Disease and Diagnosis

Dis Diagn. 2020; 9(4):140-143

doi 10.34172/ddj.2020.02

Original Article

The Association of Thyroid Hormones With β-HCG in Patients With Hydatidiform Mole

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Abstract

Background: A hydatidiform mole or molar pregnancy is the most prevalent gestational trophoblastic disease (GTD). About 55%-60% of women with trophoblastic diseases have overt hyperthyroidism at the time of diagnosis, which may have severe manifestations. This study examined the relationship between gestational hypertension and the level of thyroid hormones with beta human chorionic gonadotropin (β-HCG) in patients with a hydatidiform mole.

Materials and Methods: This cross-sectional study enrolled 65 patients with a hydatidiform mole admitted to Khalij-e Fars hospital, Bandar Abbas, Iran. Patients were divided into three groups of clinical hyperthyroidism, subclinical hyperthyroidism, and healthy. The serum levels of thyroid-stimulating hormone (TSH), T4, T3, and β-HCG were checked in all subjects, and the relationship between gestational hypertension and the level of thyroid hormones with β-HCG in patients with a hydatidiform mole was examined.

Results: The mean age of patients was 29.93 ± 9.04 years, and their mean gestational age was 11.09 ± 4.2 weeks. In this study, 12.3% of the patients had subclinical hyperthyroidism, 41.5% had clinical hyperthyroidism, and 46.2% were healthy. A significant relationship was found between the serum level of β-HCG and thyroid function in patients with clinical and subclinical hyperthyroidism compared to the healthy group (P= 0.001). No significant relationship was found between systolic/diastolic blood pressure and the serum level of β-HCG.

Conclusion: A significant relationship was observed between the serum levels of β-HCG and TSH, free T3, and free T4 in patients with a hydatidiform mole and thyrotoxicosis. Thus, early diagnosis of hyperthyroidism can help treat these patients more quickly.

Keywords: Hydatidiform mole, Thyroid hormone, β-HCG

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Received: October 8, 2020, Accepted: December 6, 2020, ePublished: December 30, 2020

Introduction

Gestational trophoblastic disease (GTD) comprises a group of interrelated tumors, including complete and partial hydatidiform moles, placental site trophoblastic tumors, and choriocarcinoma, with different tendencies for local invasion and metastasis (1). Histologically, the hydatidiform mole is characterized by a disorder in the chorionic villi, including trophoblastic proliferation and villous stromal edema (2). Hydatidiform mole is the most prevalent form of GTD (3, 4) occurring in 1 per 1000 pregnancies in the world (5, 6). The prevalence of hydatidiform mole differs in different regions. Studies in Iran have reported different prevalence rates for this disease. Rezavand et al reported the prevalence of hydatidiform mole as 3.1 per 1000 live births (5, 6). Often, vaginal bleeding is a clinical sign of hydatidiform mole in addition to signs such as enlarged uterus, vomiting, hypertensive disorders, and pelvic pain resulting from theca-lutein cysts. The risk factors of hydatidiform mole include maternal age, a history of hydatidiform mole, viral infections, maternal immune mechanism, cytogenetic disorders, nutritional status, the mother being multiparous, and history of oral contraceptives (3).

Hyperthyroidism is one of the known complications secondary to the trophoblastic disease (7, 8). The prevalence of hyperthyroidism in cases with hydatidiform mole reaches 7% (9). The mechanism of hyperthyroidism induction in hydatidiform mole is multifactorial; but the most discussed mechanisms include an increase in the beta human chorionic gonadotropin (β-HCG) level and molecular mimicry with thyroid-stimulating hormone (TSH) (10).

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Clinical hyperthyroidism is relatively prevalent and occurs in 1 per 100 pregnancies. This condition can be justified by the similarity of the β-HCG subunit to TSH (4). The relationship between increased β-HCG and TSH level during pregnancy has been known for years (4). Several studies have confirmed the thyrotropic effect of β-HCG (7, 11, 12), indicating that β-HCG can bind to TSH receptors and inhibit TSH production (13). Few studies are available on the relationship between β-HCG and the level of thyroid hormones, as well as clinical and subclinical hyperthyroidism. Therefore, considering the prevalence of the hydatidiform mole and the importance of early diagnosis and treatment of hyperthyroidism, we examined the relationship between β-HCG level and thyroid hormones (T3, T4, TSH) in patients with hydatidiform mole referred to Khalij-e Fars and Shariati hospitals (Bandar Abbas, Iran). We investigated the relationship of thyroid hormone levels with β-HCG level in these patients, so that an earlier treatment of hyperthyroidism can be offered upon an earlier diagnosis.

Materials and Methods

In this cross-sectional study, 65 patients with H. mole admitted to Khalij-e Fars hospital from March 2014 to March 2019 were selected by the census method; the diagnosis in all subjects was confirmed based on ultrasound and histological findings. To meet the exclusion criteria, patients with choriocarcinoma and partial mole, and those who were taking levothyroxine were excluded from the study. Then, the variables of the research were extracted from patients' medical records. The patients were divided into three groups of clinical hyperthyroidism, subclinical hyperthyroidism, and healthy.

