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Özgün Çalışma / Original Article

PERINATAL OUTCOMES OF GESTATIONAL THYROTOXICOSIS: SINGLE CENTER EXPERIENCE, RETROSPECTIVE COHORT

GESTASYONEL TİROTOKSİKOZUN PERİNATAL SONUÇLARI: TEK MERKEZ DENEYİMİ, RETROSPEKTİF KOHORT

Nazlı GÜLSOY KIRNAP[1], Sanem KAYHAN[2]

ABSTRACT

PURPOSE: Gestational thyrotoxicosis may lead to adverse maternal and fetal events. In this study, the aim was to compare the gestational thyrotoxicosis cases with the control group in terms of their differential diagnoses, clinical observation and gestational follow-up outcomes.

MATERIAL AND METHODS: Pregnant patients with subclinical or overt thyrotoxicosis who were followed up in Endocrinology outpatient clinic between December 2009-September 2019 were included in the study. Patients were grouped according to the diagnosis of gestational transient thyrotoxicosis (GTT), Graves' disease, toxic nodular goiter (TNG), and intra-group comparisons and comparisons with the control group were made in terms of the presence of perinatalcomplications during the gestational period, delivery week, and birthweight.

RESULTS: A total of 115 patients were divided into GTT group, which had 50 patients, Graves' group, which had 14 patients, TNG group, which had 1 patient, and control group, which had 50 patients. The prevalence of hyperemesis gravidarum was the highest in GTT group, with 40%. Eclampsia was found in 2 (14.2%) of the pregnant women with Graves' disease and was not found in other groups (p=0.01). Neonatal death was found in 3 (21.4%) of the pregnant women with Graves' disease, and 1 (2%) of the pregnant women with GTT (p=0.01). There was a significant positive correlation between delivery week and TSH (p=0.001, r:0.64), and a significant negative correlation withft3(p=0.04 r:-0.3). A significant positive correlation was detected between birthweight and TSH and delivery week (p=0.03 r:0.32 and p<0.001 r:0.41, respectively).

CONCLUSION: Gestational transient thyrotoxicosis does not affect birthweight and perinatal complications, whereas the prevalence of low birthweight and maternal eclampsia is higher in Graves' disease.

Keywords: *Gestational transient thyrotoxicosis; low birthweight; perinatal complications*

ÖZET

AMAÇ: Gestasyonel tirotoksikoz maternal ve fetal advers olaylara neden olabilir. Bu çalışmada gestasyonel tirotoksikoz vakalarının ayırıcı tanılarını, klinik izlemini ve gestasyonel takip sonuçlarını kontrol grubuna göre karşılaştırmayı amaçladık.

GEREÇ VE YÖNTEMLER: Aralık 2009-Eylül 2019 tarihleri arasında Endokrinoloji polikliniğinde takipli subklinik ya da aşikar tirotoksikozu olan gebe hastalar çalışmaya dahil edildi. Hastalar gebeliğin geçici tirotoksikozu (GGT), Graves hastalığı, toksik nodüler guatr (TNG) tanılarına göre gruplandırılarak gestasyonel süreçte perinatalkomplikasyonların varlığı, doğum haftası, doğum ağırlığınıngruplar arasında ve kontrol grubuna göre farklı olup olmadığı karşılaştırıldı.

BULGULAR: Toplam 115 hastanın 50'si GGT, 14'ü Graves hastalığı, 1 tanesi TNG ve 50'si kontrol grubuna ayrıldı. Hiperemezis gravidarum %40 oranla en sık GGT'de görülmüştür. Eklampsi Graves hastalığı olan gebelerin 2 (%14,2)'sinde olup diğer gruplarda görülmemiştir (p=0,01). Neonatal ölüm Graves hastalığı olan gebelerin 3 (%21,4)'ünde, GGT'nin 1 (%2)'inde görülmüştür (p=0,01). Doğum haftası ile TSH arasında anlamlı pozitif korelasyon (p=0,001 r: 0,64), st3 ile anlamlı negatif korelasyon (p=0,04 r: -0,3) vardı. Doğum ağırlığıile TSH ve doğum haftası arasında anlamlı pozitif korelasyon (sırası ile p=0,03 r: 0,32 p<0,001 r: 0,41) vardı.

