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THYROID FUNCTION IN PREGNANT WOMEN WITH HYPEREMESIS

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ABSTRACT
We conducted a longitudinal study of serum levels of Thyroid stimulating hormone (TSH) and free thyroxine (FT4) in 22 normal pregnant women and 31 patients with hyperemesis gravidarum. When compared with the values in non-pregnant women, the mean serum FT4 level in the normal pregnant women was decreased significantly in the second and third trimesters ($P<0.001$), while their mean serum TSH level was significantly increased in the second ($P<0.05$) and third ($P<0.001$) trimesters.

The group of patients with hyperemesis had a significantly higher mean serum FT4 in the first ($P<0.001$) and second ($P<0.05$) trimesters, and a lower mean serum TSH ($P<0.001$) in the first trimester when compared to a group of normal pregnant women matched for stage of gestation. Serum TSH was suppressed in 80% of patients with hyperemesis. Notably, at 20.9 ± 3.6 weeks gestation, serum TSH and FT4 levels had returned to normal in 95% of patients with hyperemesis.

Results of tests of thyroid function in women with hyperemesis gravidarum should be interpreted cautiously.

ABSTRAIT
Nous avons entrepris une étude longitudinale des niveaux de sérum de l'hormone stimulante thyroïde (TSH) et de la thyroxine libre (FT4) dans 22 femmes enceintes normales et 31 patients avec le gravidarum de hyperemesis. En comparaison avec les valeurs dans les femmes non enceintes, le niveau moyen du sérum FT4 dans les femmes enceintes normales a été diminué sensiblement dans les deuxièmes et troisième trimestres ($P<0.001$), tandis que leur niveau moyen du sérum TSH était sensiblement augmenté dans les deuxièmes ($P<0.05$) et troisième trimesters ($P<0.001$).

Le groupe de patients avec le hyperemesis a eu sensiblement plus haut sérum moyen FT4 dans le premier ($P<0.001$) et en second lieu les trimestres ($P<0.05$), et un sérum moyen inférieur TSH ($P<0.001$) dans le premier trimester une fois comparé à un groupe de femmes enceintes normales s'est assorti pour l'étape de la gestation. Le sérum TSH a été supprimé dans 80% de patients avec le hyperemesis. Notamment, à la gestation de $20.9 + 3.6$ semaines, les niveaux TSH et FT4 de sérum étaient revenus à la normale dans 95% de patients avec le hyperemesis.

Des résultats des essais de la fonction thyroïde chez les femmes avec le gravidarum de hyperemesis devraient être interprétés avec précaution.

INTRODUCTION

Physicians have for long recognized the existence of a delicate interplay between the thyroid gland and the physiological changes induced by pregnancy. These pregnancy-induced physiological changes include (a) the effect of increased concentration of serum thyroid binding globulin, (b) the action of human chorionic gonadotropin (hCG) on thyroid stimulating hormone (TSH) receptors, and (c) the reduced availability of iodine to the maternal thyroid gland due to increased renal clearance of iodine, as well as the transplacental diversion of iodine to the fetal complex. All of these affect the thyroid gland factors either directly or indirectly[1,2].

This delicate balance can be distorted by hyperemesis, among other factors. Emesis usually occurs in the first trimester of pregnancy when the level of serum hCG is very high. It has been well documented that hCG has thyroid-stimulating effects. Infacts, in 1993, in a study of patients with hyperemesis gravidarum, Burrow[3] found decreased serum TSH levels, in association with elevated serum free T4 levels, similar to what is typically found in patients with hyperthyroidism. Because of this, hyperemesis gravidarum has been described as a state of "gestational hyperthyroidism"[4,5]. Therefore, the usual dilemma facing a clinician is the possible misdiagnosis and treatment of a pregnant woman with hyperemesis as hyperthyroid since the two conditions present similar thyroid hormone profiles. Some workers have argued that hyperthyroidism is the cause of the hyperemesis, and so advocated the use of antithyroid therapy[6]. Such treatment was found to adversely affect the fetus, and as a result anitithyroid drugs are no longer justified in pregnant patients with hyperemesis who have no definite evidence of true hyperthyroidism[4,7,8].

Unlike true hyperthyroidism, "hyperemetic hyperthyroid" is a self-limiting condition that begins in the early weeks of gestation and resolves spontaneously by the mid trimester. The absence of a goiter and a history suggestive of hyperthyroidism are usually sufficient to differentiate "hyperemetic hyperthyroidism" from true hyperthyroidism in pregnancy.[3] However, these may not be sufficient criteria in our patients because marginal iodine deficiency has been documented to exist in our environment[9]. Onyeanusi et al[9] found low free T4 levels and increased goiter rates in a large proportion of pregnant women from the same population. Since data on thyroid function in Nigerian patients with hyperemesis gravidarum is very scanty, the current study is designed to present longitudinal data on maternal thyroid function in pregnant women with and without hyperemesis gravidarum.

