Med Clin (Barc). 2015;145(8):344–349

MEDICINA CLINICA

www.elsevier.es/medicinaclinica

Review

Thyroid dysfunction during pregnancy☆

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ARTICLE INFO

Article history:
Received 24 July 2014
Accepted 19 August 2014
Available online 16 March 2016

Keywords:
Hypothyroidism
Hyperthyroidism
Pregnancy
Clinical practice guidelines

ABSTRACT

Recent clinical practice guidelines on thyroid dysfunction and pregnancy have changed health care provided to pregnant women, although their recommendations are under constant revision. Trimester- and area-specific reference ranges for serum thyroid-stimulating hormone are required for proper diagnosis of hypothyroidism and hyperthyroidism. There is no doubt on the need of therapy for overt hypothyroidism, while therapy for subclinical hypothyroidism is controversial. Further research is needed to settle adverse effects of isolated hypothyroxinemia and thyroid autoimmunity. Differentiation between hyperthyroidism due to Graves' disease and the usually self-limited gestational transient thyrotoxicosis is critical. It is also important to recognize risk factors for postpartum thyroiditis. Supplementation with iodine is recommended to maintain adequate iodine nutrition during pregnancy and avoid serious consequences in offspring. Controversy remains about universal screening for thyroid disease during pregnancy or case-finding in high-risk women. Opinions of some scientific societies and recent cost-benefit studies favour universal screening. Randomized controlled studies currently under development should reduce the uncertainties that still remain in this area.

Disfunción tiroidea y embarazo

Palabras clave:
Hipotiroidismo
Hipertiroidismo
Gestación
Guías de práctica clínica

RESUMEN

Las recientes guías clínicas sobre disfunción tiroidea y embarazo han cambiado la atención sanitaria que se presta a la mujer gestante, pero sus recomendaciones están en constante revisión. Existe la necesidad de disponer de valores de referencia de la hormona estimulante del tiroides por trimestre y área geográfica para el correcto diagnóstico de disfunción tiroidea. No hay dudas sobre la necesidad de tratamiento del hipotiroidismo franco, pero hay opiniones variables sobre el tratamiento del subclínico. Los efectos adversos de la hipotiroxinemia aislada y de la autoinmunidad tiroidea requieren nuevas investigaciones. Es fundamental diferenciar el hipertiroidismo por enfermedad de Graves del llamado hipertiroidismo gestacional transitorio, habitualmente autolimitado. Es importante reconocer los factores de riesgo para la tiroiditis posparto. Para evitar graves consecuencias en la descendencia, se recomienda mantener una adecuada nutrición de yodo durante el embarazo mediante suplementos de este oligoelemento. Continúa la polémica sobre el cribado universal o selectivo de disfunción tiroidea durante la gestación, aunque las tendencias de algunas sociedades y de los últimos estudios de coste-beneficio son favorables al cribado universal. Los estudios aleatorizados y controlados en desarrollo actualmente deberán reducir las incertidumbres que aún persisten en el área de la disfunción tiroidea y el embarazo.

Introduction

In recent years, various scientific societies have issued their recommendations on the diagnosis and treatment of thyroid dysfunction during pregnancy.[1–8] The publication of the guides has had an impact on the actual treatment of pregnant women in both primary and specialized care. However, many of the

☆ Please cite this article as: Díez JJ, Iglesias P, Donnay S. Disfunción tiroidea y embarazo. Med Clin (Barc). 2015;145:344–349.

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2387-0206/

Table 1
Diagnostic criteria and prevalence of different forms of thyroid dysfunction during pregnancy.

Diagnosis	Criteria	Prevalence (%)
Hypothyroidism		
Overt hypothyroidism	TSH ≥ 10 mU/l or TSH > 2.5 mU/l with Free T4 < LLN	0.2–0.5
Subclinical hypothyroidism	TSH > 2.5 mU/l with normal Free T4	2–4
Isolated hypothyroxinaemia	TSH ≤ 2.5 mU/l with Free T4 < 5–10 percentile	1–2
Hypothyroidism		
Overt hyperthyroidism	TSH < 0.01 mU/l or TSH < 0.1 mU/l with Free T4 and Free T3 > ULN	0.1–0.4
Subclinical hyperthyroidism	TSH < 0.1 mU/l with normal Free T4 and Free T3	0.6–1.7
Thyroid autoimmunity		
Positive antithyroid antibodies	aTPO or TgAb > ULN	10–20

TgAb: thyroglobulin antibodies; aTPO: anti-thyroid peroxidase; LLN: lower limit of normal; ULN: upper limit of normal; TSH: thyroid-stimulating hormone.

recommendations are based on data from a small number of research ventures or scientific evidence of questionable quality. Furthermore, the guides differ in some key aspects, such as screening for thyroid dysfunction, in which the *American Thyroid Association* (ATA)[5] only recommends selective screening (SS) for the population at risk, while the *Endocrine Society* (ES)[6] offers private opinions, and the Spanish Society of Endocrinology and Nutrition (SEEN)[3,7] advocates for universal screening (US).

