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Treatment with fixed thyroxine doses in pregnant women with subclinical hypothyroidism☆

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KEYWORDS
Hypothyroidism;
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Abstract
Background: Hypothyroidism is usually treated with thyroxine doses on patient weight. In some cases, however, fixed doses have proved to useful to normalize TSH levels, which is especially important during pregnancy.
Patients and methods: Sixty-eight women diagnosed with subclinical hypothyroidism, autoimmune or not, during pregnancy were given a fixed dose of thyroxine 50 mcg/day. TSH measurements were performed to assess the need to change the dose, which was increased or decreased by 25 mcg/day when necessary.
Results: With a dose of 50 mcg/day of thyroxine, 42% of patients reached a TSH level less than 3 μU/mL, 79.4% reached a TSH level less than 4.5 μU/mL, and 20.6% had TSH levels higher than 4.5 μU/mL.
Discussion: Our data suggest that a fixed dose of thyroxine 50 mcg/day is inadequate in a significant proportion of pregnancy-diagnosed hypothyroidism regardless of whether the reference of TSH level used is 4.5 or 3 μU/mL. Starting dose of 75 mcg/day is probably more adequate, but studies are needed to evaluate the possibility of overtreatment with such dose.

PALABRAS CLAVE
Hipotiroidismo;
Gestación;
Tratamiento

Tratamiento con dosis fija de tiroxina en gestantes con hipotiroidismo subclínico

Resumen
Introducción: El tratamiento del hipotiroidismo se hace habitualmente calculando la dosis de tiroxina en función del peso del paciente. En algunas situaciones se ha comprobado la utilidad de administrar dosis fijas de la hormona para normalizar la concentración de TSH, cuyo control es especialmente importante en el caso de pacientes gestantes.

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Pacientes y métodos: Se administró una dosis fija de 50 mcg/día de tiroxina a 68 mujeres con hipotiroidismo subclínico diagnosticado durante la gestación, autoinmune o no, y se evaluó trimestralmente a través de la concentración de TSH la necesidad de modificarla. Se programaron incrementos o decrementos de 25 mcg/día en los casos en los que el cambio de dosis fuese necesario.
Resultados: El 42% de las pacientes alcanzaron una concentración plasmática de TSH inferior a 3 μU/mL con la dosis de 50 mcg/día de tiroxina. Si se toman como referencia los valores de la población general no gestante, dicha dosis fue óptima durante el embarazo en el 79,4% de las pacientes; y no lo fue en el 20,6% restante.
Discusión: Nuestros datos sugieren que una dosis fija de 50 mcg/día de tiroxina es insuficiente en un porcentaje elevado de pacientes con hipotiroidismo diagnosticado en la gestación, tanto si se toman como valores de referencia de concentración de TSH los de la población general como (especialmente) si se usan las recomendaciones más recientes. Dosis de 75 mcg/día serán probablemente más adecuadas, aunque se necesitan estudios que evalúen la posibilidad de sobretratamiento con dichas dosis.

Introduction

Primary hypothyroidism is characterized by elevated plasma TSH levels. Hypothyroidism is called subclinical when the FT4 level is normal, and overt when the FT4 level is decreased.

During pregnancy, TSH levels higher than 4.5 μU/mL have been related to impaired fetal neurological and psychomotor development and an increased risk of premature labor, pre-eclampsia, and *abruptio placentae*,[1,2] and thyroxine treatment is usually given to normalize TSH levels.[3,4] It has even been proposed that the optimum TSH level in pregnant women is less than 2.5 μU/mL during the first trimester and less than 3 μU/mL during the second and third trimesters.[3,5,6]

The most commonly used approach for starting thyroxine replacement therapy consists of calculating hormone dosage based on the weight of each patient (a mean of 1.6 μg/(kg day) are needed).[7] An alternative that has been shown to be of value for elderly or cardiovascular patients[8] consists of starting treatment at a fixed dose of 25–50 μg/day of thyroxine, with subsequent adjustment based on TSH levels. Starting treatment with a loading dose is an increasingly popular approach, particularly for the management of overt hypothyroidism in pregnant patients.[9] This study was intended to verify whether treatment with fixed thyroxine doses of 50 μg/day is effective during pregnancy.