MATERIALS AND METHODS

Thirty-four pregnant women seen at the University of Nigeria Teaching Hospital (UNTH) and Mother of Christ Hospital, both in Enugu, Nigeria because of hyperemesis gravidarum, volunteered to participate in a study of their thyroid function throughout the course of their pregnancy. A patient was said to have hyperemesis gravidarum if she had recurrent vomiting (*more than once everyday) initially presenting in the first trimester of pregnancy and which was associated with both positive ketonuria on dipstick examination and a greater than 5% weight loss*. All subjects included in the study had their onset of vomiting in the first trimester ($\leq$ 13 weeks gestation) and had no other identifiable cause for the vomiting. Hyperemesis was

considered to be mild if results of serum electrolytes and liver function tests were normal. Out of the thirty-four volunteers, three women were dropped because of a previous history of hyperthyroidism and clinical symptoms consistent with hyperthyroidism. No patient was taking antiemetic formulation at the time of initial evaluation *except* for vitamin supplements.

Forty-one age-matched non-pregnant healthy female students and staff of UNTH aged 18-37 years were selected as the "non-pregnant control group. Also, 22 pregnant women without hyperemesis gravidarum, who were studied longitudinally throughout pregnancy, served as the "normal control group".

Serum samples from patients and the control groups were frozen at 20 degrees Celsius until testing. Serum TSH was measured using a highly sensitive 'in house' immunoradiometric essay (IRMA) with reagents obtained from NETRIA (St. Bartholomew's Hospital, London, UK). The assay sensitivity, recovery and intra- and interassay variations are 0.09mU/L, 94 104%, 4.4-6.2% and 4.2-9.4%, respectively. The free T4 was measured with Serono FT4 assay kit (Serono, Switzerland). The serozyme FT4 assay employs a new technology that allows the use of the conventional enzyme immunoassay (EIA) with minimal disturbance to the free and bound T4 equilibrium. This assay technique is not affected by the concentration of thyroxine-binding globulin (TBG) and albumin. The FT4 assay unit was in pg/ml, but was converted to international unit, pmol/L[10]. Data was analysed by the paired t-test and results were presented as mean $\pm$ standard deviation (SD).

RESULTS

Table 1 shows the serum FT4 and TSH levels (mean $\pm$ SD) of 22 normal pregnant and 41 non-pregnant women. There was a significant reduction of mean serum concentration of FT4 in the second and third trimesters ($p<0.001$) when compared to the mean value in the non-pregnant control women. Also, the mean serum TSH levels of the pregnant females were significantly higher in the second and third trimesters ($p<0.05$; and $p<0.001$, respectively) when compared with the non-pregnant control group.

Figure 1 shows the changes in the mean serum FT4 and mean serum TSH concentrations during normal pregnancy. There was a progressive decline of the mean serum FT4 concentration and a progressive increase of the mean serum TSH concentration throughout gestation.

In Table 2 the longitudinal changes of the mean free T4 and TSH serum levels in normal pregnant women were compared to the mean values in patients with hyperemesis gravidarum. The mean FT4 levels in the pregnant women with hyperemesis were significantly greater in the first trimester ($p<0.001$) and second trimester ($p<0.05$) than the mean values in the normal pregnant control group. On the other hand, the mean serum TSH concentration in the pregnant women with hyperemesis was significantly lower ($p<0.001$) than the value for the normal pregnant group in the first gestational trimester.

In figures 2 and 3, the mean values of the serum TSH and free T4 levels in the pregnant patients with hyperemesis during the three gestational trimesters were compared with the values in the normal pregnant control group. The results show that, in the first trimester of gestation, the patients with hyperemesis had a markedly lower mean serum TSH

concentration and a markedly higher mean serum FT4 concentration, when compared with the control pregnant group.