SONUÇ: Gebeliğin geçici tirotoksikozu doğum ağırlığıve perinatal komplikasyonları etkilemezken, Graves hastalığında düşük doğum ağırlığıve annede eklampsi oranı daha yüksektir.

Anahtar Kelimeler: *Gebeliğin geçici tirotoksikozu, düşük doğum ağırlığı, perinatal komplikasyonlar*

[1]Department of Endocrinology and Metabolism, Baskent University Faculty of Medicine, Ankara, Turkey.
[2]Department of Internal Medicine, University of Health Sciences Diskapi Yildirim Beyazit Training and Research Hospital, Ankara, Turkey.

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Sorumlu Yazar / Corresponding Author:
Nazlı GÜLSOY KIRNAP
Başkent Üniversitesi Hastanesi Yukarı Bahçelievler, Mareşal Fevzi Çakmak Cd. No:45, 06490 Çankaya/Ankara
Phone: +90 312 304 11 18 **Gsm:** +90 505 238 09 83 **Fax:** +90 312 304 27 00
E-mail: kirnapnazli@hotmail.com

Yazar Bilgileri /Author Information:
Nazlı GÜLSOY KIRNAP (ORCID : 0000-0001-7103-9963),
Sanem KAYHAN (ORCID: 0000-0001-7736-2681) E-mail: drkayhansanem@yahoo.com

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PURPOSE

According to incidence data, the risk of hyperthyroidism during pregnancy is theoretically low, with 0.05%(1). Thyroid autoimmunity tends to improve during pregnancy (2). However, increased hCG levels during pregnancy may lead to disrupted thryoid function tests. During peak hCG concentrations (10 to 12 weeks), serum T4 and T3 concentrations usually slightly increase within the reference range and serum TSH concentrations decrease accordingly. Thus, in some women, high serum hCG concentrations in early pregnancy may lead to subclinical or slightly overt hyperthyroidism characterized by slightly low serum TSH concentrations and high-normal or slightly high serum free T4 concentrations. This phenomenon is called gestational transient thyrotoxicosis (GTT) (3). The two most common causes of gestational hyperthyroidism are GTT and Graves' disease(4,5).

The causes of thyrotoxicosis other than the gestational transient thyrotoxicosis (Graves' disease, toxic adenoma, toxic multinodular goiter) may lead to adverse maternal and fetal events (6,7). Thus, differential diagnosis in the early stage is important. There are limited data on the follow-up and outcomes of gestational thyrotoxicosis cases. In this study, the aim was to share our center experience in which we compared thyrotoxicosis cases diagnosed during pregnancy with the control group in terms of differential diagnosis, clinical observation and gestational follow-up outcomes.

MATERIAL AND METHODS

Pregnant patients who had subclinical or overt thyrotoxicosis according to their thyroid function test results and who were admitted to Endocrinology and Metabolic Diseases clinic between December 2009-September 2019, were included in the study. Patient data were obtained retrospectively from the electronic database. Patients with a known history of thyroid disease, patients with chronic diseases that may affect delivery week and patients who were diagnosed with diabetes during follow-up were excluded from the study. Final diagnoses of gestational thyrotoxicosis were evaluated and compared with the healthy pregnant control group who had no known diseases and who completed the pregnancy without complications. The patients were grouped according to GTT, Graves' disease, and TNG diagnoses and intra-group comparisons and comparisons with the control group were performed in terms of presence of gestational complications in the perinatal outcomesduring the gestational process, delivery week, birthweight. Serum TSH (0.35-4.94 mU/L), ft4 (0.7-1.48 ng/dl), ft3 (1.71-3.71 ng/L) were measured using electro-chemiluminescenceimmunoassay (ECLIA) method. Subclinical hyperthyroidism was defined as having serum TSH levels below the reference range, and ft3 and ft4 levels within the reference range. Overt hyperthyroidism was defined as having low serum TSH levels, and having either one or both of the ft3 and ft4 levels high. The differential diagnosis of GTT and Graves' disease was based on the patient's clinical and laboratory follow-up. If a positive TRAb was detected in thyrotoxicosis cases, the patients were diagnosed with Graves' disease. However, patients who had overt hyperthyroidism, ft3 dominance, increased blood supply to thyroid gland in thyroid ultrasonography and were prone to persistent thyrotoxicosis according to the laboratory results in the follow-up, even in the absence of a positive TRAb, were followed-up with the diagnosis of Graves' disease. Patients who initially did not have overt hyperthyroidism and had hyperemesis gravidarum, were followed up without medication and entered spontaneous remission in the first trimester were classified as GGT during follow-up.

