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REVIEW ARTICLE

Hypothyroidism during pregnancy and its association to perinatal and obstetric morbidity: a review

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Abstract There is currently no consensus among the different scientific societies on screening for thyroid dysfunction in the first trimester of pregnancy. Indeed, diagnosis and treatment of subclinical hypothyroidism during pregnancy are controversial, as no cut-off value for thyrotropin (TSH) is universally accepted. TSH measurement may be influenced by different factors throughout pregnancy, but especially during the first trimester. The association between overt hypothyroidism during pregnancy and obstetric and perinatal complications is well established. It is also accepted that thyroid hormones are important for neurodevelopment of the offspring. However, there is no scientific evidence available about the impact of subclinical hypothyroidism and its treatment during the first trimester of pregnancy on children's neurodevelopment. In recent years, studies conducted in the offspring of mothers with subclinical hypothyroidism have reported new biochemical parameters which may eventually serve as biomarkers of offspring neurodevelopment and which are more reproducible and are measured at an earlier time than the conventional clinical tests.

Abbreviations: TSH, thyrotropin; hCG, human chorionic gonadotropin; aTPO, anti-thyroid peroxidise; T4, thyroxine; ATA, American Thyroid Association; BDNF, brain-derived neurotrophic factor; LPA, lysophosphatidic acid; GDNF, growth-derived neurotrophic factor.

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PALABRAS CLAVE
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Hipotiroidismo durante la gestación y su asociación con la morbilidad perinatal y obstétrica: revisión

Resumen En la actualidad no existe un consenso entre las diferentes sociedades científicas para la detección de la disfunción tiroidea en el primer trimestre del embarazo. De hecho, el diagnóstico y tratamiento del hipotiroidismo subclínico durante el embarazo es controvertido, ya que no se acepta universalmente el valor límite para la tirotropina (TSH). La determinación de TSH puede estar influenciada por diferentes factores durante todo el embarazo, pero especialmente durante el primer trimestre. La asociación entre el hipotiroidismo clínico durante el embarazo y las complicaciones obstétricas y perinatales está bien establecida. También se acepta que las hormonas tiroideas son importantes para el desarrollo neurológico del feto. Sin embargo, falta evidencia científica sobre el impacto en el neurodesarrollo infantil del tratamiento del hipotiroidismo subclínico en el primer trimestre de gestación. En los últimos años, los estudios realizados en hijos de madres con hipotiroidismo subclínico han descrito nuevos parámetros bioquímicos que eventualmente pueden servir como biomarcadores del neurodesarrollo fetal, siendo más reproducibles y pudiendo determinarse en un período anterior al de las pruebas clínicas clásicas.

Introduction

Thyroid hormones are directly and indirectly involved in multiple metabolic and cell tropism processes during intrauterine life. They are crucial for a correct somatic growth and neurologic development of offspring.[1] During pregnancy, important modifications on thyroid economy occur, mainly due to the increased hormonal needs and to the transplacental trafficking of thyroid hormones to the fetus.[2]

The studies published in recent years about perinatal effects of maternal thyroid dysfunction during pregnancy have produced a growing debate on the need to establish strategies for universal or selective screening of these alterations in pregnant women.[3] After an exhaustive analysis of the current evidence, our group has advocated the implementation of a systematic screening of thyroid function in the first trimester of pregnancy as it provides a more efficient way to detect gestational thyroid dysfunction.[4] However, the introduction of universal screening of thyroid function in pregnancy in clinical practice carries multiple difficulties of interpretation and management, mainly related to both the specific physiologic characteristics of the thyroid gland in the earliest stages of pregnancy and to the technical limitations of available hormone detection methods.

Thyroid physiology changes during pregnancy

In normal pregnancy, the maternal hypothalamic-pituitary-thyroid system undergoes physiological changes to adapt to the new situation. A progressive increase in human chorionic gonadotropin (hCG) concentrations occurs in early gestation, whose ''thyrotropin (TSH)-like'' effect determines, firstly, a direct stimulation of the thyroid gland secretion which induces a preferential thyroxine (T4) production, and, secondly, causes a substantial decreasing of serum TSH.[3,5] It has been described an inverse correlation between both hormones during the first 14–15 weeks of gestation. However, this classic relationship between TSH and hCG has been recently challenged by new studies indicating a weaker mutual influence than previously described.[6] Moreover, other also recent studies have shown that there are other variables that play a significant role in the variability of TSH in the first trimester of pregnancy, which difficult the interpretation of the serum concentrations of TSH in the first weeks of gestation.[7] Plasma TSH concentrations are strongly influenced by several parameters such as body mass index,[8,9] age, ethnicity[3] and iodine deficiency in pregnancy.[10] It is also known that TSH values in the first trimester are significantly higher in patients with anti-thyroid peroxidise (aTPO) antibodies.[11] All these factors should be considered at the time of interpreting a given TSH value and its particular significance for a given woman.

As mentioned above, the TSH concentration is currently the most accepted marker of gestational thyroid status but, in specific situations, it could be also necessary to determine free T4 and/or aTPO antibodies. In fact, what really determines the offspring outcomes regarding thyroid function, is the concentration of free T4 reaching the fetus during intrauterine life. For this reason, maternal hypothyroxinemia, regardless of the maternal TSH value, has been recently considered as a relevant issue.[12–15] However, the interpretation of free T4 concentrations during pregnancy is a very difficult matter due to the enhanced circulating level of T4-binding globulin compared to the non-pregnant condition and the decreased albumin concentration, which could decrease immunoassays' reliability. The measurement of free T4 by using immunoassay techniques during pregnancy maybe strongly influenced by modifications of T4 binding proteins concentrations and composition.[16] In the last years, it has been suggested that free T4 measurement with dialysis or ultrafiltration using online solid phase extraction