DISCUSSION

Several workers have reported discordant result in studies of serum thyroid hormone levels during normal pregnancy[2,11,12,13,14]. These differences may in part be due to differences in the assay methods used or to regional difference in iodine intake of the study subjects. In the current longitudinal study, we used free T4 EIA system (Serono, Switzerland) that is not influenced by the changes in serum thyroid protein associated with pregnancy. We observed that the serum FT4 levels were significantly decreased in the second and third gestational trimesters of normal pregnancy. Conversely, the serum levels of TSH were significantly increased in the second and third trimesters. This pattern of changes suggests the existence of relative hypothyroxinaemia, which may be a reflection of (thus indicating) inadequate dietary iodine intake in this population. The current report agrees with the significant and progressive rise in the serum TSH during normal pregnancy found by Glinoer[4], and Kabyemela[11], who studied patients in iodine deficient areas. Other workers have reported no increase in TSH levels during pregnancy[13,14].

In pregnant women with hyperemesis, gestational hyperthyroidism is a self-limiting feature that resolves in the mid second trimester (20.9 ± 3.6, mean $\pm$ SE). In the present study, we found that the mean serum FT4 level of the patients with hyperemesis was significantly higher in the first ($p<0.001$) and second ($p<0.05$) trimesters, and that the mean serum TSH level was significantly lower in the first trimester ($p<0.001$), than the values for the normal control group. About 80% of the patients with hyperemesis had elevated free T4 and suppressed TSH (<0.5mU/L) levels, thus suggesting excess thyroid stimulation among these patients. Our report agrees with the works done by Goodwin et al.[4], Bouillon et al[6]. and Mori et al[7]. In contrast, Evans et al.[17] observed no relationship between the thyroid function and the degree of morning sickness during pregnancy. An interesting finding in our study was the rapid return of TSH levels of the group with hyperemesis to the levels found in the normal pregnant control group in the second trimester. The return corresponds with the resolution of hyperemesis in about 95% of the subjects in our report, and supports the hypothesis that unusually high hCG level in early pregnancy plays an important role in the etiology of hyperemesis[4]. Some variants of hCG have been identified as thyroid stimulators through their actions on TSH receptors, and others stimulate the corpus luteum to produce estradiol and progesterone[16.17]. In 1992 Goodwin et al.[4] reported a greater concentration of estradiol in patients with hyperemesis that provides a plausible link between hCG and the clinical symptoms of nausea and vomiting during pregnancy.

In our opinion, hyperemetic patients with biochemical hyperthyroidism in early pregnancy should not be treated with antithyroid drugs if the patient does not have clinical symptoms or previous history of Graves' disease. However, if subclincial hyperthyroidism is suspect, serum levels of thyroid-stimulating antibody should be determined before placing the patient on treatment.

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TABLE 1. Thyroid function in normal pregnant women and non-pregnant controls.

	Non pregnant Control N=41	1st trimester (≤ 13wks) N=22	2nd trimester (14-26wks) N=22	3rd trimester (27-41wks) N=22
Free T4 (Pmol/L)	13.41±3.24	12.49±1.96	11.08±1.51**	9.06±0.98**
TSH (mU/L)	3.10±1.03	2.84±0.51	3.45±0.39*	4.70±1.09**

Significant difference from non-pregnant control group:

* P<0.05

**P<0.001

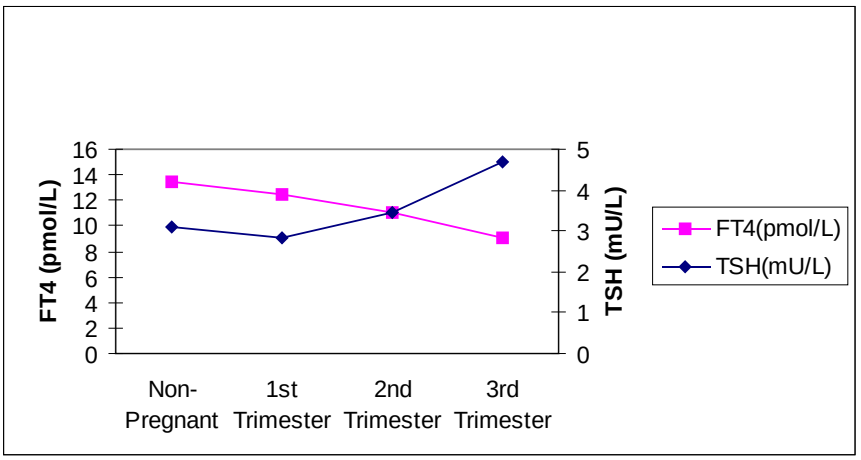

FIGURE 1. Serial changes in FT4 and TSH concentrations during normal pregnancy compared with non-pregnant control values.

