Thyroid Function and Human Chorionic Gonadotropin in Patients with Hydatidiform Mole

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Absract

Sixty-seven patients with molar pregnancy were studied on admission to Rajvithi Hospital from 1992 to 1996. Thyroid function tests and serum hCG concentrations were measured. On the basis of thyroid function test results, the patients could be subdivided into three groups ; Group I (hyperthyroid), Group II (subclinical hyperthyroid) and Group III (nontoxic). We found significant correlation between hCG and T_4, T_3 and FT_4I levels (rho=0.559, p<0.001 n=35 ; rho= 0.629, p<0.001 n=35 ; and rho=0.465, p=0.010 n=30 respectively). These findings support that a variant hCG is responsible for hyperthyroidism observed in patients with molar pregnancy.

The association between hyperthyroid and gestational trophoblastic tumors either hydatidiform mole[1-4] or choriocarcimoma[5,6] is well recognized. Since the first report of hyperthyroid in a patient with hydatidiform mole in 1955, many additional cases have been reported. The hyperthyroidism may be severe and associated with symptoms[1,2,6,7] or it may be mild with only biochemical changes[5,8]. Both biochemical and clinical features of hyperthyroidism may be modified by the pregnant state and by the underlying non-thyroidal illness[9]. These reports showed that the hyperthyroidism disappeared rapidly after removal of the molar tumor, thus suggesting that the tumor made a substance responsible for the hyperthyroidism. A thyroid-stimulating substance was isolated from the sera and tumors of patients with trophoblastic disease[10], and it was called "molar thyrotropin". The level of molar thyrotropin in the sera correlated directly with the increased serum thyroid hormone concentrations in these patients[3]. Molar thyrotropin was found to be distinct from known stimulators of the thyroid, namely pituitary thyroid stimulating hormone (TSH) and thyroid stimulating immunoglobulin (TSI), isolated from serum samples of patients with Graves' disease[11]. In 1975, it was documented that human chorionic gonadotropin (hCG), the hor-

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mone secreted by trophoblastic tumor, was molar thyrotropin[12]. However, there are doubts about the ability of hCG to act as a thyroid stimulator [13,14]. Extensive investigations have been conducted to identify this stimulator, but general consensus as to its nature has not been achieved. It is possible that the stimulator is closely related to hCG[15].

Our study presents a large series of patients with hydatidiform mole in whom thyroid function and serum hCG have been studied to evaluate the thyroid status and to determine the correlation between thyroid function and serum hCG.

METHOD

Sixty-seven patients with molar pregnancy were studied on admission to Rajvithi Hospital from 1992 to 1996. Diagnosis was made by clinical findings, ultrasonography of the uterus and the demonstration of a high titer of serum hCG. The diagnosis was ultimately confirmed by histologic examination in all patients. The patients were between 15-47 years of age (mean age=25), and none had a history of antecedent thyroid disease.

Serum thyroxine (T_4) and triiodothyronine (T_3) levels were done by radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.). Serum concentration of thyrotropin (TSH) was done by immunoradiometric assay (Incstar Corporation, Stillwater, MN, U.S.A.). T_3-resin uptake values were measured by double-antibody technique radioimmunoassay (Diagnostic Products Corporation, Los Angeles, CA, U.S.A.). Serum free T_4 index (FT_4I) was calculated as the product of the serum T_4 and T_3-resin uptake values. Antibodies directed against thyroglobulin (TGHA) and microsomal antigen (MCHA) were measured using hemagglutination technique (Murex, Dartford, UK).

Serum hCG was measured by an hCG double antibody kit (Diagnostic Products Corporation, U.S.A.)

Statistical analysis

Mann-Whitney U test was used to compare serum hCG concentrations in group I, group II and group III. Correlation was assessed by the method of Spearman. P-values of less than 0.05 was considered to indicate statistical significance.

