

The relationship between free thyroid hormone index and thyrotoxicosis in pregnancy

Gebelikte serbest tiroid hormon indeksi ile tirotoksikoz arasındaki ilişki

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SUMMARY




Objective: The aim of this study was to evaluate free thyroid hormone index (FTHI) (FT3 index/ FT4 index) as a parameter to use in differential diagnosis of gestational Graves' disease (GGD) and gestational transient thyrotoxicosis (GTT). GGD and GTT are the most common causes of thyrotoxicosis in early pregnancy and differential diagnosis is important since they are treated differently.

Method: Women who applied to our clinic with thyrotoxicosis were evaluated and 51 pregnant women were recruited to the study. Among the 51 women, 36 had GTT, 15 had GGD. The age, gestational age, thyroid stimulating hormone (TSH) levels, and FTHI (FT3 index / FT4 index) of all patients were recorded and compared. FT3/FT3 upper limit of normal (ULN) is referred as FT3 index. FT4 index is also referred as FT4/FT4 ULN. All diagnosis of GGD and GTT was confirmed with TRAb assays.

Results: The mean values of FT3, FT3 index, FTHI of the GGD group were found to be statistically significantly higher compared to GTT group (p: 0.002, p: 0.001, 0.001; respectively). No statistically significant difference was found between groups in terms of age, gestational age, FT4, FT4 index and TSH (p:0.999, p:0.730, p:0.620, p:0.570, p:0.291; respectively) FTHI values were above 1 in all patients with GGD while it was below 1 in GTT group.

Conclusions: The FTHI values above 1 may be used as a practical, cheap parameter for differential diagnosis between GGD and GTT.

Keywords: Gestational Graves' disease, gestational transient thyrotoxicosis, free thyroid hormone index, parameter.

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ÖZET

Amaç: Bu çalışmanın amacı serbest tiroid hormon kat oranları (FTHI) (FT3 index/ FT4 index) kullanılarak gebe hastalarda gestasyonel Graves hastalığı (GGH) ve gestasyonel transient tirotoksikozun (GTT) ayrıcı tanısını yapabilmektir. GGH ve GTT erken gebelikte en sık görülen tirotoksikoz nedenleridir ve farklı şekilde tedavi edildiği için tanıları ayırmak önemlidir.

Yöntem: Kliniğimize tirotoksikozis semptomları ile başvuran kadınların hormonal değerleri incelendi ve çalışmaya 51 gebe alındı. 51 gebenin 36'sında GTT, 15'inde GGH vardı. Tüm hastaların yaş, gebelik yaşı, tiroid stimüle edici hormon (TSH) düzeyleri ve FTHI (FT3 indeksi / FT4 indeksi) kaydedildi ve karşılaştırıldı. FT3 / FT3 normal üst sınırı (ULN) FT3 indeksi olarak adlandırılırken benzer şekilde FT4 indeksi de FT4 / FT4 ULN olarak değerlendirildi.

Bulgular: GGH grubunun ortalama FT3, FT3 indeksi ve FTHI deęerleri GTT grubuna gre istatistiksel olarak anlamlı derecede yksek bulundu (sırasıyla p: 0.002, p: 0.001, 0.001). Gruplar arasında yař, gebelik yaşı, FT4, FT4 indeksi ve TSH aısından istatistiksel olarak anlamlı fark bulunmadı (sırasıyla p: 0.999, p: 0.730, p: 0.620, p: 0.570, p: 0.291). GGH'li tm hastalarda FTHI deęerleri l'in zerinde iken, GTT grubunda ise l'in altında idi.

Sonu: l'in zerindeki FTHI deęerleri, GGH ve GTT arasında ayırıcı tanı iin pratik ve ucuz bir parametre olarak kullanılabilir.

Anahtar szckler: Gestasyonel Graves hastalığı, gestasyonel geici tirotoksikoz, serbest tiroid hormon indeksi, parametre

