

Revisiones

DISFUNCIÓN TIROIDEA EN EL EMBARAZO

El embarazo comporta una serie de cambios hormonales e inmunológicos que dan lugar a modificaciones en la fisiología normal del tiroides. Por tanto, la evaluación de la función tiroidea durante el embarazo debe interpretarse teniendo en cuenta estos cambios. En nuestra opinión, la gran prevalencia de trastornos tiroideos asociados al embarazo y las graves consecuencias que pueden causar a la madre y el feto apoyan la necesidad de realizar pruebas de cribado de disfunción tiroidea de manera sistemática, tanto antes como durante el embarazo. Una vez se ha diagnosticado una disfunción tiroidea será necesario realizar una monitorización frecuente para ajustar el tratamiento de forma precisa. El objetivo del tratamiento del hipertiroidismo con fármacos antitiroideos es lograr que la concentración de tiroxina sérica (T4) se mantenga en el límite alto del rango normal (T4 libre, 2-2,5 ng/dl; T4 total, 12-18 µg/dl) con la mínima dosis posible, mientras que, en el caso del hipotiroidismo, el objetivo es conseguir que la concentración de tirotrópina se mantenga entre 0,5 y 2,5 mU/l.

Palabras clave: Embarazo. Hipertiroidismo. Hipotiroidismo. Posparto. Manejo.

Thyroid dysfunction in pregnancy

JUAN CARLOS GALOFRÉ^{a,b} AND TERRY F. DAVIES^b

^a*Departamento de Endocrinología y Nutrición. Clínica Universitaria. Universidad de Navarra. Pamplona. España.*

^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 thyroxine (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.

Key words: Pregnancy. Hyperthyroidism. Hypothyroidism. Postpartum. Management.

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 gland^{1,2}. 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 gonadotrophin. Rising plasma levels of placental human chorionic gonadotrophin (hCG), which has a weak thyrotropin (TSH) agonist action due to the structural homology

Correspondencia: Dr. J.C. Galofré.
Room 2F-26, Bronx VAMC Research Division.
130 West Kingsbridge Rd., New York, NY 10468. USA.
E-mail: jcgaloFRE@unav.es

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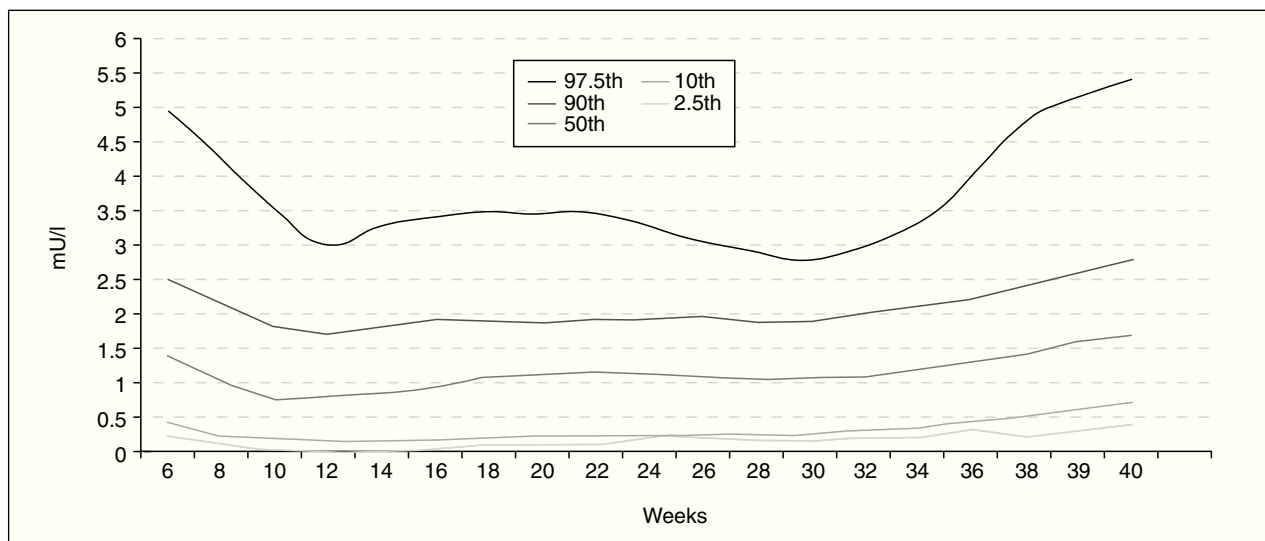


