

Maternal Thyroid Function during Pregnancy and Puerperal Period

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Abstract. It has been noted that hypothyroidism in pregnant women can adversely affect the children's subsequent psychoneurotic development. Also, transient elevation of serum free thyroxine is occasionally seen in the first trimester of normal pregnancy. However, normal thyroid function during pregnancy and the puerperal period has not been clearly defined in Japan. The aim of this study was to assess maternal thyroid function during pregnancy and puerperal period in Japan. The concentrations of thyroid stimulating hormone (TSH), free triiodo-thyronine (free T_3), free thyroxine (free T_4) and thyroid binding capacity (TBC) of 522 normal pregnant and puerperal women (119 in the first trimester; 132 in the second trimester; 135 in the third trimester and 136 in the early puerperium) were measured by electrochemiluminescence immunoassay. We compared the measured data with those of healthy nonpregnant control. Twenty-six (21.8%) of 119 women in the first trimester had lower TSH levels and 23 (16.9%) of 136 women in the early puerperium had higher TSH levels than the normal range of healthy nonpregnant controls. Free T_3 gradually decreased during pregnancy, although it remained within the normal control range. Eight (6.7%) of 119 women in the first trimester had high free T_4 levels, which gradually decreased during pregnancy. Sixty (44.4%) of 135 women in the third trimester had low free T_4 levels. The values of TBC in the second trimester increased compared with the first trimester and did not change in the third trimester and decreased after delivery. There were no correlations between maternal TSH and levels of thyroid hormones (free T_3 or free T_4), except for TSH and free T_4 in the first trimester. In conclusion, we showed that maternal thyroid function, especially TSH and free T_4 , changed during the course of pregnancy. In assessing the thyroid function associated with pregnancy, one needs to keep in mind the tendency toward low free T_4 levels in the third trimester and high TSH levels in the early puerperal period.

Key words: Thyroid function, Pregnancy, Puerperium, Electrochemiluminescence immunoassay

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THYROID disorders are observed more frequently in women of childbearing age, and pregnancy is often complicated by these disorders. Hormonal changes and metabolic demands during pregnancy result in profound alterations in fetomaternal thyroid function. Glinioer *et al.* [1] studied the precise mechanism regulating the maternal thyroid function and concluded that thyroid changes in pregnancy were generally minor and consisted primarily of an increase in thyroid binding globulin (TBG). However, our understanding of

thyroid function associated with pregnancy has evolved significantly over the past several years and Glinioer's review [2] reported that previous assumptions were far from the truth. New findings have yielded a new concept of gestational transient hyperthyroxinemia [3–6]. A study by Haddow *et al.* [7] documented maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. Further studies highlighted the complex relations that exist between maternal thyroid deficiency during pregnancy and its possible consequences for the neuropsychointellectual development of the fetus and child [8, 9]. Undiagnosed subclinical hypothyroidism in pregnant women is probably more prevalent than usually considered. In this article, we examined data regarding changes in maternal thyroid function during pregnancy

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to assist in the systematic detection of thyroid abnormalities associated with pregnancy in Japan.

Patients and Methods

Patients

Five hundred and twenty-two pregnant women were enrolled at Koike Hospital. The study was limited to women with viable singleton pregnancies. The number of primigravida was 271 while multigravida was 251. Birth weight was 3073 ± 374 gram (mean \pm standard deviation).

Methods

For cross-sectional analysis of thyroid function during pregnancy and puerperium, serum of thyroid stimulating hormone (TSH), free triiodo-thyronine (free T_3), free thyroxine (free T_4) and thyroid binding capacity (TBC) were measured in 522 normal pregnant and puerperal women. These 522 subjects consisted of 119 in the first trimester (less than 14 weeks of gestation), 132 in the second (14–27 weeks of gestation), 135 in the third trimester (more than 28 weeks of gestation) and 136 in the early puerperium (3–4 days after delivery). All hormone assays were measured by electrochemiluminescence immunoassay (ECLusys, Roche, Tokyo) [10].

Statistical analyses of data were performed by non-repeated measures ANOVA.

All research was conducted with informed consents of the patients.

