Original Article

WHEN ANTITHYROID DRUGS MUST BE STARTED IN PATIENTS WITH HYPEREMESIS GRAVIDARUM?

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ABSTRACT

Objective: To find out role of anti-thyroid drugs in patients with Hyperemesis gravidarum and thyroid dysfunction.

Methodology: One hundred thirty five patients with hyperemesis gravidarum who were admitted to obstetric and gynecology hospital were enrolled in this study. Thirty two patients were excluded because of diabetes mellitus and thyroid diseases. Hence, one hundred three patients underwent investigations including thyroid function test and ß-hCG (Human chorionic gonadotropin).

Results: Thirty five women were found with abnormal thyroid function test with FT_4I (Free Thyroxin Index) 4.74±0.54 and in another group (68 women) was 2.9±0.39 (P<0.0001). B-hCG in first group was 59406±14899 miu/ml and in second group was 6750±3476 miu/mL (P<0.0001). In five patients PTU (propylthiouracil) was started due to severe sign and symptoms of hyperthyroidism. Thyroid function test was rechecked for all of 35 patients after four weeks routine therapy for hyperemesis gravidarum. Thyroid function test was normalized in 11 patients with hyperemesis graridarum but remained abnormal in 22 patients.

Conclusion: In our study thyroid dysfunction in hyperemesis gravidarum was 35% and, 20% of patients needed anti-thyroid therapy. Routine assessment of thyroid function is necessary for women with hyperemesis gravidarum especially in patients with clinical features of hyperthyroidism. We must consider PTU (propylthouracil) in hyperemesis gravidarum with severe weight loss, vomiting and biochemical hyperthyroidism.

KEY WORDS: Hyperemesis Gravidarum, Thyroid Function Test, Hyperthyroidism.

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INTRODUCTION

Hyperemesis gravidarum is marked by profound vomiting during early gestation, which may result in electrolyte imbalance and dehydration. High serum free T4 (Thyroxin) and T3 (Tri-iodothyronin) concentrations are a common finding in women with hyperemesis gravidarum, having been reported in 25% to 75% of patients in various series.[1] Women with hyperemesis and high serum free T4 and T3 concentrations have higher serum hCG (Human chorionic gonadotropin) concentrations

than normal pregnant women.[1] Their serum hCG concentrations correlate with the degree of elevation of serum free T4 and T3 concentrations and with serum thyroid-stimulating activity, as measured by bioassay. Vomiting is also more severe in women who have higher serum hCG concentrations, suggesting that another factor induced by hCG, perhaps estradiol, may be responsible for the vomiting.[2,3] The hyperthyroxinemia is usually transient, resolving by 18 weeks gestation without antithyroid therapy.[4] The degree of thyroid stimulation varies with the hCG concentration and correlates with the symptoms of hyperemesis.[3,5] Antithyroid therapy should be considered for women with persistent hyperemesis and hyperthyroxinemia past 20 weeks gestation.[6]

METHODOLOGY

One hundred thirty five women were admitted with hyperemesis gravidarum and 32 patients were excluded due to other illness such as diabetes mellitus and thyroid disease or patients who had history of specific drugs such as antithyroid drugs or levothyroxine. Each woman was examined for clinical signs of thyroid disease and underwent investigations including electrolytes, liver enzyme test, ß-hCG, urine ketone and thyroid function test.

The severity of the hyperemesis gravidarum was evaluated by the degree of ketonuria and weight loss. An ultrasound to confirm the gestational age and multiple gestation and to exclude a trophoblastic disease was carried out. In patients with abnormal thyroid function test (biochemical hyperthyroidism) Anti–TPO (Thyroid Peroxidase) was measured. In patient with severe sign and symptoms of hyperthyroidism, PTU (propylthiouracil) was started and thyroid function test was repeated four weeks later. SPSS softwere version 11 was used for statistical analysis and t-test was performed for comparisons between groups. Values of $P<0.05$ were considered statistically significant, and all data are presented as mean±SD.

RESULTS

Baseline characteristics of 103 patients whit hyperemesis gravidarum are shown in Table-I. Mean age of pregnancy at the admission was 15.34±2.61 weeks and age of starting vomiting was 7.42±2.14 weeks of gestation. Twenty eight patients (27%) had positive family history of hyperemisis gravidarum in first degree relative families. Forty patients had gravida two or more and 25 (62.5%) of them had history of hyperemisis gravidarum in previous pregnancy. Thirty five patients (34%) had biochemical hyperthyrodism (suppressed thyroid stimulathing hormone and incressed FT_4I). Sixty eight patients (66 %) had normal thyroid test. Camparison of two groups are show in Table-II.

Propylthiouracil was started in five patients at time of diagnosis because of severe biochemical and clinical signs and symptomes of hyperthyroidism. Mean dose of PTU was 170±55 mg/d. Thyroid function test was repeated after one month. Thyroid function tests normalized in 11 patients (31.42%) and two patients were lost to follow up while 22 patients (68.85%) still had abnormal thyroid function test. They were put on propylthiouracil therapy with mean dose of 60 mg/d and followed with thyroid frnction tests mounthly. Anti TPO was measured in 22 patients with abnormal thyroid function tests and it was found positive in three of them.

Table-I: Characteristics of parameters in 103 patients

Parametrs	*Max*	*Min*	*mean± SD*
T_4 µg/dL	20	9	13.13±2.4
T_3 Îg/dL	300	100	179.7±52.48
TSH mu/mL	1	0.01	0.23±0.25
$T_3RU_{\%}$	38	22	26.5±2.9
FT_4I	7.6	2/2	3.53±0.98
ß-hCG mIu/mL	91200	1000	24643±26646
Na meq/L	146	128	133.89±4.45
K meq/L	3.9	2.9	3.31±0.27
ALT U/L	85	10	41.62±15.51
AST U/L	89	15	33.6±14.01
Weight loss (kg)	8.9	3	4.88±1.1
Score of nausea and vomiting	12	7	9.19±1.26

Table-II: Comparison of parameters in two groups.