RESULTS

On the basis of thyroid function test results, it was noted that patients could be subdivided into the following groups

Group I (Hyperthyroid) TSH concentrations less than normal value (<0.35 m IU/L) together with unequivocal evidence of raised FT_4I, serum T_4 and T_3 (the T_3 concentrations in three patients being normal)

Group II (subclinical hyperthyroid) TSH <0.35 m IU/L with normal FT_4I, total T_4 and total T_3 (the total T_3 concentrations in four patients being low, total T_4 and T_3 were within the range for normal pregnancy).

Group III (non-toxic) TSH concentration >0.35 m IU/L (The TSH concentration in one patient being 6.15) with normal FT_4I normal T_4 and T_3. (total T_4 concentration in one patient and total T3 concentrations in three patients being low)

The mean values for serum hormone concentrations relating to each group are shown in Table 1. Circulating thyroid antibodies were measured in forty-five patients, all were negative.

Table 1. Thyroid function tests in patients with hydatidiform mole.

	Total groups (n=67)	Group I Hyperthyroid (n=37)	Group II Subclinical hyperthyroid (n=20)	Group III Nontoxic (n=10)
T_4 (μg/dl)	16.837±6.830	22.12±3.69	10.96±3.269	9.030±2.373
T_3 (ng/dl)	233.955±141.200	328.2±117.1	125.25±64.5	112.0±59.429
FT_4I	4.621±2.885	6.731±2.436	2.449±0.728	1.991±0.533
TSH (mIU/L)	0.488±1.157	0.081±0.0298	0.097±0.043	2.311±1.974
T_3/T_4	13.216±4.675	14.642±4.258	11.185±4.910	12.251±4.521

All data expressed as mean ± SD.
Normal range : T_4=4.5-11.5 μg/dl, T_3=60-170 ng/dl, FT_4I=1.33-3.67, TSH=0.35-5.2 mIU/L

Serum hCG concentration

The mean and standard deviation of serum hCG in group I, group II and group III were 98117.9 ± 712718.8 (n=19), 922302.0 ± 998706.6 (n=10) and 194637.8 ± 376739.8 (n=6), respectively. Serum hCG concentrations were not significantly higher in group I than either group II or group III (p=0.482 and p=0.429, respectively), and also there was no significant difference between group II and group III (p=0.393).

Among the fifty-five serum hCG were measured, the precise values could not be achieved due to initial analysis values for the exact number were not done in 20 patients (i.e. the results reported as >200,000 in 11 patients, >300,000 in 8 patients and <200,000 in one patient). Only 35 serum hCG were available for analysis.

Correlation of serum hCG and thyroid hormone concentrations

Analysis of the resulting data from 35 patients revealed a significant correlation between values of the serum hCG and total T_4 concentration (rho=0.559, p<0.001) (Fig. 1). A significant

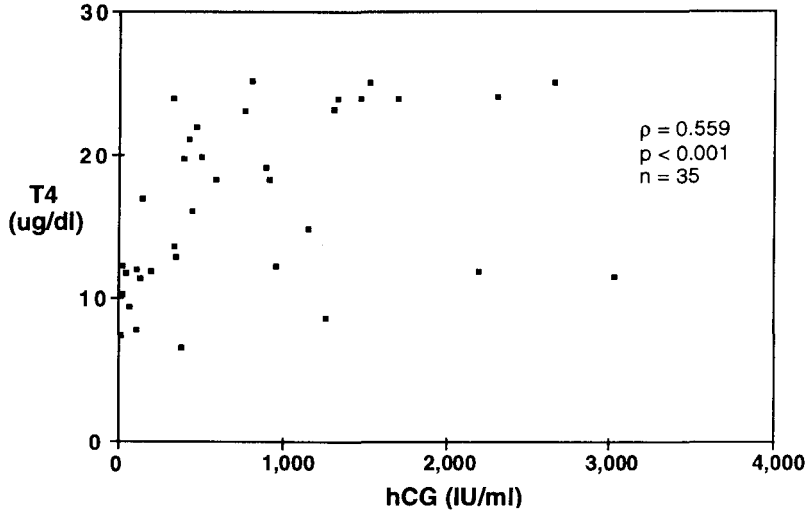

Fig. 1. Correlation between serum hCG and serum T_4 in patients with hydatidiform mole. A significant correlation was seen.