Fig. 1. Thyroid-stimulating hormone (TSH) plasma concentration expressed in percentiles according to gestational age. TSH was measured in 13,599 singleton pregnancies. Gestational age-specific. Modified from Dashe et al³³.

between both hormones, have a major thyroid stimulatory influence. hCG increases during the first trimester and plateaus from midgestation to shortly after delivery³. 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 glycosylation⁴. 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 delivery⁵. 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 excretion⁶. Therefore, iodine intake needs to be increased to accommodate the continuing thyroid hor-

mone synthesis. In addition, transplacental passage of T4 may also stimulate the maternal thyroid by depleting maternal circulating T4⁷.

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^{8,9}. This particular situation can be extremely important to autoimmune reactions and most autoimmune diseases, including thyroid disorders, tend to improve during gestation¹⁰.

Maternal thyroid function is totally reset to normal activity by 6 months after delivery unless thyroid dysfunction develops¹¹.

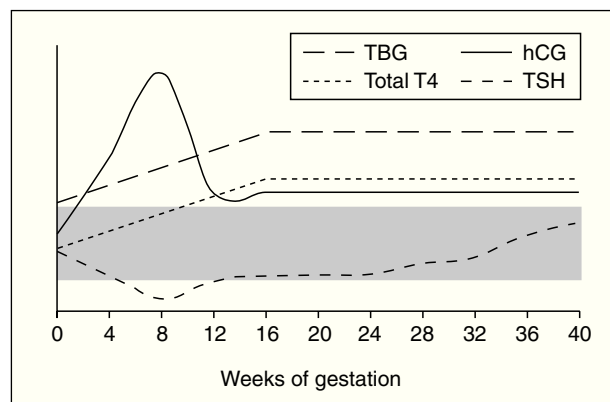


Fig. 2. Changes in plasma concentrations of thyroid function test and hCG according to the evolution of pregnancy. The shaded area corresponds to the normal range in non-pregnant women. hCG: human chorionic gonadotrophin; TBG: thyroid-binding globulin; T4: thyroxine; TSH: thyroid-stimulating hormone. Modified from Brent GA. Maternal thyroid function: interpretation of thyroid function tests in pregnancy. Clin Obstet Gynecol. 1997;40:3-15.

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 important¹². D3 is by far the most prevalent isoform in the placenta and consequently fetal T3 plasma concentrations are low until the 30th week of gestation¹³.

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 review¹⁴⁻¹⁶.

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 care¹⁷. Indeed, thyroid diseases are the most common group of pre-gestational endocrine diseases that persist during pregnancy¹⁸. 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 prevalent¹⁹. The presence of either hyperthyroidism or hypothyroidism as evidence of autoimmune thyroid disease (AITD) leads to adverse reproductive outcomes and may severely affect pregnancy and offspring^{18,19}.

Screening programs

The controversy. Surprisingly, the need for routine thyroid evaluation in early pregnancy is far from being unanimously supported²⁰⁻²², 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^{19,23-28}. 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 pregnancy²⁹. This screening should include determination of thyroid antibodies, which also represent important consequences for pregnancy outcome^{30,31}. The recommendation for aggressive case finding in women with increased risk for thyroid disease is nonsense in light of the high frequency of these disorders²⁰.

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 levels²⁸. Usually, an abnormally high TSH concentration is of autoimmune origin and is associated with thyroid autoantibodies (TAb). 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 assays²⁸. 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

TABLE 1. Routine recommendations for normal pregnancy

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

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

*See text.

Once the diagnosis of pregnancy is confirmed, or preferably, before pregnancy occurs, iodide 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 $< 2.5 \mu\text{U/ml}$ (fig. 1) and simultaneous TT4 (which is expected to be a maximum of $1.5 \mu\text{g/ml}$ above the normal range of non-pregnant women because of the increased TBG levels)^{5,11}. A common practice in pregnancy has been determination of plasma FT4 to bypass the changes in TBG plasma levels^{19,28,32}. 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 TBG⁵. Moreover, there is no absolute value of FT4 that defines hypothyroxinemia. 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 1.5⁷. 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)^{21,33,34}, although locally generated trimester-specific reference levels should be applied when available^{6,33}. Notably, the upper 95% confidence limit for serum TSH in the first trimester has been reported to be 2.5 mU/l ³⁵. 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 ends¹¹.