This review explains the most controversial aspects of the different forms of thyroid dysfunction that can complicate pregnancy. Their frequency of presentation (Table 1)[2,5,6,9,10] and healthcare importance are well known.

Hypothyroidism

Diagnostic criteria

For the diagnosis of hypothyroidism in the first trimester of pregnancy it is necessary to have clear criteria regarding the normal upper limit of the *thyroid-stimulating hormone* (TSH). The guidelines recommend this limit to be 2.5 mU/l for the first trimester and 3.0 mU/l for the second and third trimesters,[2,5,6,8] but they stress that these limits should be applied only in cases where there are no characteristic reference intervals for each trimester.

During the first trimester of the FaSTER study,[11] performed on 10,990 pregnant women, the normal upper limit of TSH was 4.28 mU/l. Studies in Spain show similar results. In Catalonia, Vila et al.,[12] found that the upper limit for TSH was 5.76 mU/l. In Aragon[13] this limit was somewhat lower (2.63 mU/l), while in El Bierzo (3.59 mU/l),[14] Cartagena (3.71 mU/l),[15] Jaen (4.18 mU/l)[16] and Valladolid (4.05 mU/l)[17] the results are clearly above 2.5 mU/l.

Isolated hypothyroxinaemia is characterized by a decrease in the concentration of free thyroxine (T4) with normal TSH. Its diagnosis is difficult because the usual immunoassays in clinical laboratories do not determine the concentration of Free T4 in pregnancy reliably due to the physiological changes during pregnancy.[5] Therefore, in the absence of characteristic reference values, we can use the criteria listed in Table 1.

Impact of hypothyroidism

Overt hypothyroidism is associated with maternal adverse effects (hypertension-preeclampsia, *placental abruption*, abortion, caesarean section, postpartum haemorrhage) and foetal adverse effects (preterm birth, low birth weight and increased perinatal morbidity and mortality),[5,6] but these associations are not evident in the subclinical state. The FaSTER study found no association between subclinical hypothyroidism or hypothyroxinaemia and obstetric adverse effects.[11] Pregnant women with high TSH according to ATA and ES cut-offs, had no increased risk of preterm birth based on the Generation R study findings.[18]

Impact of hypothyroidism on the offspring's neurocognitive development was established through the Haddow et al. study,[19] which showed that children born to hypothyroid mothers had a lower intelligence quotient (IQ) at 7–9 years of age compared to euthyroid women children. Isolated hypothyroxinaemia has also been associated with delayed motor and mental development in some studies,[20,21] but not in others.[22] The recent *Controlled Antenatal Thyroid Screening* (CATS) study[23] evaluated 21,846 pregnant women randomized into a control group and a US group. Among the women who were diagnosed with hypothyroidism, 390 were treated with levothyroxine (L-T4) and 404 were untreated, with no IQ differences between the groups in children at 3 years of age.

Following the above, both SEEN[3] and ES[6] recommend treatment in subclinical hypothyroidism regardless of antibody titre, while ATA[5] recommends treatment only in women with subclinical hypothyroidism with positive antithyroid antibodies. None of the guidelines recommends treatment for isolated hypothyroxinaemia.

Thyroid autoimmunity

Pregnancies in euthyroid women with positive *anti-thyroid peroxidase* (aTPO, "thyroid peroxidase antibodies") are associated with an increased risk of abortion and premature birth.[10,24,25] Some authors have also found an association with delayed intellectual and motor development in the offspring.[20]

Treatment with L-T4 has been used only in a small number of euthyroid pregnant women with positive autoimmunity. The study of Black et al.[25] included a group of 57 pregnant women with positive aTPO treated with L-T4, another group of 58 aTPO positive, untreated, and a control group of 869 with negative autoimmunity. The abortion and preterm delivery rates were significantly higher in women with positive aTPO, untreated, compared with those treated or those in the control group.[25]

Since women with positive aTPO known before pregnancy have an increased risk of developing hypothyroidism during pregnancy, the guidelines recommend determining serum TSH during the first half of pregnancy every 4 weeks and at least once between weeks 26 and 32.[5] However, this protective approach applies only to women who know their antibody status. The guidelines consider that there is insufficient evidence to recommend screening antibodies during the first trimester.[5,6] There is no strong evidence to justify recommending treatment with L-T4 to antibody positive euthyroid women.

Hyperthyroidism

Diagnostic criteria

The lower limit of normal TSH also varies with gestational age and the population studied.[26] In Spain, we found values of 0.1–0.5 mU/l for the first trimester, from 0.21 to 0.36 mU/l for the second, and from 0.29 to 0.36 mU/l for the third.[12–16] In case of not having the characteristic intervals, the guidelines recommend of