INTRODUCTION

Thyrotoxicosis in pregnancy is relatively rare due to the low pregnancy rates and increased pregnancy loss in patients with hyperthyroidism. The average incidence of gestational thyrotoxicosis is about 0.1-0.4% and Graves' diseases (GGD) (nearly 85-90% of all cases) comprises the majority of them ¹. Another common cause of thyrotoxicosis in pregnancy is gestational transient thyrotoxicosis (GTT) which affects up to 2-3% of pregnancies and is not considered as a disease ². In fact, GTT is a biochemical thyrotoxicosis which develops due to the stimulation of TSH receptor by high human chorionic gonadotropin (hCG) in pregnancy ². GTT is mostly associated with hyperemesis gravidarum which causes nausea, vomiting, weight loss, dehydration and ketonuria in early pregnancy period ^{3, 4}. Patients with GTT and hyperemesis gravidarum may be hospitalized, if necessary, and administered proper treatment with supportive care for dehydration ⁴. GTT which is defined as transient because of hCG, generally recovers by itself until the 20th week of pregnancy ⁵. Graves' disease is an autoimmune disease which becomes severe during the early period of pregnancy and severity of GGD decreases depending on the immune suppressive effect of the future pregnancy periods ⁶. The autoimmunity is against TSH receptors resulting with TSH receptor antibodies leading to hyperthyroidism ⁷. The insufficient control of maternal hyperthyroidism with excessive thyroid hormones is associated with maternal (preeclampsia, heart failure), fetal (abortions, premature labor, stillbirth) and neonatal complications (low birth weight) ⁸. These complications may be prevented and alleviated with early and optimal treatment with antithyroid drugs (ATDs) ⁹. However, neither ATDs nor any specific medication are recommended for GTT treatment ^{9,10}. Regarding the risks which may occur in the fetus and the mother due to the different treatment and follow-up, the differential diagnosis of GTT and GGD is important.

In terms of laboratory evaluation, GTT is defined by an elevated serum thyroid hormone levels and low or undetectable serum TSH level in absence of

TRAb. GGD has similar laboratory findings with TRAb positivity.

In this study, we aimed to investigate the serum values of free thyroid hormone index (FTHI) (FT3 index / FT4 index) as a cheap routinely used additional parameter besides the serum TRAb titer to differentiate GTT and GGD.

MATERIAL AND METHODS

This present study was conducted between December 2015 and June 2016 at XXXX Training and Research Hospital, Sivas, Turkey. Informed written consent was obtained from all participants. The study was approved by the local ethics committee of the university (Number 2015-10/09).

Patient selection and study design:

Referred pregnant patients (before 20 weeks of gestation) with low TSH values (<0.1 μ IU/ml in 1st trimester and <0.2 μ IU/ml in the 2nd trimester of pregnancy), with free T4 and/or T3 levels that exceed trimester specific normal reference ranges diagnosed as overt hyperthyroidism were included to the study. Patients who were diagnosed with GTT and GGD comprised study groups. The age, gestational age (week), free T3 (FT3), free T4 (FT4), (TSH), FT3 index (FT3/FT3 upper limit of normal (ULN), FT4 index (FT4/FT4 ULN) and FTHI (FT3 index / FT4 index) were recorded. The all values above were compared between the groups. FTHI and other tests were also evaluated in eligible non-pregnant patients, in case of detecting and comparing normal ranges without pregnancy due to the low number of GGD.

GTT was defined as low or undetectable TSH, high free thyroid hormone levels in first or early second trimester with normal TRAb level ¹¹⁻¹³. Generally, these patients had no symptoms or symptoms like hyperemesis gravidarum with absence of clinical findings of GGD. Moreover, they had no history of hyperthyroidism before pregnancy.

Patients with low or undetectable TSH, high free thyroid hormone levels in first or early second trimester with high TRAb level with presence of

clinical findings (tremor, palpitation, etc.) or physical findings such as thyroid enlargement or exophthalmos were diagnosed GGD¹¹⁻¹³. All diagnosis of GGD and GTT was confirmed with TRAb assays and clinical follow during the pregnancy.

Multiple pregnancies, patients with destructive thyroiditis or other reasons of hyperthyroidism, history of thyroid surgery, radioactive iodine ablation therapy, history of radiation exposure to the neck and patients who had been treated with drugs that alter thyroid functions at the time of the blood tests were excluded.

Eventually, a total of 177 women newly diagnosed with thyrotoxicosis were found to be eligible for the whole study. Of these 177 cases, 51 cases were pregnant and comprised study group. Remaining of 126 were included in non-pregnant GD group to check the values in non-pregnant cases due to low number of GGD.

Hormone assays and statistical analysis:

Serum samples of all patients were collected after an overnight fast and sent immediately for laboratory assessment on the day of admission. Serum FT3, FT4 and TSH levels were measured by the chemiluminescent immunoassay using Beckman Coulter DxI 800 immune-analyzer with original reagents.

The clinical features of both groups were compared with the Statistical Package for Social Sciences

(SPSS) for Windows, version 22.0 (SPSS Inc. IL, USA). Normality of data distribution was tested with Kolmogorov-Smirnov test. Data was presented as means \pm SD for continuous variables. We used median for nonparametric variables and showed minimum–maximum levels. To assess the differences in variables between groups, the independent t test was used. Values of $p < 0.05$ was accepted as statistically significant.

