REVIEW ARTICLE
THYROID FUNCTION TEST IN PREGNANCY

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INTRODUCTION

Disease of the thyroid gland has been implicated in many reproductive system disorders like menstrual irregularities, infertility, premenstrual syndromes and recurrent abortions (1).

Severely, hypothyroid patients do not become pregnant because of elevated levels of prolactin found in their circulation. The high level prevents ovarian follicular development and maturation (2,3).

Hyperthyroid patients with severe thyrotoxicosis may have menstrual irregularities like altered intermenstrual intervals, reduced menstrual flow and amenorrhoea (2,3). Most cases of hyperthyroidism however, still remain ovulatory and get pregnant. These severe cases with ovulatory cycles have increased risk of spontaneous abortions (3).

Pregnancy is a hyperoestrogenic state due to increased metabolism of androgens to oestrogens (4). These oestrogens induce formation of plasma proteins, particularly thyroid hormone binding globulin, but there is no increase in the production of proteins of liver origin like albumin and pre-albumin (5,6).

EFFECT OF PREGNANCY ON THYROID FUNCTION

The thyroid gland produces thyroid hormones, thyroxine (T_4) and triiodothyronine (T_3) by reaction requiring iodine uptake by the gland, and tyrosine in thyroglobin in follicular cells. T_4 is the hormone predominantly secreted while T_3, the biologically active thyroid hormone, is secreted only in small amounts. Approximately, 85% of circulating T_3 is produced by monodeiodination of T4 in other tissues, particularly the liver, muscle and kidney (7,8,9). These hormones are transported bound to thyroxine binding globulin, thyroxine binding pre-albumin and albumin. The unbound thyroxine is the free hormone and it is small (0.3% for T_4 and 0.01% for T_3). This free hormone gains entry into cells to produce the necessary action of thyroid hormone. T_4 binds more avidly to these proteins than T_3 and so T_3 is easily displaced from its protein binding, making it more available for action than T_4 (8, 10, 11). Production of T_3 and T_4 is stimulated by thyrotropin (TSH) whose release is controlled by circulating thyroid hormone via negative feedback mechanism. These hormones accomplish their activity by stimulating metabolic processes that are specific to the target organs (9).

In pregnancy and lactation, the foetus and infant depend on the mother as the source of iodine. The increase in demand for iodine leads to many changes in the thyroid gland including goitre, appearance of a bruit over the thyroid because of increased blood flow and increase basal metabolic rate (BMR) from increased basal oxygen consumption (9, 11). In fact, the BMR is increased by between 15% and 20% in late pregnancy, to accommodate the work of the foetus and the uterus at this time (12).

The hormonal changes and metabolic demands in pregnancy result in complex changes in thyroid function to maintain the euthyroid state. Thyroid function parameters vary in different trimesters of pregnancy (11, 13). Total serum T_4, T_3 and reversed T_3 (rT_3) are elevated owing to the influence of oestrogen-induced increases in thyroid hormone – binding globulin (12). Plasma levels of free T_4 and free T_3 are elevated in the first trimester and decreased during the second and third trimesters of pregnancy (13). Values return to normal within six weeks postpartum. Plasma thyrotropin level is undetectable in the first trimester and becomes normal in the second and third trimesters (13,14). The changes in these thyroid function parameters are not due to the low albuminaemic state of the third trimester but are thought to be due to the fact that in early pregnancy, placental human chronic gonadotropin (HCG), which has a bioactivity of up to 0.7mU of TSH per unit of HCG, is legated in early pregnancy, and low in late pregnancy. This activity of HCG which leads to increase in thyroid hormone in the first trimester also falls in the last trimester(15). Thyroid hormone levels should therefore be interpreted in relation to the trimester in which they have been performed.

THYROID FUNCTION TESTS

There are two main categories; those that involve the ingestion of radioactive iodine and those that are preformed on the patents blood. In pregnancy, due to the tendency to cause mutation in the foetus, tests that involve the administration of radioisotope should be avoided if diagnosis can be made without their use.

Thyroid function tests involve the estimation of thyroid hormone levels. The hormones estimated are T_4, T_3, free T_3, free T_4 index TSH. Reagent for the estimation of free T_4 and free T_3 are not readily available in developing countries. Therefore only total hormones are usually estimated. Stimulation tests could be done when indicated. These include TSH and thyrotropin-releasing hormones(TRH) to distinguish between secondary and tertiary thyroid disorders.

THYROXINE (T_4)

Total serum T_4 levels are elevated in the first and second trimester of pregnancy (11, 14). This is due to the oestrogen – induced increase in plasma thyroid hormone binding globulin. The free T_4 level is normal or low in second and third trimesters. This is so because T_4 binds more avidly to its binding proteins, so that the toxic effects of thyroid hormones, which are usually caused by the free hormone, are not manifest in pregnancy (6, 12, 13). Free T_4 is normal or mildly elevated in the first trimester of pregnancy and low normal or low by the third trimester (10, 14). The normal or mildly elevated free T_4 is due to increase in activity of HCG from the placenta. This HCG has TSH activity leading to increase in thyroid hormone production. In late pregnancy, HCG levels fall therefore, free T_4 levels fall because of low circulating HCG concentration.

TRIIODOTHYRONINE (T_3)

Total serum T_3 level may be normal or elevated in early pregnancy. This is due to high level of circulating HCG giving rise to more T_4 from which T_3 is formed peripherally (12, 14).

