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Thyroid Function in Early Normal Pregnancy: Transient Suppression of Thyroid-Stimulating Hormone and Stimulation of Triiodothyronine

Abstract

In order to determine the effect of gestation on thyroid function in healthy subjects, we have prospectively evaluated thyroid function in pregnant individuals undergoing termination of pregnancy, and repeated the tests 2–3 months later. Venous blood was tested for human chorionic gonadotropin (hCG), thyroid-stimulating hormone (TSH), free thyroxine (FT4) and total triiodothyronine (TT3). Early pregnancy thyroid function tests showed a significant decrease ($p < 0.001$) in TSH and a significant increase ($p < 0.001$) in TT3 as compared to the nonpregnant state; FT4, however, did not change significantly. In 8 (11.2%) pregnant subjects, TT3 levels were above the normal range for nonpregnant controls. Elevated thyroid function in early pregnancy is transient, and does not usually warrant antithyroid treatment. Thus, any conclusion regarding thyroid function in early pregnancy should be based on pregnant controls rather than general population controls.

Key Words

Pregnancy
Thyroid
Thyroid-stimulating hormone
Total triiodothyronine
Free thyroxine

Introduction

Pregnancy is associated with changes in thyroid function [1–3] which may cause confusion with regard to the indication for therapy. Of particular interest is the association of hyperthyroidism and hyperemesis gravidarum, a condition of which the etiology is still an enigma [4–10]. These associations suggest that human chorionic gonadotropin has physiologic thyrotrophic properties [11–13]. However, the clinical approach to pregnant individuals with elevated thyroid function is equivocal, mainly because reference laboratory values are obtained from nonpregnant subjects of different age and sex.

In order to determine the effect of early gestation on thyroid function we have prospectively evaluated this correlation in healthy pregnant individuals undergoing termination of pregnancy. Tests were repeated 2–3 months later, thus establishing reference values for early pregnancy.

Materials and Methods

Pregnant subjects undergoing elective termination of pregnancy, and who gave their consent to take part in this study, were evaluated before the procedure, which was performed upon their request based on medical and social reasons such as: unmarried women, age >40 years, previous exposure to irradiation, or previous use of medications which might have teratogenic effects.

Each subject was asked to fill in a detailed questionnaire containing demographic information (age, previous pregnancies, last menstrual period) and the following items: previous medical record; known thyroid disease; known endocrinologic disorder; excessive nausea and vomiting during pregnancy; weight change during pregnancy.

Subjects with known thyroid disorder, or symptoms of hyperemesis gravidarum accompanied with weight loss were excluded from the study. A total of 72 subjects were included. Based on our criteria, 6 women were excluded. At the time of the procedure, the mean gestational age was 9 weeks (from last menstrual period), mean patient's age was 28.1 (SD = 8.9).

Prior to the procedure, which was performed under general anesthesia, 5 ml of venous blood was obtained and tested for human chorionic gonadotropin (hCG), thyroid-stimulating hormone (TSH),

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Table 1. Serum hCG, TSH, TT3 and FT4 before termination of pregnancy and 2–3 months later

	Before termination of pregnancy	After termination of pregnancy	Normal non-pregnant values
Number of patients	70	35	
Serum hCG, IU/l·10^3	175±91	–	<10
Serum TSH, mU/l	1.125±0.92	2.34±1.2*	up to 5
Serum TT3, nmol/l	2.11±0.47	1.65±0.57*	1.0–2.5
Serum FT4, pmol/l	18.1±3.1	16.2±2.6	10.5–25.7

Means ± SD.
* $p < 0.001$ vs. value before termination.

Table 2. Correlations between serum hCG and TSH, TT3 and FT4 concentrations in early pregnancy

	Correlation	Correlation coefficient	Significance (p)
Serum hCG/TSH	negative	0.282	<0.05
Serum hCG/TT3	positive	0.35	<0.05
Serum hCG/FT4	positive	0.32	<0.05

free thyroxine (FT4) and total triiodothyronine (TT3). Blood was withdrawn before any anesthetic medication was given. All tests were performed using the following commercially available radioimmunoassay kits: serum FT4 (Amersham International Ltd., Amersham, UK) sensitivity, intra- and interassay variability were 0.1 pmol/l, 2.5–5.8% and 5.1–8.6%, respectively; serum TT3 (Kodak Clinical Diagnostics Ltd, Amersham, UK) sensitivity, intra- and interassay variability were 0.15 nmol/l, 1.6–3.7% and 3.2–4.9%, respectively; serum TSH (Serono Diagnostic SA, Coisins, Switzerland) sensitivity, intra- and interassay variability were 0.04, 1.6–3.1% and 3.1–3.9%, respectively; serum hCG (Serono) sensitivity, intra- and interassay variability were <1.0 IU/l, 1.4–2.3% and 3.1–4.1%, respectively.