Diagnosis of hyperthyroidism

Diagnosis of hyperthyroidism may be supported biochemically when very low TSH serum levels are found ($< 0.1 \text{ mU/l}$) in the presence of concurrently elevated T4 concentrations. However, 10-20% of pregnant women may have low plasma TSH levels without concurrent thyrotoxic symptoms¹⁹. Half of these women have detectable but subnormal serum TSH serum levels, whereas the other half has fully suppressed concentrations³⁶. 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 straightforward⁶. 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, $> 2.5 \text{ mU/l}$ is too high for the first trimester¹¹, and when serum TSH is $> 4 \text{ mU/l}$ irrespective of the presence (or absence) of thyroid antibodies, there is no doubt about the presence of thyroid hypofunction¹⁹. To confirm the diagnosis and severity, TT4¹¹ or FT4^{7,18,32} must be measured. Normal pregnancy TT4 may be increased by $4\text{-}5 \mu\text{g/dl}$ ($50\text{-}60 \text{ nmol/l}$) 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 physiological¹⁹.

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 pregnancy³⁷. T cell function and antibody (Ab) secretion are both depressed during normal pregnancy, as reflected in the measurement of a wide variety of pathological antibodies and quiescence of many autoimmune diseases³⁸.

Thyroid autoantibodies

TABs are present at birth in normal individuals³⁹ 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)⁴⁰, 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 thyroiditis⁴¹. Thyroid antibody levels fall significantly during pregnancy and then rebound in the postpartum once the suppression of pregnancy is lost (fig. 3).

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

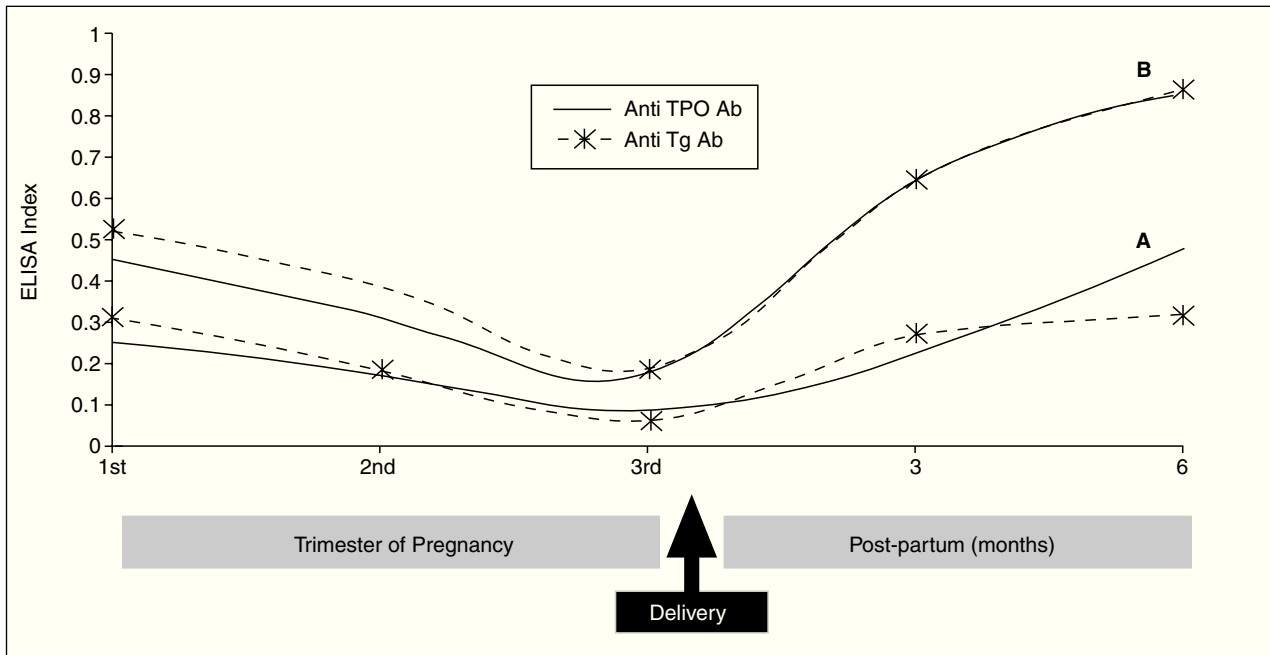


Fig. 3. Thyroid autoantibody titer expressed as the mean at each time point of a study of a group of 33 euthyroid pregnant women who did not develop postpartum thyroiditis (group A) and a group of 33 euthyroid pregnant women who developed postpartum thyroiditis (group B). On average, Ab titers were two-fold 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 al³⁸.