As pregnancy progresses, T_3 level falls due to the fact that it binds less avidly to its specific binding protein – TBG whose level increases in pregnancy. T_3 is therefore easily liberated from TBG into the free pool and metabolised (5, 6, 12). T_3 – TBG binding falls as pregnancy progresses with less stimulation by HCG for thyroid hormone production. T_3 binds to the other plasma proteins – albumin in late pregnancy, the levels of these other binding proteins are low and their binding to T_3 also falls. This also contributes to the low level of total or free T3 in late pregnancy (12, 16).

Total serum T_3 is therefore not ideal for thyroid hormone assessment in pregnancy in suspected cases of thyroxicosis. Free T_3 may be used especially in T_3 – toxicosis, when the level is very high. While in normal pregnancy it is usually low normal (14, 16).

SERUM THYROTROPIN (TSH)

TSH level is either low or undetectable in early pregnancy and rises to normal level in second and third trimesters (12, 13, 15). This is due to the TSH activity of HCG which is high in early pregnancy and low in late pregnancy due to high and low concentration of HCG respectively. HCG has a bioactivity of 0.7Nu of TSH per unit of HCG (17). In early pregnancy, the high level of HCG stimulates production of thyroid hormones. These thyroid hormones act on the anterior pituitary (via negative feedback mechanism) to reduce the secretion of TSH in the first trimester. In the second and third trimesters, HCG level falls, thyroid hormone production is reduced resulting in less negative feedback inhibition on the anterior pituitary, and more TSH is released which can be detectable in plasma (12, 16, 17).

With barely detectable TSH in early pregnancy, but an increased TSH bioactivity, there is increase in thyroid volume, which has been found in about 30% of cases at 36-week gestation. This is particularly significant in areas of borderline iodine intake and in patients that are thyroid autoantibody negative (18). In patients with hydatidiform mole, chorion carcinoma or metastasis from embryonal carcinoma of the testes, the TSH bioactivity of HCG may be so elevated that the patients present with clinical and biochemical features of frank thyrotoxicosis (8, 10).

THYROID- HORMONE RELEASING HORMONE (TRH)

This is a tripeptide released from the hypothalamus and acts on the anterior pituitary to release TSH. TSH acts on the thyroid gland to produce T_3 and T_4 in early pregnancy, TSH response to stimulation may be subnormal but becomes normal in late pregnancy (12, 13, 18). This subnormal response is due to the high level of HCG, which stimulates TSH – receptors resulting in thyroid hormone production, with consequent increased negative feedback inhibition on anterior pituitary. When TRH is injected, there is a subnormal response as the pituitary is already being acted upon by thyroid hormone to decrease production of TSH. TSH stimulation test should therefore not be carried out in early pregnancy, when there is stimulation interplay by HCG (18). It should however be carried out in patients with conditions associated with high levels of HCG like hydatidiform mole,where TSH response is subnormal.

OTHER TESTS OF THYROID FUNCTION

(i) Free thyroxin FT4 index (FTI)

This is one of the complex tests of thyroid function. Free thyroxin index is calculated as plasma T_4 multiplied by T3 resin uptake also known as thyroid hormone binding ratio (THBR) or thyroid hormone binding index (THBI). The normal value ranges from 52% to 142% (14,19).

Free T4 index was designed to correct for binding protein abnormalities (mainly TBG) as in pregnancy, patients on oestrogens and TBG deficiency. Most measurements of FT4I produce results that are higher than those of equilibrium dialysis technique in cases of elevated TBG (20). In TBG deficiency the FTI is falsely low, and is falsely subnormal in some euthroid patients with non- thyroid illness (20, 21).

(ii) T3 – uptake

This is also known as thyroid hormone binding ratio or index (THBR or THBI). It determines the binding capacity of thyroid hormones to TBG. It involves mixing serum, a resin and T3. In pregnancy, due to high TBG level, resulting in increased available binding sites, the T3 can still be absorbed by the serum after resin has been bound to the sites, as the binding site on TBG have not been completely occupied. The test will be low in pregnancy. It is therefore not a helpful test in detecting thyrotoxicosis during this period (12, 20, 21, 22).

(iii)Radioactive iodine uptake (RAIU)

RAIU, thyroid iodine clearance rate and generally, protein bound iodine are increased in pregnancy (12, 14, 15, 22) RAIU and thyroid iodine clearance rates are increased due to the iodine deficiency state of pregnancy as a result of an increase in renal iodine clearance (22). These return to the non – pregnant levels within 6 weeks postpartum. This test is to be avoided in pregnancy due to the tendency for mutagenesis.

(iv)Glucose – 6 – phosphate dehydrogenase (G-6-PD)

The activity of G-6-PD is increased in most cases of hyperthyroidism (16). In pregnancy when all the other tests of thyroid function are elevated, particularly when the total serum hormone levels are elevated as in the first trimester, G-6-PD may be a good adjunct test for the detection of thyrotoxicosis. In normal pregnancy, G-6-PD levels are normal, but high in pregnancy with thyrotoxicosis. G-6-PD assays may also be carried out in borderline cases of thyrotoxicosis.

CONCLUSION

Total serum thyroid hormone estimations are of little value in assessing thyroid status during pregnancy. This is more so in the first trimester because of the high level of HCG, which leads to, increased thyroid hormone production and increased TBG for binding of thyroid hormones. However, in many parts of the world where there are no facilities for other assays other than thyroid hormone assays, the levels of these hormones should be interpreted with caution and with particular reference to the trimester of pregnancy during which the hormones are assayed.

TSH is a more reliable indicator of thyroid status in the second and third trimesters. In the first trimester, some patients may have low undetectable levels. A third generation sensitive TSH assay method should be used to ascertain accuracy of detection of TSH.

Free hormones are the best indicators of thyroid status generally, but they are not readily available in developing nations. Other tests like G-6-PD could be used in pregnancy but this may also not be available in developing countries.

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