Results

The biochemical parameters of thyroid function are given in Table 1. Reference values are expressed as the mean values with the normal range of nonpregnant subjects in parentheses. TSH showed the lowest values in the first trimester and the highest values in the early puerperium. Free T_3 gradually decreased during pregnancy and increased in the early puerperium, although it remained within the normal control range. Free T_4 showed the highest values in the first trimester, gradually decreased during pregnancy and then increased in the early puerperium. TBC in the second trimester increased compared with the first trimester and did not change in the third trimester. After pregnancy, TBC decreased. Table 2 shows the total numbers and percentages of subjects with abnormal values compared with the normal range for nonpregnant subjects. In the first trimester, 26 (21.8%) of 119 subjects had abnormally low values of TSH. In the early puerperium, 23 (16.9%) of 136 subjects had abnormally high values of TSH. The values of free T_3 during pregnancy and puerperal period are within early the same range as in nonpregnant subjects. In the first trimester, 8 (6.7%) of 119 subjects had abnormally high values of free T_4 . In the second and third trimester, 28 (21.2%) of 132 subjects and 60 (44.4%) of 135 subjects had abnormally low values of free T_4 . In the early puerperium, 41 (30.1%) of 136 subjects indicated abnormally low values of free T_4 . In the first trimester, the values of TBC remained in the same range as for nonpregnant subjects. Afterward, TBC in most subjects rose and was maintained at high levels until term. After delivery, it decreased. Table 3 shows the normal range of thyroid function for pregnant and puerperal women based on our data.

Table 1. Biochemical parameters of thyroid function during gestation and early puerperal period

	pregnancy			puerperium
	first trimester (n = 119)	second trimester (n = 132)	third trimester (n = 135)	3–4 days (n = 136)
TSH (0.27–4.2 μ U/ml)	1.05 ± 0.97^a	1.51 ± 0.94^b	1.23 ± 0.75^c	2.96 ± 0.51^d
free T_3 (2.6–5.1 pg/ml)	3.60 ± 0.50^a	3.39 ± 0.44^b	3.17 ± 0.43^c	3.57 ± 0.55^d
free T_4 (1.0–1.8 ng/dl)	1.43 ± 0.21^a	1.11 ± 0.13^b	1.02 ± 0.15^c	1.08 ± 0.14^d
TBC (0.8–1.3 TBI)	1.07 ± 0.09^a	1.32 ± 0.09^b	1.32 ± 0.08^c	1.27 ± 0.08^d

Values are given as the mean \pm SD. Reference ranges for nonpregnant subjects are indicated in parentheses.

TSH: a–b; $P < 0.001$, b–c; $P < 0.05$, a–d, b–d, c–d; $P < 0.0001$

free T_3 : a–b, b–c; $P < 0.001$, a–c, c–d; $P < 0.0001$, b–d; $P < 0.05$

free T_4 : a–b, a–c, a–d, b–c; $P < 0.0001$, c–d; $P < 0.01$

TBC: a–b, a–c, a–d, b–d, c–d; $P < 0.0001$

Table 2. Fractional distribution of lower or higher thyroid function

		pregnancy			puerperium
		first trimester (n = 119)	second trimester (n = 132)	third trimester (n = 135)	3–4 days (n = 136)
TSH	low value (%)	26 (21.8)	6 (4.5)	10 (0.74)	1 (0.7)
	high value (%)	3 (2.5)	2 (1.5)	0	23 (16.9)
free T ₃	low value (%)	2 (1.7)	1 (0.8)	1 (0.7)	1 (0.7)
	high value (%)	0	0	0	0
free T ₄	low value (%)	0	28 (21.2)	60 (44.4)	41 (30.1)
	high value (%)	8 (6.7)	0	0	0
TBC	low value (%)	0	1 (0.8)	0	0
	high value (%)	0	90 (68.1)	83 (61.5)	49 (36.0)

Table 3. Proposed normal range of thyroid function for pregnant and early puerperal women

	pregnancy			puerperium
	first trimester	second trimester	third trimester	3–4 days
TSH (μIU/ml)	0.04–3.39	0.17–3.72	0.04–3.30	0.90–5.81
free T ₃ (pg/ml)	2.68–4.59	2.56–4.11	2.53–4.10	2.62–4.46
free T ₄ (ng/dl)	1.16–1.95	0.89–1.39	0.77–1.27	0.81–1.34
TBC TBI	0.89–1.24	1.13–1.43	1.15–1.45	1.12–1.42

Table 4. Correlation between TSH and thyroid hormones

		coefficient of regression	R	P value
first trimester	TSH and free T ₃	0.14	0.271	<0.01
	TSH and free T ₄	–0.112	0.527	<0.0001
second trimester	TSH and free T ₃	–0.12	0.255	<0.01
	TSH and free T ₄	–0.027	0.188	<0.05
third trimester	TSH and free T ₃	–0.101	0.178	<0.05
	TSH and free T ₄	–0.043	0.225	<0.05
3–4 days after delivery	TSH and free T ₃	–0.061	0.165	0.06
	TSH and free T ₄	–0.013	0.141	0.11

We investigated the correlation between TSH and thyroid hormones (Table 4). There is a negative correlation between TSH and free T₄ (R = 0.527) only in the first trimester. We detected a weak negative correlation between TSH and free T₄ in the second and third trimesters, and found a weak negative correlation between TSH and free T₃ during pregnancy. No correlations between TSH and thyroid hormones were detected during early puerperium.