This study was approved by Başkent University Institutional Review Board (Project No: KA 19/429 Date: 24/12/2019). All patients provided informed consents for the procedure and allowed use of their medical information for research purposes at the time of admission.

Statistical Analysis

Statistical analysis was performed using SPSS Version 25. Normality distribution analysis of the data was performed by using Kolmogorov-Smirnov and Shapiro-Wilk tests. Data that did not fit to normal distribution were presented as median (interquartile range, 25-75%). Non-normally distributed data were expressed as the median values and compared using the Kruskal–Wallis and Mann–WhitneyU-test. Chi-square test was used to analyze categorical variables. Correlation analysis was performed using Spearman's rank correlation coefficient; $p<0.05$ was considered significant.

RESULTS

A total of 115 patients were divided into GTT group, which had 50 patients, Graves' group, which had 14 patients, TNG group, which had 1 patient, and control group, which had 50 patients. Demographic and gestational characteristics and laboratory data of the patients were shown in Table 1. The groups were similar in terms of patient age, mode of conception (spontaneous, in vitro fertilization-IVF/intrauterine insemination-IUI), type of pregnancy (single/multiple). TSH level was lower than GTT and ft3 and ft4 levels were higher in Graves' disease ($p<0.001$, $p<0.001$, $p=0.003$, respectively). Hyperemesis gravidarum was the most prevalent in GTT, with 40%, which was significantly higher than Graves' disease and control groups ($p=0.016$, $p=0.03$, respectively). The gestational week thyrotoxicosis was detected was similar in GTT and Graves diseases ($p=0.43$) **(Table 1).**

All groups were similar in terms of the rate of mode of delivery (vaginal/cesarean) rates ($p= 0.33$). All groups were similar in terms of delivery week ($p= 0.27$). Birthweight was significantly lower than the GTT and control groups in Graves' disease group ($p= 0.03$ and $p= 0.004$, respectively), and was similar in GTT and control groups ($p= 0.44$) **(Table 2).**

Table 1 Demographic, clinical, radiological data of patients by groups

Patients	GTT n:50	Graves'Disease n:14	TNG n:1	Control n:50	p
Age (year), median (%25-%75)	32 (28-34)	34.5 (27.5-37.25)	32	32 (30-35.25)	0.73
Mode of conception					0.06
Spontaneous, n (%)	40 (80)	14 (100)	1 (100)	48 (98)	
IVF/IUI, n (%)	10 (20)	-		1 (2)	
Type of pregnancy					0.16
Single, n (%)	42 (84)	12 (85.7)	1 (%100)	50 (100)	
Multiple, n(%)	8 (16)	2 (14.3)	-	-	
Type of hyperthyroidism					**<0.001***
Overt hyperthyroidism, n (%)	9 (18)	10 (71.4)	1 (100)		
Subclinical hyperthyroidism, n(%)	41 (82)	4 (28.6)			
TSH mU/L, median (%25-%75)	0.06 (0.17-0.18)	0.005 (0.001-0.007)	0.002	1.9 (1.75-2.2)	**<0.001***
ft3 ng/L, median (%25-%75)	3.31 (2.91-3.66)	4.84 (4.22-8.3)		3.1 (3-3.4)	**<0.001***
ft4 ng/dl, median (%25-%75)	1.25 (1.06-1.45)	1.61 (1.44-2.43)		1.1 (0.98-1.23)	**0.003***
Hyperemesis gravidarum, n(%)	20 (40)	2 (14.2)	-	7 (14)	**0.016*** **0.003****
Thyrotoxicosis week, median (%25-%75)	9 (8-12)	8 (6-14.5)			0.43

p*:Difference between GTT and Graves' **: Difference between GTT and control group IUI: Intrauterine insemination IVF: In vitro fertilization ft3: free triiodothyronine ft4: free tetraiodohydronine TNG: Toxic nodular goiter TSH: Thyroid stimulating hormone