RESULTS

There were 51 pregnant patients recruited for the study. Among the 51 women, 36 had GTT, 15 had GGD. The maternal age, gestational age and laboratory features of the patients in groups were shown in Table 1. No statistically significant difference was found between groups in terms of age, gestational age, FT4, FT4 index and TSH ($p:0.999$, $p:0.730$, $p:0.620$, $p:0.570$, $p:0.291$; respectively) (Table 1). Values of FT3 and FT3 index were found to be statistically significantly higher in GGD group ($p:0.002$, $p:0.001$, respectively), however no differentiating threshold was found.

FTHI values were showed in Figure 1. FTHI was also found to be statistically significantly higher in GGD group especially above 1 in all pregnant patients. It was below 1 in all patients in GTT group. Additionally, FTHI was found to be above 1 (slightly lower than GGD) in all nonpregnant Graves patients (Figure 1).

Table 1: Comparison of maternal and gestational age and laboratory values of groups.

	GGD N=15 mean \pm SD	GTT N=36 mean \pm SD	P value
Age (year)	27.20 \pm 14.04	27.33 \pm 4.87	0.999
Gestational age(week) Median (min-max)	12 (6-20)	10.5 (5-16)	0.730
FT3 (pg/mL)	10.57 \pm 8.23	4.74 \pm 1.35	0.002
FT3I	2.40 \pm 1.87	1.06 \pm 0.31	0.001
FT4 (ng/dl)	2.37 \pm 1.68	2.06 \pm 0.56	0.620
FT4I	1.39 \pm 0.99	1.21 \pm 0.33	0.570
TSH (μ IU/ml)	0.01 \pm 0.01	0.02 \pm 0.02	0.291
FTHI	1.72 \pm 0.87	0.87 \pm 0.07	0.001

GGD: Gestational Graves' disease, GTT: Gestational transient thyrotoxicosis, FT3: free T3, FT3I: FT3 index, FT4: free T4, FT4I: FT4 index, TSH: Thyroid stimulating hormone, FTHI: Free thyroid hormone index, Min: Minimum, Max: Maximum, SD: Standart Deviation.

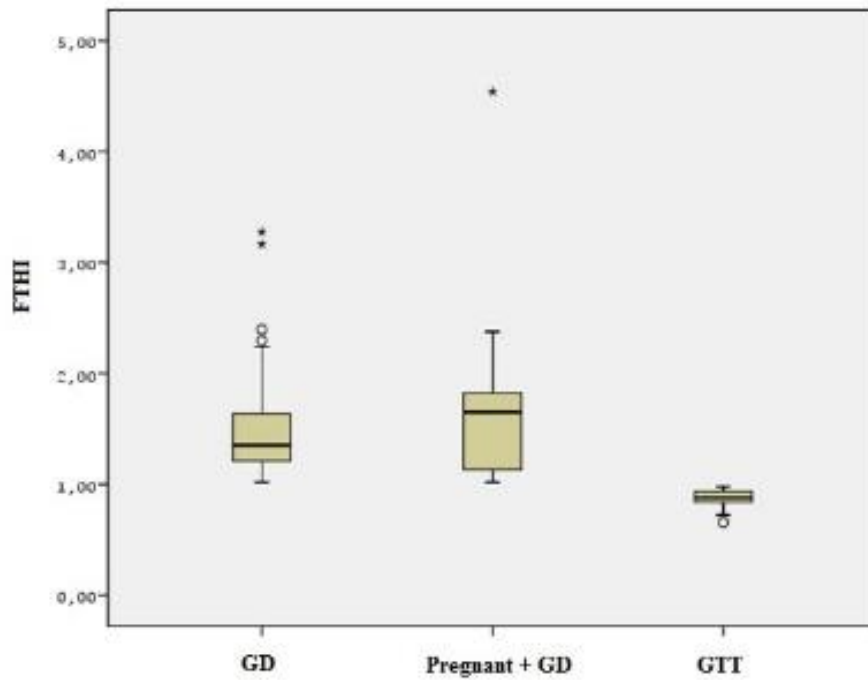


Figure 1: Comparison of groups according to free thyroid hormone index (FTHI)

Table 2: The features of nonpregnant patients with GD.

	Non-pregnant GD mean±SD n=126
Age (year)	38.95±14.04
FT3 (pg/mL)	12.24±6.81
FT3I	2.76±1.51
FT4 (ng/dl)	3.24±1.72
FT4I	1.91±1.01
TSH (μIU/ml)	0.01±0.01
FTHI	1.46±0.37

GD: Graves' disease, FT3: free T3, FT3I: FT3 index, FT4: free T4, FT4I: FT4 index, TSH: Thyroid stimulating hormone, FTHI: Free thyroid hormone index, Min: Minimum, SD: Standard Deviation.

