Subclinical thyroid dysfunction in pregnancy

Disfunción tiroidea subclínica en la gestación

Federic Tortosa

Servicio de Endocrinología y Nutrición, Hospital Universitari Vall d’Hebron, Barcelona

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Normal thyroid function is essential to ensure normal pregnancy and delivery at term. Subclinical thyroid changes (subclinical hyperthyroidism and hypothyroidism) are the thyroid function abnormalities most common in pregnant women and have an obvious clinical impact on both the fetus and the mother. Hence the importance of their early detection by thyroid function assessment during the first trimester of pregnancy or even in the pregestational state. Such detection is particularly indicated in patients at risk, such as those with a personal or family history of thyroid disease, goiter, positive anti-thyroid antibodies, signs or symptoms suggesting thyroid dysfunction, type 1 diabetes mellitus or other autoimmune diseases, prior neck irradiation, infertility, or a history of prior miscarriage or preterm delivery.

Subclinical thyroid disease involves two disorders that may only be detected by laboratory tests. In non-pregnant subjects, physical examination is not able to identify subclinical thyroid dysfunction in isolated cases. In groups of patients categorized by dysfunction severity (based on thyroid-stimulating hormone [TSH] levels) the group with more overt thyroid dysfunction, is required to show statistically significant differences or, alternatively, large groups with a high number of participants may be used. Another question is whether, once statistically significant differences have been shown, these are clinically relevant and thus have actual practical consequences, or whether they are clinically irrelevant.

This is why current advances allowing for more sensitive serum TSH measurements have made possible an increased understanding of thyroid functional status, and TSH levels have therefore become the best tool for this purpose, even during pregnancy.

Indeed, procedures to measure TSH have greatly improved since the first generation of tests, which were based on radioimmunoassay and were used from 1965 to 1985. This procedure lacked the sensitivity required to detect the lower limit of normal (0.4 mIU/L) and used polyclonal antibodies that cross-reacted with human chorionic gonadotropin (hCG). The second generation, introduced in the 1980s and based on immunometric methods, rapidly replaced radioimmunoassay because of its greater sensitivity (0.1 mIU/L) and its ability to detect the lower TSH levels characteristic of hyperthyroidism. The third generation, also based on the immunometric procedure but with an even greater sensitivity, with a lower limit of 0.01 mIU/L, has become the current procedure of choice. This third-generation immunometric method does not cross-react with hCG either and makes it possible to distinguish the lower TSH levels which commonly occur in the first trimester of pregnancy.

There is still substantial controversy regarding the TSH reference range, particularly the upper reference level, in the non-pregnant population. While there appears to be agreement regarding lower normal limit ranges of from 0.3 to 0.4 mIU/L, widely different values, ranging from 2.1 mIU/L to 7.5 mIU/L, have been suggested as the upper limit of normal. Such wide variability should be attributed to the demographic characteristics of the population such as...
sex, age, race, iodine provision, the inclusion of positive autoimmunity or otherwise and, finally, to the specific characteristics of the different immunometric methods that measure different circulating isoforms of TSH. International clinical guidelines recommend that TSH be measured before pregnancy in women with known hypothyroidism treated with thyroxine to adjust dosage and achieve TSH levels of 2.5 mIU/L or less. In pregnant women, TSH levels should be kept below 2.5 mIU/L during the first trimester and below 3 mIU/L in the second and third trimesters. To achieve these TSH levels, thyroxine doses should therefore be adjusted, or replacement treatment should be started in pregnant women with TSH values higher than those previously reported.

There are two major hormone changes occurring during pregnancy and influencing thyroid function. On the one hand, an increase occurs in serum levels of thyroid hormone binding protein (TBG), and on the other hand, there is an increase in serum hCG levels. TBG levels double during pregnancy because estrogens stimulate its synthesis, and its renal clearance decreases in parallel due to changes in its glycosylation. This situation leads to increased total T4 levels in serum at about week 10 of pregnancy, and such levels persist until the time of delivery.