Patients and methods

All patients diagnosed with subclinical hypothyroidism during pregnancy in the Vigo healthcare area from May 2010 to March 2011 were systematically screened for study entry. Patients with overt hypothyroidism and hypothyroidism diagnosed before pregnancy were excluded. The resulting sample consisted of 68 patients. All these patients received iodine replacement therapy at doses ranging from 200 to 300 μg/day throughout pregnancy.

All patients were given a dose of levothyroxine 50 μg/day on diagnosis of subclinical hypothyroidism, regardless of weight. Each patient was given, until delivery, three-monthly blood tests which included measurements of TSH and FT4 levels, and antiperoxidase and antithyroglobulin antibodies. TSH, FT4, and antiperoxidase and antithyroglobulin antibody tests were performed at the hormone laboratory of Xeral-Cíes de Vigo Hospital. TSH levels were measured using an electrochemiluminescent immunometric analysis (Cobas 6000, Roche Diagnostics, Mannheim, Germany). FT4 and RT3 levels were measured using an electrochemiluminescent competitive immunoassay (Cobas 6000, Roche Diagnostics, Mannheim, Germany). Antithyroglobulin antibodies were tested using a chemiluminescent immunometric test (Immulite 2000, Siemens, Los Angeles, CA, USA), and thyroid peroxidase antibodies by electrochemiluminescent competitive immunoassay (Cobas 6000, Roche Diagnostics, Mannheim, Germany). TSH levels (with a normal range of 0.3–4.5 U/mL, provided by the manufacturer for the non-pregnant overall population) were used to diagnose hypothyroidism and modify thyroxine dosage (which was increased or decreased by 25 μg/day if the TSH level was outside the reference range). The normal range of plasma FT4 levels was 0.7–2 ng/100 mL, and thyroid autoimmunity was defined as antiperoxidase antibody levels higher than 35 IU/mL and/or antithyroglobulin levels higher than 40 IU/mL.

Quantitative variables are given as mean ± standard deviation, and qualitative variables as percentages ± standard error.

Results

Mean patient age was 31.9 years, and mean TSH level at diagnosis of gestational hypothyroidism was 6.3 ± 2.15 μU/mL. Mean FT4 level was 1.05 ± 0.2 ng/100 mL. Positive antiperoxidase or antithyroglobulin antibodies were found in 36% of patients.

Hypothyroidism was diagnosed during the first trimester in 91.2% (62 patients), in the second trimester in 7.4%

(5 patients), and in the third trimester in 1.4% of patients (one patient).

Among the 62 patients diagnosed and initially treated with 50 μg/day in the first trimester, 26 (42%) and 53 (85.5%) patients respectively achieved TSH levels less than 3 μU/mL and less than 4.5 μU/mL in the second trimester. Among those maintained on a dose of 50 μU/day in the second trimester, 50% achieved TSH levels less than 3 μU/mL in the third trimester. Of the 9 patients in whom levothyroxine dose had to be increased to 75 μU/day in the second trimester, 44.5% (4 patients) achieved TSH levels less than 3 μU/mL in the third trimester, and 100% (9 patients) levels less than 4.5 μU/mL.

When treatment effectiveness was analyzed based on TSH levels at diagnosis, the patients with the highest TSH levels (ranging from 6.37 to 12.59 μU/mL) in the first term of pregnancy, who were also treated with levothyroxine 50 μU/day, were studied. In the second trimester, forty percent of them achieved TSH levels less than 3 μU/mL, 85% TSH levels less than 4 μU/mL, and in the remaining 15%, the dose had to be increased to 75 μg/day because they had levels ranging from 4.5 to 5.5 μU/mL. The results achieved in this group of pregnant women with the highest TSH levels were similar to those seen in patients with subclinical hypothyroidism and less elevated TSH levels. No significant differences were found in the proportion of patients who achieved the target limit of TSH level.