The features of nonpregnant patients with GD were summarized in Table 2. The mean age of non-pregnant GD patients was higher than pregnant patients. Except for TSH and FTHI all other values of thyroid indices were slightly higher than GGD group.

None of the women had a hydatidiform mole or choriocarcinoma.

DISCUSSION

This study reports that FTHI (FT3 index / FT4 index) may be used to differentiate GGD and GTT in the early period of pregnancy especially in places where TRAb assays are not widely available or routinely used because of expensive costs. To our knowledge this is the first study that FTHI is used to distinguish diagnosis of GGD and GTT and is original.

It is well known that the most common causes of hyperthyroidism in pregnancy are Graves' disease and GTT⁷. Regarding fetal risks, treatment and follow-up periods the differential diagnosis of GTT and GGD is important both for clinicians and patients². A careful history and physical examination is vital in distinguishing the etiology. Although nonspecific symptoms of hyperthyroidism may occur during pregnancy, palpitation, anxiety, tremor in hands and heat intolerance are common clinical findings of both conditions¹³. The presence of orbitopathy suggests GGD, however severe orbitopathy in women under the age of 40 is very rare¹⁴. In the absence of clinical features and to confirm the exact diagnosis, laboratory tests are routinely used. The TRAb assays are performed to make the differential diagnosis between GGD and GTT when investigating hyperthyroidism of uncertain etiology, including thyrotoxicosis associated with hyperemesis gravidarum^{13,15}. Unfortunately, long time and high costs are needed to get results of this highly sensitive and specific TRAb tests. Moreover, these assays are not available in many clinics. Therefore, we attempt to use this FHTI to differential diagnosis between GGD and GTT.

Park et al.,¹⁶ investigated the association of TSH, FT4, FT3, and metabolic parameters and found that higher FT3/FT4 ratio was associated with increased risk of metabolic syndrome parameters and insulin resistance. They also mentioned that the FT3/FT4 ratio was good predictive parameter in metabolic syndrome. In another study, Yoshihara et al.¹⁷ evaluated serum hCG as a parameter for differentiating between active Graves' disease (GGD) and GTT. They reviewed 135 cases (103 GTT, 32 GGD) during 7th to 14th week of pregnancy and showed that serum hCG level of the GTT group was significantly higher than in the active GGD group, but it was not a good parameter for differentiating between the two groups. They also revealed that the FT3/FT4 ratio of the active GGD was significantly higher than in GTT group, and a better parameter for differentiation¹⁷. In addition, Tagami et al.,¹⁸ evaluated serum FT3/FT4 ratio of GGD patients and found higher values compared to GTT group.

In our study, it was aimed to obtain how much serum FT3 and FT4 increased compared to their ULN and aimed to find the ratio of these increases. Therefore, we used index of hormones in this study as a parameter. Moreover, a significant difference between the groups in terms of FT3 and FT3 index was found, but there were no thresholds to distinguish the diseases. FT3 index increased more than FT4 and FTHI was >1 in patients diagnosed

with GGD during pregnancy. In Graves' disease, there is higher T3 production from the thyroid gland and serum T3 and free T3 levels are found to be increased compared to serum T4 and free T4 levels¹⁹. This may be an explanation of our results. On the other hand, GTT is generally associated with hyperemesis and there is T4 thyrotoxicosis, particularly²⁰. As mentioned above, the increase of T3 is more than T4 in GGD and that the increase of T4 is higher in GTT, however the extent of this increase has not been established yet.

Due to the low number of patients diagnosed with GGD in our study, we also evaluated these rates in non-pregnant GD patients. Similarly, in GGD group, FTHI was found to be above 1 in non-pregnant GD patients. This situation supported our results. Except for TSH and FTHI all other values of thyroid indices were slightly higher than GGD group. The physiological changes in pregnancy and immunosuppressive effect may be the reason of this result.

There are several limitations in this study. First, the numbers of each group were small. Secondly, the serum hormone index was measured only once in every subject and was not compared after treatment or in third trimester of pregnancy.

Nevertheless, the current study has definitive strengths. First, to our knowledge, this study was the first to distinguish the diagnosis of GGD and GTT by using FHTI (FT3 index/FT4 index).

In conclusion, only controlling the increase rates in free thyroid hormones by using FHTI (FT3 index/FT4 index), the differential diagnosis of GGD and GTT can be distinguished. Since FTHI can be estimated from routine free hormones, it is widely available. The FTHI values may be used as a practical, cheap parameter for differential diagnosis between GGD and GTT.

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