Table 2 Perinatal characteristic and complications of patients by groups

Patients	GTT Median n:50	Graves'Disease Median n:14	TNG n:1	Control n:50	p
Delivery type					0.33
Normal vaginal, n (%)	17 (35.1)	3 (21.4)		13 (26)	
Cesarean, n(%)	33 (64.9)	11 (79.6)	1(100)	37 (74)	
Birthweight, gr median (25-75%)	3155 (2950-3605)	2600 (2470-3000)	2900	3300 (3025-3592)	**0.03*** **0.004**** 0.44***
Delivery week, median (25-75%)	38.6 (38-39.3)	38.35 (33.75-39)	36.2	38.5 (38.2-39)	0.27
Preterm activity	6 (12)	5 (35.7)	-	3 (6)	0.1
Maternal HT, n (%)	3 (6)	2 (14.2)		2 (4)	0.77
Preeclampsia, n (%)	-	-	-	-	
Eclampsia, n (%)	-	2 (14.2)	-	-	**0.01**
Plasental abruption, n (%)	-	-	-	2 (4)	0.53
Neonatal death n (%)	1 (2)	3 (21.4)	-	-	**0.001*** **0.001****

p*:Difference between Graves' and GTT **: Difference between Graves' and control group***: Difference between GTT and control group GTT: Gestational transient thyrotoxicosis HT: Hypertension TNG: Toxic nodular goiter

When perinatal complications were evaluated; it was found that the groups were similar in terms of preterm activity and maternal hypertension (p=0.1 and p=0.77, respectively), and none of the patients included in the study had preeclampsia. Eclampsia was observed in 2 (14.2%) of the pregnant patients with Graves' disease, and was not found in other groups (p=0.01). Placental abruption was found in 2 (4%) pregnant women in the control group. Neonatal death was observed in 3 (21.4%) of the pregnant patients with Graves' disease,

and this rate was singificantly higher than the GTT group (n:1, 2%) and control group (n:0, 0%) (p=0.001, p=0.001, respectively) **(Table 2).**

There was a significant positive correlation between delivery week and TSH (p= 0.001 r:0.64), anda significant negative correlation between delivery week and ft3 (p=0.04 r:-0.3) **(Table 3).** A significant positive correlation was detected between birthweight and TSH and delivery week (p=0.03 r:0.32, p<0.001 r:0.41, respectively) **(Table 4).**

During the time of diagnosis, 82% (n:41) of the patients in GTT group had subclinical hyperthyroidism, and there was overt hyperthyroidism in 71.4% (n:10) of the patients in Graves' disease group (p<0.001) (Table 1). Median remission time in GTT was 2.5 months (interquartile range 1.5-4.2 months). GTT subgroups with overt or subclinical hyperthyroidism were similar in terms of remission time (median: 2 months, median: 2 months, respectively, p=0.1).

Table 3 Correlation between delivery week and parametric data

Patients n:	r	p
Age	-0.07	0.39
TSH	0.64	**0.001**
ft3	-0.3	**0.04**
ft4	-0.08	0.58
Birthweight	0.41	**<0.001**

ft3: free triiodothyronine ft4:free tetraiodothyronine
TSH: Thyroid stimulating hormone

Table 4 Correlation between birthweight and parametric data

Patients n:	r	p
Age	-0.12	0.25
TSH	0.32	**0.03**
ft3	-0.29	**0.07**
ft4	-0.07	0.64
Delivery week	0.41	**<0.001**

ft3: free triiodothyronine ft4: free tetraiodothyronine
TSH: Thyroid stimulating hormone

DISCUSSION

In our study, the most common thyroid function disorder during gestation was GTT. This was followed by Graves' disease, and more rarely, by TNG. Gestational transient thyrotoxicosis occurs due to aberrant hCG secretion. It is the most commonly found form of hyperthyroidism during the first three months of pregancy (8,9). Toxic nodular goiter is usually found in those aged 40 and above in iodine-deficient areas (10). This can be the reason behind the low TNG prevalence during reproductive period. The data in our study on thyrotoxicosis prevalence during pregnancy is in line with the literature (1,8). In gestational transient thyrotoxicosis, abnormal thyroid functions are typically transient (1). However, in real hyperthyroidism, thyrotoxicosis continues. In our study, thyroid functions revert to normal after a median time of 2 months during the follow up of GTT.