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

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

loss³⁰, probably related to a more generalized immune instability.

2. Women with TAb 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 TAb is associated with higher rates of obstetric complications⁴².

4. The presence of TAb is directly related to the development of the postpartum thyroid syndromes⁴³.

The first reports of an association between an increase in early abortions and the presence of thyroid autoimmunity were published more than 15 years ago³⁰. The presence of TAb 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 anti-thyroglobulin Ab (anti-Tg), but without anti-thyroperoxidase Ab (anti-TPO), also had an increased risk of very premature delivery⁴⁴ in the absence of a significant association with TSH.

As mentioned earlier, there are several possible explanations for the association between TAb and fertility-related adverse effects. Some authors have suggested that the presence of TAb signals an autoimmune reproductive diathesis. TAb could simply be a marker of an underlying more generalized autoimmune imbalance that would explain a greater rejection rate of the fetal graft. Whether this putative imbalance is of fetal or maternal origin is not known. However, a direct TAb effect on the fetus or placenta may also exist, although evidence in humans is lacking. Nevertheless, immunization of mice with thyroglobulin induces increased fetal loss in experimental autoimmune thyroiditis⁴⁵. AITD delays the occurrence

of conception and women become older when they conceive³¹. 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 TABs⁴⁶, others have reported prevention of pregnancy loss⁴². 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 women⁴⁶.

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 dysfunction²⁸. 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 subtle⁴⁷. 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 cases⁴⁸. In addition, gestational transient thyrotoxicosis (GTT) occurs even more frequently but is not a disease¹⁹.

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 pregnancy⁴⁹.

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^{18,50}, while the fetus may be stillborn, small-for-

gestational age, or have congenital malformations⁵. 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 hyperthyroidism⁵¹.

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 warranted⁵².

Gestational transient thyrotoxicosis

GTT consists of biochemical hyperthyroidism in women with an otherwise normal pregnancy secondary to the thyrotrophic 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 declines⁵. 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 observed¹⁹.

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 involved⁵ (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^{53,54}. 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

TABLE 3. Management of hyperthyroidism in pregnancy

Treatment	Indications	Recommendations	Comments
Antithyroid drug	Drug of choice: PTU (100-150 mg/8 h)	Monthly monitoring: Clinical: mother and foetus. Ultrasound: foetus. Biochemical (TSH and T4*): mother	Maternal hormone target levels: TT4: 12-18 µg/dl or FT4: 2-2.5 ng/dl. TSH: 0.1-0.4 mU/l (in late gestation)
Surgery	Uncontrolled maternal hyperthyroidism with high doses of ATD (over 300 mg of PTU or 40 mg/day MMI)	Second trimester	
Beta-adrenergic blockers	Preparation for surgery Serious hyperthyroidism	Should be temporarily used (no more than 4 weeks) until ATD becomes effective	Side effects: increased risk of abortion or small-for-date infants
Radioactive iodine therapy	Contraindicated		Possible teratogenic effects

ATD: anti-thyroid drugs; FT4: free thyroxine; MMI: methimazole; PTU: propylthiouracil; T4: thyroxine; TSH: thyrotropin; TT4: total thyroxine.

*See text.

Management of hyperthyroidism in pregnancy requires frequent monitoring. Treatment initially consists of anti-thyroid drugs. It is important to avoid hypothyroidism in the fetus.

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 levels⁵. 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 accordingly¹⁹. Monitoring consists of assessing maternal pulse, weight gain, thyroid size and measurements of TT4 (or FT4) and TSH with the recommended therapeutic target being TT4: 12-18 µg/dl (or FT4, 2-2.5 ng/dl)⁵⁵. Normalizing TSH in early gestation to the non-pregnant range is not desirable, since the level in normal pregnancy is often low (fig. 1) and if significantly suppressed by excess thyroid hormone can remain suppressed for many weeks after regularization of peripheral hormones. The recommended range for TSH in patients on ATDs has been suggested to be 0.1-0.4 mU/l¹⁹. 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 hypothyroidism⁵⁵.