Parametrs	*Normal TFTN=68*	*Abnormal TFTN=35*	*P-Value*
Age (years)	23.73±3.85	23.74±4.27	NS[1]
ß-hCG mIu/mL	6750±3476	59406±14899	<0.0001
FT_4l	2.9±0.39	4.47±0.54	<0.0001
TSH mL/mu	0.21±0.14	0.08±0.05	<0.0001
T_3 Îg/dL	148.55±30.3	240±27.4	<0.0001
T_4 µg/dL	11.67±1.38	15.97±0.99	<0.0001
T_3RU %	24.84±1.65	29.65±2.12	<0.0001
Na meq/L	134.5±3.74	132.68±2.4	<0.01
K meq/L	3.36±0.27	3.2±0.22	<0.3
ALT U/L	26.82±8.16	46.77±17.9	<0.0001
AST U/L	36.54±10.73	51.48±14.69	<0.0001
Weight loss (kg)	4.91±1.5	4/82± 1/2	NS
Nausea and vomiting (w[2])	7.3±3.2	7.62±2.04	NS
Gestational age (w[2])	15.36±2.8	15.31±2.24	NS
Score of nausea and vomiting	8.67±0.98	10.2±1.15	<0.0001
Orthostatic hypotension (PR[3])	37 (54%)	34 (97%)	<0.0001
Orthostatic hypotension (BP[4])	41 (60%)	32 (91%)	<0.0001
Degree of goiter (2&3)	5 (7%)	25 (71%)	<0.0001

NS[1] = Not Significanct W[2] = Week
PR[3] = Pulse Rate BP[4] = Blood Pressure

DISCUSSION

Hyperemesis gravidarum is characterized by nausea and vomiting, which in severe cases may lead to dehydration and require hospitalization.[4] Mild hyperthyroidism may be associated with hyperemesis gravidarum, perhaps due to higher serum concentrations of human chorionic gonadotropin which may have more thyroid stimulating activity.[7]

In several studies thyroids dysfunction is reported from 25% to 75%.[6] In our study thyroid dysfunction was 34% in hyperemesis gravidarum. Most of patients had greater than 5% weight loss (4.88±1.1 kg) especially in patient with thyroid dysfunction (Table-II). Score of nausea and vomiting with Rhodes index[8] criteria was higher in patients with thyroid dysfunction (P<0.0001). Hyperthyroid patients were more likely than euthyroid patients to have abnormal electrolyte level or increased liver enzyme (Table-II). This finding also show that the severity of hyperemsis and weight loss were found to vary directly with the degree of hyperthyroidism. The etiology of transient hyperthyroidism of hyperemesis gravidarum is unclear. Some investigator feel that the hyperthyroidism is the cause of the hyperemesis, whereas others disagree.[9]

Hyperthyroidism in trophoblastic tumor is higher than hyperemesis gravidarum.[10,11] In our study ß-hCG in hyperthyroid patients was significantly higher than patients with normal thyroid function (Table-II) and thyroid stimulating hormone was significantly suppresed in first group (Table-II).

Twin or more gestation are more often associated with sustained elevation of ß-hCG and 60% suppression of thyroid stimulating hormone and hyperemesis gravidarum is more frequent in these groups than single fetus.[12,13] In this study stage of goiter was higher in hyperthyroid patients than patients with normal thyroid function. The result of the present research also show that higher stage goiter are see more in hyperemesis gravidarum with thyroid dysfunction that is not reported in other studies.

Our results are suggestive of the involvement of hyperthyrodism and fetal sex in the pathegenesis of hyperemesis gravidarum and several other studies have also reported this finding.[14,15] We observed a famale predominance among the offspring of mothers with hyperemesis gravidarum. In this study 14 famale infants and 9 male were delivered. It included 16 uni fetus, 2 twins and one triple fetus.

Although clinical features of thyrotoxicosis are usually absent, or overlooked, in women with hyperemesis gravidarum, some have clinically evident thyrotoxicosis.[12] In our study hyperthyroidism was severe in five patients in which PTU was started after diagnosis. Three of them were Anti-TPO antibody positive. In another patients throid function test was repeated four weeks later. In patients with Anti-TPO antibody positive, PTU was started with mean dose 170±57 mg/d with 5.33±0.5 months during pregnancy and continued one month after delivery. Serial throid function test was done monthly. FT_4I and thyroid stimulating hormone in hyperthyroid patients with Anti-TPO negative were 4.73±0.3 and 0.11A±0.08/ mu mL respectivily. PTU was started during pregnancy with mean dose 60 mg/d and duration of 2.67±2.16 months in this group. In this study PTU therapy significantly improved hypermesis in several weeks. Improvement of nausea, vomiting and significant weight gain (1.25±0.38 kg/month) were noted.

Finally routine assessment of thyroid function is necessary for women with hyperemesis gravidarum especially in patients with clinical features of hyperthyroidism. Symptoms of hyperemesis gravidarum usually resolve by 18th week of gestation, regardless of therapy. Antithyroid therapy should be considered for women with persistent hyperemesis and hyperthyroxinemia past 18-20th week gestation especially in patients with hyperemesis gravidarum and severe weight loss, vomiting and biochemical hyperthyridism.[6,13-15]

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