TABLE 2. Comparison of thyroid functions in longitudinal studies among normal pregnant control and hyperemetic pregnant groups

	1st Trimester (13wks)		2nd Trimester (14 -26wks)		3rd Trimester (27-41wks)	
	Control N=22 MGW±SE (10.7±4.2)	Hyperemesis N=31 MGW±SE (10.4±4.3)	Control N=22 MGW±SE (21.4±3.2)	Hyperemesis N=31 MGW±SE (20.9±3.6)	Control N=22 MGW±SE (32.8±3.4)	Hyperemesis N=31 MGW±SE (33.2±4.6)
Ft4 (Pmol/L)	12.49±1.96	16.34±1.34**	11.08±1.51	11.78±1.21*	9.06±0.98	9.42±1.06
TSH (MU/L)	2.84±0.51	1.32±0.45*	3.45±0.39	3.24±0.84 NS (p<0.10)	4.70±1.09	4.42±1.12 NS (p<0.25)

Significant difference from normal pregnant control group, **P<0.001 and *P<0.05.
MGW±SE=mean gestational week, SE= Standard error; Ft4±SD =free thyroxin; TSH±SD= thyroid stimulating hormone, SD= standard deviation. NS=Non significant.

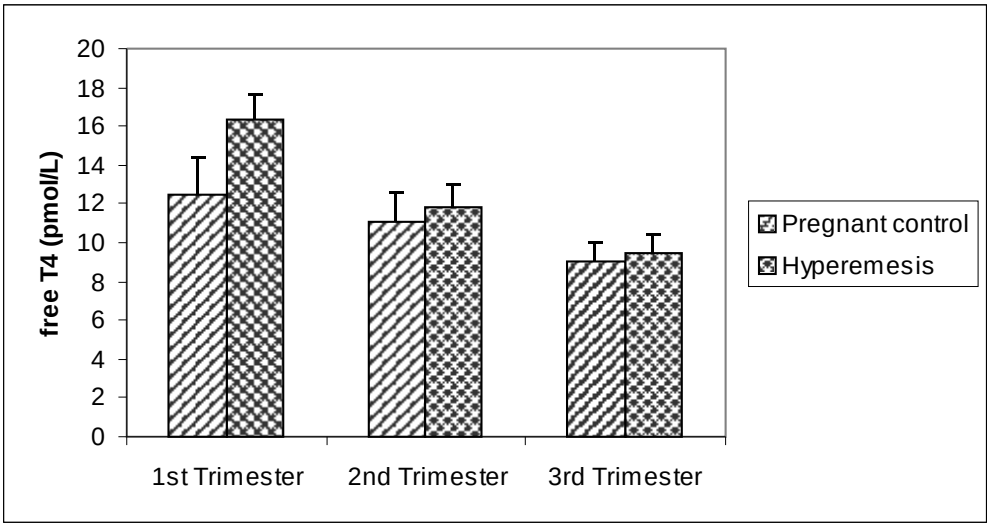

FIGURE 2. The Changes in serum FT4 values in hyperemesis and pregnant control group.

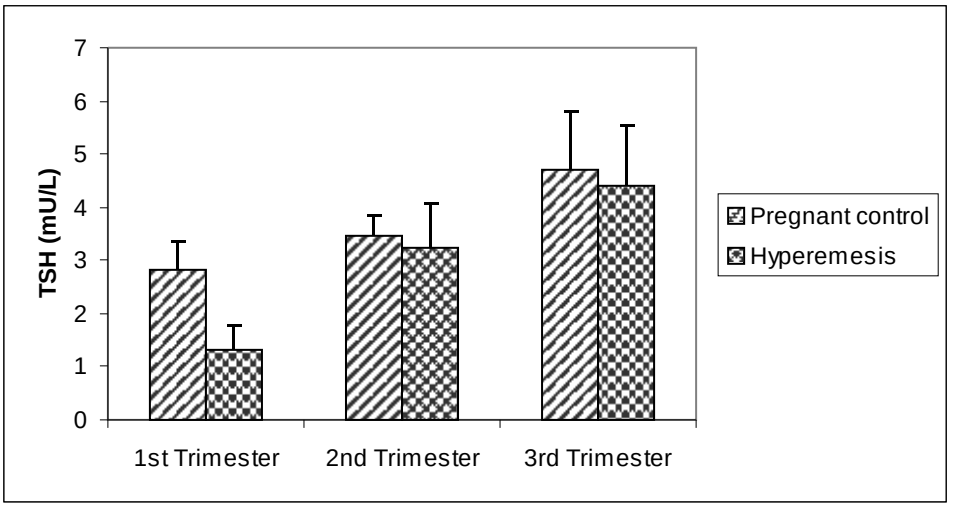

FIGURE 3. Mean Serum TSH changes in Hyperemesis and pregnant control group.

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