No change in levothyroxine dose of 50 μg/day was required in 79.4% of pregnant women because they had TSH levels in the normal range. Levothyroxine dose had to be increased (to 75 μg/day) in the remaining 20.5%, and this new dose achieved normal TSH levels until the time of delivery in all patients. However, if a TSH level less than 3 μU/mL had been taken as a reference in the second trimester, 58% of pregnant patients would have required an increase in levothyroxine dose to 75 μg/day.

Discussion

In our healthcare area, plasma TSH levels are tested in all pregnant patients in the first trimester. Patients who have increased TSH levels are referred to the endocrinology outpatient clinic. For this reason, the enrolled sample optimally reflected the population it represented. Mean patient age was similar to that of all pregnant women during this period in our healthcare area (unpublished data).

Hypothyroidism was diagnosed in most patients based on tests in the first trimester, despite the fact that TSH levels are usually particularly low at this time. This agrees with data from prior publications,[3] confirms the early occurrence of hypothyroidism during pregnancy, and supports the convenience of testing TSH in the first trimester of pregnancy.

Although no study patient had known hypothyroidism before pregnancy, the prevalence of antithyroid antibodies in our sample was substantial. We suspect that these patients probably had undiagnosed thyroid autoimmunity before pregnancy, which may have promoted the development of hypothyroidism with pregnancy.[10] The potential role played by iodine supplementation during pregnancy at doses of 200 μg/day, taken by all of our patients and which has been related to maternal thyroid dysfunction in iodine-deficient areas, should be emphasized.[11]

Our data suggest that treating patients diagnosed subclinical hypothyroidism during pregnancy with levothyroxine 50 μg/day is inadequate in more than 20% of cases if TSH levels for the general, non-pregnant population are taken as a reference, and in even more than 50% of pregnant women if we attempt to achieve the TSH values recently recommended for this particular population. This is a very high proportion in a condition where subclinical hypothyroidism has been associated with significant comorbidity and rapid correction is required. An initial dose of 75 μg/day appears adequate if the target plasma TSH level is less than 4.5 μU/mL. Further studies are needed to assess whether this or higher doses are adequate to achieve lower TSH levels which have been suggested as optimal in recent reports.[3,6,10]

Conflicts of interest

The authors state that they have no conflicts of interest.

References

1. La Franchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? Thyroid. 2005;15:60–71.
2. Haddow JE, Palomaki GE, Allan WC. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. N Engl J Med. 1999;341:549–55.
3. Galofré Ferrater JC, Corrales Hernández JJ, Pérez Corral B, Cantón Blanco A, Alonso Pedrol N, Pérez Pérez A, et al. Guía clínica para el diagnóstico y el tratamiento de la disfunción tiroidea subclínica en la gestación. Endocrinol Nutr. 2009;56:85–91.
4. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. Obstet Gynecol. 2008;112:85–92.
5. Abalovich M, Amino N, Barbour LA, Cobin RH, Dc Groot UT, Glinoer D, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2007;92 Suppl. 8:S1–47.
6. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab. 2010;95:E44–8.
7. Douglas S Ross. Subclinical hypothyroidism [Monografía en Uptodate]. UpToDate 2011. Available from: http://www.uptodate.com/
8. Roos A, Linn-Rasker SP, Van Domburg RT, Tijssen JP, Berghout A. The starting dose of levothyroxine in primary hypothyroidism treatment: a prospective, randomized, double-blind trial. Arch Intern Med. 2005;165:1714–20.
9. Vaidya B, Hubalewska-Dydejczyk A, Laurberg P, Negro R, Vermiglio F, Poppe K. Treatment and screening of hypothyroidism in pregnancy: results of a European survey. Eur J Endocrinol. 2012;166:49–54 [Epub 2011 Oct 24].

10. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. Levothyroxine treatment in euthyroid pregnant women with autimmune thyroid disease: effects on obstetrical complications. J Clin Endocrinol Metab. 2006:1719–22.

11. Rebagliato M, Murcia M, Espada M, Älvarez-Pedrerol M, Bolúmar F, Vioque J, et al. Iodine intake and maternal thyroid function during pregnancy. Epidemiology. 2010;21: 62–9.