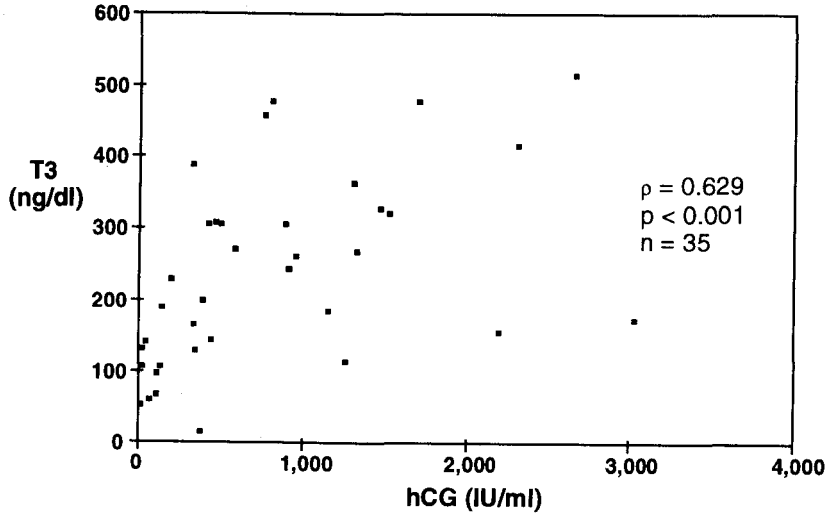

Fig. 2. Correlation between serum hCG and serum T_3 in patients with hydatidiform mole. A significant correlation was observed.

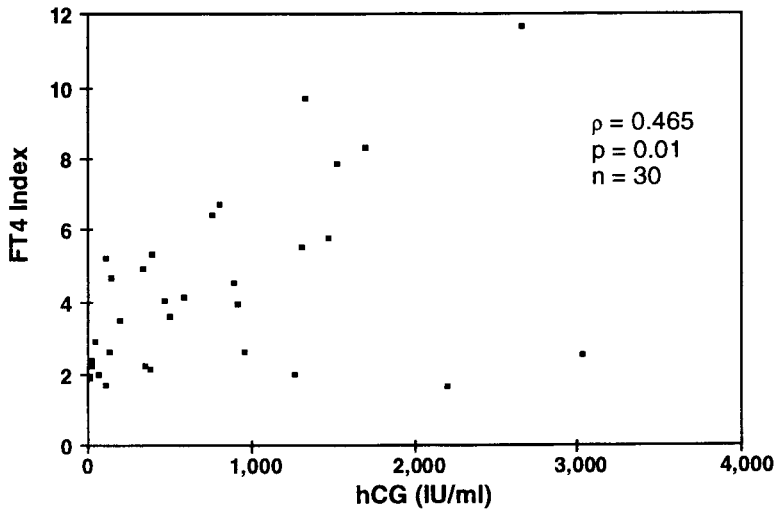

Fig. 3. Correlation between serum hCG and FT_4I in patients with hydatidiform mole. A significant correlation was observed.

Table 2. Thyroid function tests and serum hCG of two patients with clinical hyperthyroidism.

Patient number	T_4 (μg/dl)	T_3 (ng/dl)	FT_4I	TSH (mIU/L)	hCG (mIU/ml)
1	24	269	9.69	0.07	1,331,850
2	24	476	8.29	0.08	1,700,000
one week postevacuation	9.7	52	3.06	0.07	-

correlation was also observed between values of the serum hCG and total T_3 concentration (rho= 0.629, $p<0.001$) (Fig. 2). In 30 patients in whom the FT_4I and serum hCG were measured, there was a significant correlation between serum hCG concentrations and values of the FT_4I (rho=0.465, p=0.010) (Fig. 3).

Clinical state of the patients

Two patients in group I were clinically hyperthyroid. Their thyroid function tests and serum hCG are shown in Table 2. Patient 1 developed pulmonary complication before uterine evacuation. Patient 2 developed pulmonary complication following evacuation and whose thyroid function tests became normal one week after evacuation. Both of them died of pulmonary edema and sepsis.