Hyperemesis gravidarum prevalence was marked in GTT. There are limited number of reports on thyroid function disorder in patients with hyperemesis gravidarum. Since thyroid stimulating hormone and hCG have a similar α subunit, hCG can bind TSH receptor and increase T4 secretion and slightly suppress TSH (11). Previous studies have shown a negative correlation between hCG levels and TSH (12). Since more laboratory tests might have been performed in pregnant women with hyperemesis gravidarum, the prevalence of thyroid function disorder could be found higherin these patients. However, when isolated patients with thyroid function disorder were analyzed in our study, hyperemesis gravidarumprevalence was significantly higher in GTT than the control group and Graves' disease group. As TRAbs are responsible for the pathophysiology of Graves' disease, hCG is not the cause of hyperthyroidism in these patients, which could be why hyperemesis gravidarumprevalence was found to be much lower than GTT prevalence. This indirectly explains why hyperemesis gravidarumrather depends on hCG levels than TSH, ft3 and ft4 levels. In our study, hCG levels at the time of thyrotoxicosis detection were not analyzed. Studies which simultaneously analyze hCG levels in Graves' disease and GTT will be enlightening.

In our study, although all groups were similar in terms of gestational week, birthweight in Graves' disease patient group was notably low. There was a negative correlation between TSH levels and delivery week and birthweight. There are reports oflow birthweight in Graves' diseasein the literature (13). It is not always easy to distinguish between gestational transient thyrotoxicosis and Graves' disease. Thyroid receptor antibody (TRAb), which is specific for Graves' disease, may not be positive at all times(1). Orbitopathy can be found in Graves' disease, but orbitopathy is rarely observed in patients under 40 (14)and since our patient group comprised patients of reproductive age,patients under 40 constituted the patient group.Laboratory tests can be helpful to distinguish Graves' disease from GTT. In our study, majority of those with Graves' disease had overt hyperthyroidism at the time of diagnosis, and the majority of those with GTT had relatively mild subclinical hyperthyroidism. Patients with overt hyperthyroidism at the time of diagnosis should be carefully evaluated for Graves' disease.

According to the literature, toxic nodular goiter during pregnancy is very rare (less than 1-2 cases in 100,000 per annum) (15). In our study, only one patient was diagnosed with TNG. Our data is in line with the literature.

In our study, perinatal complications were the most common in Graves' disease group. In Graves' disease, hyperthyroidism is not only found in the mother and the fetus can also have this condition, and the pregnancy might be lost (6). In maternal Graves' disease, TRAb can cross the placenta and stimulate the fetal thyroid. This is not observed in thyrotoxicoses other than Graves' disease. Thus, the risk of fetal loss is high (6,16,17). Thereported rates of fetal death and stillbirth in treated or untreated pregnant patients with Graves' disease were 5% to 6% (7). There are studies reporting a 5-fold increase in the rate of preeclampsia and 10-fold increase in the rate of low birthweight in pregnant patients with Graves' disease who were poorly controlled and untreated (7). In our study, preeclampsia was not observed in any of the groups, including the Graves' disease group. This can be attributed to the number of patients in our study. It can also be attributed to the fact that patients with Graves' disease were followed-up in a tertiary healthcare institution and the necessary multidisciplinary approach was being used. In line with the literature, our study found that the rate of low birthweight was higher in patients with Graves' disease. Therefore, in order to prevent perinatal complications, it is important to perform the differential diagnosis of thyrotoxicosis in pregnant women in the earliest stage.

CONCLUSION

Gestational thyrotoxicosis is rarely observed during the course of pregnancy. Its most common cause is gestational transient thyrotoxicosis. There are no negative perinatalcomplications in gestational transient thyrotoxicosis. However, Graves' disease detected during pregnancy is associated with increased perinatalcomplications.

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Data Availability: This study has been approved by Başkent University's Medical Sciences Ethics Committee, and therefore performed per the ethical standards laid down by the 1964 Declaration of Helsinki and its later amendments.

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