Two to three months later, 5 ml of venous blood was withdrawn and the tests (excluding hCG) were repeated. Recent menstrual history was obtained to rule out the possibility of another pregnancy in 35 women that appeared for a follow-up visit.

Statistical analysis was performed using Student's t test and Pearson's correlation coefficient. $p < 0.05$ was considered significant.

Results

Early pregnancy thyroid function tests showed a significant decrease in TSH and a significant increase in TT3 as compared to the nonpregnant state. FT4, however, did not change significantly (table 1). In 8 (11.2%) pregnant subjects, TT3 levels were above the normal range for nonpregnant subjects in our laboratory, while only 2 had high levels of FT4 (3%).

There was a significant inverse correlation between hCG and TSH concentrations, and a significant positive correlation between hCG and TT3 and between hCG and FT4 (table 2).

Discussion

Our longitudinal study confirms previous reports [12, 13] that normal early pregnancy is associated with a significant change in thyroid function. Most significantly is the decrease in TSH concentrations paralleling the appearance of hCG in the serum. Moreover, hCG is positively correlated with both FT4 and TT3, suggesting a direct thyrotropic effect in addition to increased levels of thyroid-binding globulin (TGB).

The association between hyperthyroxinemia and hyperemesis is often suggested. These patients often lack specific signs of thyrotoxicosis, [8], and usually demonstrate a spontaneous resolution of hyperthyroidism in a matter of a few weeks [9], suggesting a direct thyrotropic effect. The few patients that present with hyperthyroidism late in their pregnancy probably have an underlying thyroid disease. Evans et al. [14] presented data suggesting that hyperemesis patients have higher hCG, TSH, free T4 and total T3 compared with controls. Serum hCG correlated with the degree of thyroid stimulation and the severity of vomiting. This correlation between the degree of hyperthyroidism and the severity of hyperemesis symptoms is controversial [8, 9]. Those who found such an association raise the question of antithyroid therapy aiming at ameliorating the hyperemesis state [7]. Unfortunately, clear evidence for that therapeutic potential is lacking. Moreover, the cause and effect association between hyperemesis and hyperthyroxinemia is not well established. It is also possible that the cause of vomiting is independent of the cause of thyroid stimulation.

Recently, it has been convincingly demonstrated that hCG does indeed stimulate the function of human thyroid cells [15]. It is also generally agreed that hCG exerts a thyroid-stimulating effect in certain pathologic conditions, such as molar pregnancy [16]. Kennedy et al. [17] have shown that while hCG may contribute to the thyroid changes in early pregnancy, the poor correlation between thyroid-stimulating activity and thyroid tests suggests that other factors may be involved. It has been suggested that hCG exists in isoforms which vary in carbohydrate content, and could also vary in their thyroid-stimulating activity [18]. Furthermore, maternal thyroid hyperactivity could be physiologically needed at a time when the placenta is permeable to thyroid hormones which are essential for fetal development.

While molar pregnancy is a distinct pathologic process, hyperemesis gravidarum is considered to be an extreme physiologic response, since some degree of nausea and vomiting occurs frequently in the first trimester of pregnancy. Our data show that a normal pregnancy in a normal woman is associated with a significant change in thyroid function, reflecting a hyperthyroxinemic state without clinical symptoms of hyperemesis or hyperthyroidism. Based on our 70 patients a considerable overlap between pregnant and nonpregnant thyroid function values is obvious. However, the changes in mean values for TSH and TT3 were highly significant ($p < 0.001$), suggesting that the normal range for pregnant subjects is significantly different compared to their nonpregnant counterparts. Therefore, the decision to prescribe antithyroid therapy for pregnant subjects should be based, in addition to the clinical presentation, on the normal range of thyroid functions obtained from pregnant subjects, and not on the general population standard range. The scale applicable for the pregnant state should be established by every laboratory.

In summary, hyperthyroidism manifested as suppressed TSH and elevated TT3 is common in healthy women in the first trimester of pregnancy. This elevation is transient, and does not usually warrant antithyroid treatment.

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