DISCUSSION

In this study of sixty seven patients with hydatidiform mole only two had clinical hyperthyroidism. Both of them died of pulmonary edema which was the most serious complication in hyperthyroid due to molar pregnancy. This was frequently refractory to standard medical management[8]. The etiologies of acute pulmonary edema may be due to trophoblastic embolization, hyperthyroidism, fluid overload, dilutional anemia and pre-eclampsia[16]. Thirty-five patients were biochemically hyperthyroid but clinically euthyroid. Nagataki et al[4] studied 15 patients with molar pregrancy and found elevated serum thyroid hormone concentration in half of them, but none had clinical hyperthyroidism. Galton et al[2] found that, although increased thyroid function was common in women with moles, clinical hyperthyroidism was unusual. However, several reports found frank clinical hyperthyroid with molar pregnancy[1,3,6]. The explanation for the lack of clear clinical features of hyperthyroidism in patients with elevated thyroid hormone level is unclear[4], it may be related to the relatively brief duration of the in-

creased thyroid function. Clinical features of hyperthyroidism may be overlooked in patients with hydatidiform mole because attention is often focused on the toxemia that frequently accompanies it[17].

Hydatidiform mole patients in group I had unequivocal evidence of biochemical hyperthyroidism, with suppressed TSH concentration and an increase in serum T_4, T_3 and FT_4I. However, increases in thyroid hormone concentration were not as high as those seen in Graves' disease[9]. Explanation for these findings include the possibilily that the putative thyroid stimulator of hydatidiform mole is far less potent than that of Graves' disease. Indeed, hCG has been shown to have relatively low thyroid stimulating properties [13]. The normal serum T_3 concentration in these patients in group I may be attributable to the reduced peripheral conversion of T_4 to T_3 in systemic illness[9,18]. These findings support reports that hyperthyroidism associated with illness may result in impaired conversion of T_4 to T_3[18]. The effect of nonthyroidal illness on thyroid function was more evident in group II and III. Group II patients were biochemical subclinical hyperthyroid and clinically euthyroid. Group III patients were euthyroid biochemically and clinically. The low T_3 concentrations in group II and III may be attributable to the reduced peripheral conversion of T_4 to T_3 in nonthyroidal illness[19]. The low T_3 : T_4 ratio was observed in all three groups which was in contrast to that observed in patients with Graves' disease (22.918 ± 12.218 as calculated from 68 cases seen in our endocrine clinic). The low T_3 : T_4 ratio may be due to increased serum thyroxine-binding globulin concentration[2] and decreased peripheral conversion of T_4 to T_3 in this condition.

It is of interest that TSH concentrations were suppressed in group I and II. Wehmann et al [20] suggested that non-thyroidal illness may have a direct suppressive effect on pituitary thyrotroph secretion and this is a consideration in group II because the FT_4I were normal. Lower serum TSH concentrations have been reported in pregnancy [21], thus the possibility that suppressed TSH concentrations recorded in euthyroid patients with hydatidiform mole were due to pregnancy, cannot be excluded. One patient in group III had a TSH concentration above the reference range (6.15), but she had normal thyroid hormone concentrations and was clinically euthyroid. In view of the fact that transient hyperthyrotrophinemia, without hypothyroidism, has been described in ill patients [22], this patient was not considered to be hypothyroid.

