mu g$/day$^5$. When equilibrium is achieved, some authors advocate that monitoring can be performed with TSH alone$^6$, although we prefer both TSH and FT4$^7$. The fetal risk from maternal over-treatment is generally low$^1$.

**LT4 interactions.** Possible interactions with concurrent diseases such as gastritis$^8$ or medications such as iron supplements, calcium, vitamins, and omeprazole, etc., may reduce LT4 absorption$^9$. In these cases, a 4-hour delay is recommended between these medications and LT4.

**Post-partum.** After delivery, LT4 requirements usually return to pre-pregnancy levels. However, some women may present discordance in LT4 dosage requirements before and after pregnancy. This LT4 variation seems to occur more frequently in women with AITD (70%) rather than athyreotic women (20%)$^{10}$.

**CONCLUSIONS**

Thyroid diseases, especially those of autoimmune origin, are common in women of childbearing age. These disorders are significantly influenced not only by a variety of changes in thyroid function that take place during normal gestation, but also by the particular privileged immune state that occurs in pregnancy. Therefore, interpretation of thyroid function tests needs to relate to normal pregnancy ranges, which are not widely available. Adequate screening programs should be established to prevent the considerable consequences of delay or misdiagnosis of thyroid dysfunction during pregnancy, which can have significant adverse effects both on mother and offspring. Furthermore, the correct approach to the diagnosis and treatment of thyroid dysfunction in pregnancy requires frequent fetal and maternal monitoring continuing into the postpartum period.

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**TABLE 5. Management of hypothyroidism in pregnancy**

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication</th>
<th>Recommendations</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>LT4</td>
<td>High TSH</td>
<td>Dosage: New diagnosis: start with 1.8-2 µg/kg (overt disease)</td>
<td>Maternal hormone target levels: FT4: 12-18 µg/dl or FT4: 2.2-5 µg/dl TSH: 0.5-2.0 mU/l</td>
</tr>
<tr>
<td></td>
<td>Presence of TAb$^*$</td>
<td>or 100 µg/day (mild cases i.e., TSH &lt; 10 mU/l)</td>
<td>Possible drug interactions Postpartum period requires adjustments</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Patients on LT4: increase dosage from 25% to 50%</td>
<td>Monthly monitoring Clinical mother Biochemical (TSH and T4)$^*$ mother</td>
</tr>
</tbody>
</table>

$^*$Some authors recommend initiating treatment in euthyroid pregnant women if positive thyroid autoantibodies (TAb) are found, but this indication is not universally accepted and requires further investigation.

Management of hypothyroidism in pregnancy requires frequent monitoring. Treatment consists of levothyroxine (LT4). The adverse consequences of hypothyroidism should be prevented in the fetus.

**Adequate screening programs should be established to prevent the considerable consequences of delay or misdiagnosis of thyroid dysfunction during pregnancy, which can have significant adverse effects both on mother and offspring. Furthermore, the correct approach to the diagnosis and treatment of thyroid dysfunction in pregnancy requires frequent fetal and maternal monitoring continuing into the postpartum period.**
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