Subclinical hyperthyroidism was described as TSH <0.03 mIU/mL and normal levels of free T4 (0.8-2.8) ng/mL and free T3 (2.3-4.2) ng/mL. Clinical hyperthyroidism was described as TSH<0.03 mIU/mL and high levels of free T4 with or without free T3. Gestational hypertension was defined by the new onset of hypertension (systolic hypertension ≥140 mm Hg and/or diastolic hypertension ≥90 mm Hg) on two separate occasions at least 4 hours apart in a pregnant woman after 20 weeks of gestation without the presence of protein in the urine or other signs of pre-eclampsia (14). Then, the relationship between gestational hypertension and the level of thyroid hormones with β-HCG in patients with a hydatidiform mole was examined.

The data were analyzed using IBM SPSS Statistics for Windows, version 22 (IBM Corp., Armonk, N.Y., USA). The means of quantitative variables were compared via ANOVA, and qualitative variables were compared using Fisher exact test and the chi-square test.

Results

In the present study, 65 patients with hydatidiform mole were examined. The mean age of the patients was 29.93 ± 9.04 years and their mean gestational age was 11.09 ± 4.2 weeks. In addition, their mean systolic blood pressure and diastolic blood pressure was 113 ± 10.3 mmHg and 70.04 ± 7.5 mm Hg, respectively. The patients were divided into three groups based on thyroid tests: subclinical hyperthyroidism: 8 patients (12.3%), clinical hyperthyroidism: 27 patients (41.5%), and without thyroid disease: 30 patients (46.2%) (Table 1).

As for the relationship between patients' age and thyroid function, no significant difference existed among the mentioned groups ($P=0.66$). The mean age of the patients was 30.6 ± 9.1 years in the healthy group, 29.8 ± 9.5 in the clinical hyperthyroidism group, and 27.3 ± 6.9 in the subclinical hyperthyroidism group. In terms of the relationship between gestational age and thyroid function, the mean gestational age was 10.7 ± 4.2 weeks in the clinical hyperthyroidism group, 11 ± 3.4 in the subclinical hyperthyroidism group, and 11.4 ± 4.9 in the healthy group. However, this difference was not significant ($P=0.88$; Table 1).

A significant relationship was observed between the β-HCG level and thyroid function ($P=0.001$). The mean β-HCG level was 514338.3 ± 351134 mIU/mL in the clinical hyperthyroidism group, 140217.3 ± 86020.7 mIU/mL in the subclinical hyperthyroidism group, and 109403.8 ± 124620.3 mIU/mL in the healthy group (Table 1).

Regarding the relationship between systolic blood pressure and thyroid function, no significant difference was found among the groups in terms of mean systolic blood pressure ($P=0.98$); the mean systolic blood pressure was 114 ± 13.2 mm Hg in the group with clinical hyperthyroidism, 113.7 ± 9.1 mmHg in the group with subclinical hyperthyroidism, and 113.5 ± 8.4 mm Hg in the healthy group (Table 1).

Regarding the relationship between diastolic blood pressure and thyroid function, we found no significant difference among the groups ($P=0.3$); the mean diastolic blood pressure was 71.5 ± 8.5 mm Hg in the group with clinical hyperthyroidism, 67.5 ± 7.07 mm Hg in the group with subclinical hyperthyroidism, and 69.6 ± 7.02 mm Hg in the healthy group (Table 1).

Moreover, no significant relationship was found between systolic/diastolic blood pressure and the serum level of β-HCG ($P=0.96$ and $P=0.42$, respectively).

Discussion

The main objective of this study was to examine the relationship between the level of thyroid hormones and hypertension with β-HCG in patients with hydatidiform mole. Much effort has been made to determine the relationship between serum β-HCG concentration and thyroid function in patients with trophoblastic tumors because both factors are increased in this disease. A positive correlation has been observed between serum

Table 1. The Relationship Between Hyperthyroidism and Variables of Age, Gestational Age, β-HCG Level, Systolic and Diastolic Blood Pressure

Variables		Number	Mean	SD	*P* Value
Age (y)	Group1 hyperthyroidism	8	27.37	6.92	0.66
	Group2 subclinical hyperthyroidism	27	29.88	9.59	
	Group 3 healthy	30	30.66	9.17	
	All patients	65	29.93	9.04	
Gestational age (wk)	Group 1	8	11	3.46	0.88
	Group 2	18	10.7	4.22	
	Group 3	26	11.46	4.92	
	All patients	52	11.15	4.42	
β-HCG (mIU/mL)	Group 1	8	140217.37	86020.79	0.001
	Group 2	27	514338.37	351134.29	
	Group 3	30	109403.88	124620.37	
	All patients	65	281399.86	311744.57	
Systolic BP (mm Hg)	Group 1	8	113.75	9.16	0.98
	Group 2	27	114	13.23	
	Group 3	30	113.5	8.42	
	All patients	65	113.73	10.60	
Diastolic BP(mm Hg)	Group 1	8	67.5	7.07	0.3
	Group 2	27	71.59	8.72	
	Group 3	30	69.66	7.06	
	All patients	65	70.2	7.8	