Some investigators have attempted to correlate parameters of thyroid function with elevated serum hCG levels in patients with hydatidiform mole. It was expected that high serum hCG levels in these patients would be associated with biochemical and clinical evidence of thyroid hyperfunctions if hCG is indeed a thyroid stimulator in human. However, there are doubts about the ability of hCG to act as a thyroid stimulator. Several studies have revealed conflicting results. Serum hCG correlated with serum T_3 concentrations in patients with hydatidiform moles[3]. In five women with trophoblastic hyperthyroidism, hCG levels correlated with serum T_4, FT_4 and T_3 levels[6]. In contrast, others found only a weak correlation between hCG and T_4 concentration and no correlation of hCG with FT_4I or T_3 levels in a large group of patients with hydatidiform mole[23]. Kennedy et al[24] reported that there was no direct correlation between hCG and any measure of thyroid function although mean hCG was clearly higher in those patients with hyperthyroidism. Our data revealed significant correlation between hCG and T_4, T_3 and FT_4I levels. It appears most likely that hCG itself is not the principal thyroid stimulator secreted by the moles. The stimulator may be a variant of hCG which may result either from an altered biosynthesis of hCG by trophoblastic tumor cells or by metabolism of native hCG in the course of its circulation in the blood. Such variant forms of hCG have been identified[25,26]. The hCG is not a single molecule, but, like other glycoprotein hormones exhibits some degree of microheterogeneity. The microheterogeneity of hCG can be visualized by isoelectric focusing and relates to isoforms of the molecule containing varying amounts of sialic acid[27]. The thyrotropic potency of hCG isohormones with different isoelectric points is an area of controversy. Mann et al[26] demonstrated that the acidic hCG variants in human testicular tumor and trophoblastic disease were more thyroactive than native hCG. In contrast, Yoshimura et al[28] demonstrated that the basic isoforms of hCG with less sialic acid content may be more responsible for hCG induced thyroid stimulation.

Hydatidiform mole occurs in about 1 in 2,000 pregnancies in the United States and is 10 times more common in Asian countries. In Rajvithi Hospital, the incidence of hydatidiform mole is one in 724 deliveries(29).

In conclusion, the data in this paper suggest that clinical hyperthyroidism is not common despite the relative frequency with biochemical hyperthyroidism. Demonstrations of significant correlation of serum hCG and T_4, T_3 and FT_4I concentrations support that a variant hCG is thyroid stimulator secreted by the moles.

SUMMARY

The biochemical thyroid status of sixty-seven patients with hydatidiform mole was assessed with the aid of TSH measurement by immunoradiometric assay and measurement of total thyroid hormone and FT_4I concentrations. It was subdivided into three groups ; Group I (hyperthyroid) Group II (subclinical hyperthyroid) and Group III (nontoxic). Thirty-seven patients in group I were found to be biochemically hyperthyroid. Of these thirty-seven patients, only two were clinically thyrotoxic. The most serious complication of thyrotoxicosis was life-threatening acute pulmonary edema. Nonthyroidal illness played an important role in Group II and III. A significant correlation (rho=0.559, p<0.001, n=35) between the serum hCG levels and serum total T_4 concentration was observed. Also there was a significant correlation (rho=0.629, p<0.001, n=35) between serum hCG levels and serum total T_3 concentrations. Analysis also revealed a significant correlation (rho=0.465, p=0.010, n=30) between the serum hCG and serum FT_4I values. These findings support that a variant hCG is responsible for hyperthyroidism observed in patients with molar pregnancy.

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การศึกษาฮอร์โมนของต่อมไทรอยด์และ hCG ในเลือดของผู้ป่วยตั้งครรภ์ไข่ปลาอุก

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ได้ศึกษาผู้ป่วยตั้งครรภ์ไข่ปลาอุก จำนวน 67 ราย ของโรงพยาบาลราชวิถี ตั้งแต่ปี พ.ศ. 2535-2539 โดยตรวจเลือดหาฮอร์โมนของต่อมไทรอยด์และ hCG เพื่อศึกษาการเปลี่ยนแปลงของฮอร์โมนจากต่อมไทรอยด์ในผู้ป่วยเหล่านี้ พบว่าสามารถแบ่งเป็น 3 กลุ่ม คือ กลุ่ม 1 hyperthyroid กลุ่ม 2 subclinical hyperthyroid และกลุ่ม 3 เป็น nontoxic นอกจาก นี้ยังพยายามหาความสัมพันธ์ระหว่างฮอร์โมนของต่อมไทรอยด์ กับ hCG พบว่าความสัมพันธ์ระหว่าง hCG กับ T_4, T_3 และ FT_4I ดังต่อไปนี้ rho=0.559, rho=0.629 และ rho=0.465 ตามลำดับ เป็นความสัมพันธ์อย่างมีนัยสำคัญ แสดงว่า variant hCG มีบทบาทในการกระตุ้นต่อมไทรอยด์

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