Serum levels of hCG increase immediately after ovum fertilization, reaching a peak at 10-12 weeks of pregnancy. This hormone has a slight stimulating effect upon the TSH receptor because of its structural homology to TSH. During this period, serum levels of free T4 and T3 slightly increase, usually within the normal limits, and TSH levels concomitantly decrease, with TSH levels in women during the first trimester of pregnancy being lower as compared to non-pregnant women. The decrease in TSH is inversely correlated to hCG elevation and free T4 levels. During the second half of pregnancy, TSH levels gradually return to normal pregestational values and remain stable unless there is adequate iodine provision or an intercurrent thyroid autoimmune condition. In such cases, TSH levels gradually increase, and they even eventually exceed the upper normal limit. These changes in TSH during pregnancy have suggested the need to define the specific reference values for each trimester of pregnancy, which should in turn be for a particular geographic area in order to eliminate the abovementioned demographic variables (ethnic differences and degree of iodination in a given region). That is, reference values during pregnancy should not only be trimester-specific, but also geographic-specific. However, this does not appear to be the definitive solution, because it is not free from disadvantages. In order to prepare reference values for each trimester, small groups of participants are generally used, with the resultant inherent risk of including some extreme values, low or high, that conditions the final reference values. Thus, if one includes a few cases with positive anti-peroxidase antibodies, which usually have higher TSH levels, this conditions the upper reference value, while if women with twin pregnancies or hyperemesis gravidarum, typically having lower TSH values, are included, the lower reference value may also be affected. Therefore, even if the abovementioned variables are strictly controlled, different reference TSH values will be obtained because of the specific characteristics of the various immunometric methods used to quantify the different circulating isoforms of TSH.

Thyroid volume also increases during pregnancy due to gland hyperplasia, and thyroid hormone production increases up to 50% as compared to the pregestational state to meet the requirements of pregnancy. This increased thyroid hormone production, together with the increase in renal clearance of iodide due to the physiological increase in glomerular filtration rate occurring during pregnancy, accounts for the increased need for iodine intake during this period. The WHO recommends 250 mg/day during pregnancy and 300 mcg/day during lactation. It should be noted that 100 mcg of thyroxine only provide 65.3 mcg of iodide, and patients treated with thyroxine will therefore also require additional iodine provision during pregnancy and lactation to achieve the recommended goals.

It is true that chronic iodine deficiency increases TSH levels, which are maintained within normal reference values in cases with mild deficiency and may show a pattern typical of subclinical or overt hypothyroidism when moderate or severe deficiency exists. However, it is also true that, during pregnancy, the thyroid gland of the mother is able to adapt itself to these states of mild to moderate iodine deficiency in order to meet the increased requirements inherent in pregnancy, and the measurement of TSH is of little value in ascertaining the degree of iodine deficiency during pregnancy. Clinical expression of iodine deficiency shows a great individual variability even in endemic areas because it is multifactorial, involving dietary, environmental, and genetic factors. Thus, in order to comply with the recommendations of international organizations such as the WHO and IOM (US Institute of Medicine) for iodine provision during pregnancy in countries where there is no universal iodination of salt, iodine supplementation should be started even months before pregnancy and be continued until the end of lactation.

Recent studies have located expression of the iodine transport protein (NIS) at the apical membrane of enterocytes from rat and mouse small bowel, which suggests that NIS not only transports iodine at thyroid level, but is crucial for the iodine absorption process in the bowel. If this is confirmed in humans, intestinal iodine absorption will be a new variable to be considered when iodine metabolism in humans is assessed. This circumstance could be of special interest regarding subjects and pregnant women with a history of prior bariatric bypass surgery.

To sum up, TSH measurement is required during pregnancy to identify overt or subclinical thyroid dysfunction, although an adequate interpretation of the results requires a good understanding of the demographic characteristics of the population, the degree of iodination and supplementation, the method used (sensitivity, specificity, and reference values), and the different hormonal changes that occur during pregnancy.

References