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 hydropic 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 management⁵⁶.

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 serious 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 infants⁵⁵.

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 outcome⁵⁷. Because of the risk of fetal goiter, iodide use is not recommended except perhaps to prepare for surgery¹⁹.

Surgery. Subtotal or total thyroidectomy is indicated when, for any reason, ATDs fail to control the hyperthyroid disease¹⁹. The appropriate time is the 2nd trimester⁵⁵. 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 contraindicated⁵ 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 fetuses⁵⁸.

Special considerations in Graves' disease

In general, the management of GD follows the same recommendations as those for any cause of hyperthy-

roidism in pregnancy with the distinctiveness of determining thyrotropin-receptor (TSHR)-Abs, the presence of which confirms the diagnosis and also allows prediction of neonatal hyper- or hypothyroidism⁵⁵. TSHR-Abs are IgG antibodies and, therefore, cross the placental barrier and interact with TSH receptors in the fetal thyroid gland triggering neonatal thyroid dysfunction.

In contrast with toxic multinodular goiter, GD usually improves as pregnancy progresses for several reasons¹⁹. 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 Ab⁵⁹ but other authors disagree⁶⁰. Whatever the case, a fluctuating clinical course can be expected with exacerbation during the first trimester and improvement during the latter half⁵. Consequently, ATD dosage is normally adjusted downward after the first trimester¹⁹ 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 necessary⁶¹.

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 of having hyperthyroidism, 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 (TSI) 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 euthyroidism¹⁹. This situation resembles the block and replacement approach.

As previously stated, measurement of TSHR-Ab at 26 to 28 weeks' gestation is recommended to evaluate the likelihood of neonatal hyperthyroidism^{5,62}. 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-Abs titers. In any event, neonatal GD is self-limiting and resolves in 5-10 months⁵⁵.

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

TABLE 4. Specific recommendations for Graves' disease

Condition	Recommendations for the mother	Recommendations for the fetus	Treatment
Pregnancy in active GD	Monitoring TFT every month, and adjusting treatment accordingly. Assessment of TSHR-Ab titers (3rd trimester) to observe if the foetus is at risk. Reassessment after delivery	Monitoring fetal pulse, which should not be tachycardic (> 160 bpm). If maternal TSHR-Ab titers are positive, neonatal thyroid function should be investigated after delivery	Mother should continue with ATD. Foetal tachycardia should respond to ATD
New diagnosis of GD during pregnancy	Treatment should be started with ATD as soon as the diagnosis is made		
Relapse during early pregnancy	Medication should be restarted		
Pregnancy after a previous ablative treatment (surgery or radioiodine) for GD	Maternal hyperthyroidism is impossible. Reassess TSHR-Ab levels at the beginning of pregnancy to determine the probability of fetal or postnatal hyperthyroidism		If foetal 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

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 foetus. Stimulatory antibodies (TSHR-Ab) can stimulate both thyroids.

livery⁶². The frequency of relapses varies from 30% to 70% of cases⁶³. Hence, reinstitution of ATD has been recommended after delivery, even when medication has been stopped¹⁹. These patients may also have silent postpartum thyroiditis. Low uptake in the radioactive iodine scan evaluation will differentiate both situations, which is important for an appropriate therapeutic approach. Some reports support the idea of continuous ATD use during pregnancy and the postpartum to prevent recurrences after delivery, even in women with negative TSHR-Abs. This is not our recommendation. In addition, an increased risk of developing GD after pregnancy may be greater in older patients (35-39 years) and this risk continues to be present for many years after delivery⁶⁴.

HYPOTHYROIDISM AND PREGNANCY

Epidemiology and etiology

Overall, the prevalence of hypothyroidism during pregnancy is approximately 2.5%, including both overt and mild (subclinical) cases⁶⁵. However, transiently high serum TSH levels in the first trimester can occur in two-thirds of women in certain populations, probably related to iodine deficiency⁶⁶. 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-afflicted gland^{19,67}.