β-HCG and free T4 or free T3 concentration in some patients, indicating that β-HCG itself increases serum T4 in addition to other reasons (6). Results of a study by Düğeroğlu and Özgenoğlu on 50 patients diagnosed with complete and partial hydatidiform mole demonstrated that patients with complete hydatidiform mole had a higher mean age ($P=0.003$), more pregnancies ($P=0.032$), a lower TSH level ($P=0.01$), and higher free T4 levels ($P=0.028$, $P=0.04$, respectively) compared to those who had partial hydatidiform mole. Moreover, from among 30 patients with an HCG titer > 200 000 mIU/mL, 13 patients had a TSH level > 0.2 IU/L, and the remaining 17 patients had a TSH level < 0.2 IU/L. Out of the 20 patients with an HCG titer > 400 000 mIU/mL, 5 patients had a TSH level > 0.2 IU/L, and 15 patients had a TSH level <0.2 IU/L (15). In our study, no significant relationship was found between hyperthyroidism and variables of patient age and gestational age. More than half of the patients had a low TSH level and high free T4 and free T3 levels; these patients also had a higher β-HCG level ($P<0.001$). Nankali et al examined the levels of thyroid hormones and their relationship with human placental gonadotropin on 146 patients with molar pregnancy admitted to the gynecology/obstetrics ward of Imam Reza hospital during 5 years (2009-2013). According to their results, the majority of patients (49%) had subclinical hyperthyroidism, no patient had clinical hyperthyroidism, and 51% of the patients were healthy in terms of thyroid disease. In addition, 41.9% of the patients had a serum β-HCG level up to 10 000 mIU/mL, and 58.1% had a serum level >10 000 mIU/ml. A significant negative correlation was found between β-HCG and TSH ($P=0.05$). Also, a significant positive correlation was found between β-HCG and T3 ($P=0.01$) and T4 ($P=0.01$). The mean β-HCG level was 50000 mIU/mL in the group with subclinical hyperthyroidism and 20000 mIU/mL in the rest of the patients without subclinical hyperthyroidism, demonstrating a significant relationship between β-HCG level and subclinical hyperthyroidism. In our study, a significant relationship existed between β-HCG and TSH, T3, and T4 (4). In the present study, 12.3% of the patients had subclinical hyperthyroidism, 41.5% had clinical hyperthyroidism, and 46.2 did not have thyroid disease. Similar to the cited study, a significant negative correlation existed between β-HCG and TSH, and a positive correlation existed between β-HCG and T3 and T4 ($P<0.001$). The mean level of β-HCG was higher in the group with clinical hyperthyroidism (~500 000 mIU/mL) than that of the group with subclinical hyperthyroidism (~140000 mIU/mL). It was also higher in the group with subclinical hyperthyroidism than that in the healthy group (~100000 mIU/mL). Salavatian et al studied 48 patients with hydatidiform mole and examined the correlation between β-HCG and thyroid function tests. Based on their results, a clear linear correlation was found between the serum level of β-HCG and total serum T4 and FT4I ($P<0.001$ and $P=0.002$, respectively), and between β-HCG and total serum T3 and FT3I ($P=0.02$

and $P=0.02$, respectively). In addition, a weak correlation was found between high β-HCG levels and low serum levels of TSH ($P=0.04$) (16).

One of the main limitations of current study is its relatively small sample size. Another limitation is related to inability to check the laboratory tests in one center.

We found a significant association between the serum levels of β-HCG and thyroid hormone in patients with hyperthyroidism and hydatidiform mole. Thus, early diagnosis and treatment of hyperthyroidism is recommended in this group of patients.

Conclusion

In this study, a significant relationship was observed between the serum level of β-HCG and TSH, T3, and T4 in patients with hydatidiform mole. Thus, early diagnosis of hyperthyroidism can help these patients be treated earlier.

Conflict of Interest Disclosure

The authors declare that they have no conflict of interests.

Acknowledgements

We are sincerely thankful to Miss Tayyebeh Zarei in Clinical Research Development of Shahid Mohammadi Hospital.

Ethical Statement

This study was extracted from a PhD dissertation supported by Clinical Research Development Center of Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar-Abbas, Iran (Ethical Code: IR.HUMS.REC.1398.476).

Authors' Contributions

HR.S and M.KJ contributed to conception, design and statistical analysis. Other authors contributed to data collection and manuscript drafting. M.KJ supervised the study. All authors approved the final version of the manuscript.

Funding/Support

The Cardiovascular Research Center and Clinical Research Development Center of Shahid Mohammadi Hospital, Hormozgan University of Medical Sciences, Bandar Abbas, Iran funded this study.

Informed Consent

All participants provided written informed consent.

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