Discussion

Pregnancy is accompanied by alterations in thyroid

function because of the rise in hCG and thyroglobulin. Glinier *et al.* [1] indicated that free hormone concentrations decrease during pregnancy. However, free T₄ concentration remained within the reference range for nonpregnant subjects in most women. The negative feedback control system of hypothalamic-pituitary-thyroid axis functions is normal in pregnant women, which means that serum thyrotropin concentrations during most pregnancies are similar to those in nonpregnant women [11].

Women with hypothyroidism who become pregnant carry an increased risk for obstetrical complications such as intrauterine fetal death, gestational hypertension, placental abruption, and poor perinatal outcome

[12–15]. Until now we have diagnosed hypothyroidism during pregnancy by means of low levels of free T_3 and T_4 and high levels of TSH and positive thyroid antibodies, using the reference range established for nonpregnant subjects. Recently, it has become possible to measure thyroid related hormones by means of the highly sensitive electrochemiluminescence immunoassay [10]. While serum albumin during pregnancy shows lower levels than the normal range of healthy nonpregnant controls, this method is not so influenced by albumin or blocking antibody (human anti mouse antibodies, anti T_3 and T_4 antibody) [16]. Electrochemiluminescence immunoassay of free T_3 thus led to correct values according to the patients' thyroid status [17]. Therefore we should reinvestigate the normal range of thyroid related hormones and CBC during pregnancy and puerperal period by means of this measurement. In the second and especially in the third trimester, many subjects showed low values of free T_4 , even though they had normal TSH and free T_3 levels. Thus, we can evaluate maternal thyroid function in the second and third trimester by examining TSH and free T_3 . Maternal low T_4 concentration and an increase of TBC are thought to be physiologically normal in the second and third trimester during pregnancy. Therefore, the relationship between thyroid hormones and TSH during pregnancy differs from that in the nonpregnant period. Hormonal changes and metabolic demands during pregnancy results in profound alterations in the biochemical parameters of thyroid function. These results occurred due to high estrogen levels, human gonadotropin levels and modifications in the peripheral metabolism of thyroid hormones through transplacental passage and deiodination [8].

The major cause of hyperthyroidism in women of childbearing age is Graves' disease. Accurate diagnosis of Graves' disease is important, because untreated hyperthyroidism is associated with fetal loss, premature labor and low birth weight [18]. It is recommended that TSH receptor antibody (TRAb) titers be assayed because high serum TRAb value during pregnancy is one of the risk factors for poor perinatal out-

come [19, 20]. Gestational hyperthyroidism of non-autoimmune origin occurring in women with normal pregnancy has recently been established [6]. This type of gestational transient thyrotoxicosis (GTT) differs from Graves' disease as it occurs in women without a past history of Graves' disease and without detectable thyroid stimulating antibody (TSAb). In a review article [21], it is reported that the prevalence of GTT may be as high as 2–3% of all pregnancies. In our study, some subjects, whether they had clinical symptoms or not, showed high values of free T_4 (6.7%) and low values of TSH (21.8%). It is not necessary to treat such patients for hyperthyroidism. A previous report [3] by means of other assay and our results are the same.

The clinical courses of autoimmune thyroid disorders associated with Graves' disease generally tend to improve during pregnancy, because there is a progressive decrease in the titers of autoimmune antibodies and an increase of hormone-binding capacity due to rise in TBG and estrogen. Hashimoto's disease also has the same clinical course because of the decrease in the titers of autoimmune antibodies. Due to large changes of antibodies and hormones, this latter disease may get worse after delivery, hence we must carefully monitor puerperal maternal thyroid function. However, our data indicated low free T_4 and high TSH levels in the early puerperal period and these findings suggested that the cause of the high initial TSH values was not autoimmune disease. The same argument was reported by Lao *et al.* and Sack *et al.* [22, 23]. Therefore, the early puerperal period is not an appropriate time to assess the postpartum maternal thyroid function.

In conclusion, further studies are needed to assess the specific aspects of thyroid function associated with pregnancy.

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