Determining the etiology of maternal hypothyroidism is important. The most common cause of hypothyroidism in women of reproductive age in the absence of iodine deficiency is AITD. A history of past total or subtotal thyroidectomy, radioiodine 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 periods¹¹. However, the presence of TSHR blocking Ab is a rare cause of maternal hypothyroidism (1 in 180,000 live births)⁶⁷. These antibodies may be transferred to the fetus and cause intrauterine or transient neonatal hypothyroidism¹⁹.

Clinical features

Hypothyroidism is associated with ovulatory dysfunction and consequently hypothyroid women have difficulty becoming pregnant⁴⁶. 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 disease¹⁹.

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 morbidity¹⁸. 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 abortions⁶⁸. Gestational hypertension occurs more often in overtly hypothyroid patients (36%) than in those with subclinical disease (25%) or in the general population (8%)⁶⁹.

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 neuropsychointellectual development in early childhood^{7,19,46,62,70}.

Management

Prevention of hypothyroid disease. Iodine supplements are critical to prevent non-autoimmune maternal hypothyroxinemia during pregnancy, especially in iodine-deficient areas⁶². Women of childbearing age with normally functioning glands should have an average iodine intake of 150 µg/day. During pregnancy and breast feeding, women should increase their daily iodine intake to 250 µg on average^{6,32,71}. LT4 therapy is required if, despite iodine supplementation, abnormal serum TSH levels are detected (table 1).

Levothyroxine supplements. As in non-pregnant situations, treatment of hypothyroidism depends on LT4 supplementation⁷² (table 5). To respond to the increased demands and to compensate the augmented binding capacity of thyroid hormone transport proteins, hypothyroid pregnant women already taking LT4 replacement therapy will require a dosage increase from 25% to 50% on average to maintain desirable TSH concentrations⁷³. Two-thirds of hypothyroid pregnant women need a dosage increase during the first trimester. In the second trimester there is usually a plateau in LT4 requirements but 25-40% of patients may require a further dosage increase in the third trimester^{19,74}. The increase is at least partly dependent on the patient's thyroid reserve. Hence, those patients with a history of a total thyroidectomy will be most dependent. Generally, patients with Hashimoto's thyroiditis require a 25% increase in dosage while the increase should be 50% in full replacement therapy.

When high TSH is found for the first time during pregnancy, the test should be repeated but treatment

TABLE 5. Management of hypothyroidism in pregnancy

Treatment	Indication	Recommendations	Comments
LT4	High TSH. Presence of TABs ^a	Dose: New diagnosis: start with 1.8-2 µg/kg (overt disease) or 100 µg/day (mild cases: i.e., TSH < 10 mU/l) Patients on LT4: increase dosage from 25% to 50% Monthly monitoring Clinical: mother Biochemical (TSH and T4 ^b): mother	Maternal hormone target levels: TT4: 12-18 µg/dl or FT4: 2-2.5 ng/dl TSH: 0.5-2.0 mU/l Possible drug interactions Postpartum period requires adjustments

FT4: free thyroxin; T4: thyroxin; TSH: thyrotropin.

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

^bSee text.

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

must be started without confirmation to save the loss of time⁷. Several factors should be considered in selecting the most appropriate dose when the diagnosis is made, such as the trimester of gestation, the etiology and the severity of the disease^{19,75}. From a practical point of view, the recommended starting LT4 daily dose should be 1.8-2 µg/kg for overt disease and 100 µg/day for mild cases (i.e., TSH < 10 mU/l).

As there is wide individual variability in dose requirements, dose adjustment requires thyroid function testing at regular intervals, such as every 4 weeks⁷³. The endpoint is a maternal serum TSH concentration between 0.5 and 2.5 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 and should be maintained in the upper third of the normal range. 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 µg/day; for those with concentrations between 10-20 mU/l, 75 µg/day; and for those with concentrations > 20 mU/day, 100 µg/day⁷⁶. When equilibrium is achieved, some authors advocate that monitoring can be performed with TSH alone⁵, although we prefer both TSH and TT4⁷⁴. The fetal risk from maternal over-treatment is generally low⁵.

LT4 interactions. Possible interactions with concurrent diseases such as gastritis⁷⁷ or medications such as iron supplements, calcium, vitamins, and omeprazole, etc., may reduce LT4 absorption⁷⁸. 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%)⁷⁹.

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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