Fetal-Maternal Outcomes of Isolated Hypothyroxinemia in Pregnancy

Gebelikte İzole Maternal Hipotiroksinemi Sıklığı ve Maternal-Fetal Etkileri

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Abstract

Purpose: The prevalence of isolated hypothyroxinemia (IH) ranges between 1.3 and 30%. Thus, the goal of our study was to determine the prevalence of IH in our region, and to explain the maternal-fetal effects of IH.

Material and Method: One hundred-ninety-six pregnant women without previous thyroid disease were included. Six pregnant women did not complete the study due to abortion during the first trimester. All of these patients were euthyroid. Hypothyroidism was detected in three and hyperthyroidism was detected in 2 pregnant women, who were excluded from the study. The remaining 185 pregnant women underwent free T3, free T4, thyroid stimulating hormone, antithyroid peroxidase antibody, antithyroglobulin antibody, and urinary iodine measurements during the three trimesters.

Results: We detected IH among 38% of pregnant females in our population. When the assessment was performed for each trimester; IH was not detected in any patient at the 1st trimester, IH was detected in 59/185 and in 50/185 pregnant women at the 2nd and the 3rd trimesters, respectively. While 13 of these patients detected at the last trimester had new onset IH, in 37 of patients, IH was present even during the 2nd trimester. Even though iodine deficiency was higher in IH group, the difference was statistically insignificant. Fifty percent of the 50 patients with IH who returned for the post-partum examination were noted to have improved thyroid function.

Discussion: No negative effect of IH was observed on fetal development and obstetric outcomes. In the light of current knowledge, therapy is not recommended for patients with IH. The effect of iodine supplementation on fT4 decrease has not been shown to IH patients should also be given iodine supplementation should be given and the doseshould be the same as recommended to pregnant women. *Turk Jem 2014; 18: 106-110*

Key words: Isolated hypothyroxinemia, pregnancy, iodine deficiency, obstetric outcomes

Conflict of interest: The authors reported no conflict of interest related to this article.

Özet

Amaç: İzole hipotiroksinemi (İH) sıklığı %1,3-30 arasında bulunmuştur. Bölgemizde İH sıklığını belirlemek, İH'nin maternal ve fetal etkilerini incelemek amacıyla çalışmayı planladık.

Gereç ve Yöntem: Öncesinde tiroid hastalığı olmayan 196 gebe çalışmaya dahil edildi. Altı gebe ilk trimesterde abortus olması nedeni ile çalışmayı tamamlayamadı. Bu olguların tümü ötiroiddi. Üç gebede hipotiroidi, 2 gebede hipertiroidi saptandı ve çalışma dışı bırakıldı. Geri kalan 185 gebenin tamamının üç trimesterde serbest T3, serbest T4, tiroidi stimüle eden hormon, anti-tiroid peroksidaz antikoru, antitiroglobulin antikoru ve idrar iyot ölçümleri yapıldı.

Bulgular: Popülasyonumuzda gebelerin %38'inde İH saptadık. Her trimester için ayrı ayrı değerlendirme yapıldığında; 1. trimesterde İH saptanan hastamız yoktu, 2. trimesterde 59/185 hastada, 3. trimesterde ise 50/185 hastada İH saptandı. Son trimesterde İH saptanan hastaların 13'ü yeni gelişen İH iken, 37 hasta 2. trimesterde de İH mevcuttu. İyot eksikliği İH saptanan gebelerde daha fazla olmasına rağmen fark istatistiksel olarak anlamlı değildi. İzole hipotiroksinemisi olan 50 hastanın %50'si postpartum kontrole geldi ve tiroid fonksiyonlarının düzeldiği görüldü.

Tartışma: İzole hipotiroksinemili olgularda, fetal gelişim ve obstetrik sonuçlar üzerine olumsuz etki gözlenmemiştir. Güncel bilgiler ışığında İH hastalarına tedavi önerilmemektedir. İyot suplementasyonunun fT4 düşmelerine etkisi gösterilememiştir. IH hastalarına da diğer gebelere önerilen miktarda iyod desteği verilmelidir. *Turk Jem 2014; 18: 106-110*

Anahtar kelimeler: İzole hipotiroksinemi, gebelik, iyot eksikliği, obstetrik sonuçlar

Çıkar çatışması: Yazarlar bu makale ile ilgili olarak herhangi bir çıkar çatışması bildirmemişlerdir.

Introduction

Normal thyroid activity undergoes significant changes throughout pregnancy. At the first trimester, there may be transient increases in free T4 (fT4) levels with the suppression of thyroid stimulating hormone (TSH) suppression depending on human chorionic gonadotropin (hCG) stimulation. Following that period, fT4 concentration decreases slightly (10-15% on an average) and serum TSH levels return to normal (1). Throughout pregnancy, according to the gestational age, fT4 and TSH reference levels can change. Therefore, commenting on the thyroid function of pregnant patients according to the reference range for those who are not pregnant can create diagnostic errors (2,3). The fetus is unable to have thyroid hormone production until the 18-20 week of pregnancy. Until fetal hormone secretion starts, fetal development depends on the level of thyroxin in the circulation from the mother (4). The literature of the last few decades provides evidence that any decrease in thyroid hormone levels during pregnancy can prove harmful for both, the mother and the fetus (5,6,7). Isolated maternal hypothyroxinemia is characterized by low serum fT4 but normal serum TSH concentrations (6,7). Even though there are studies (8,9,10) showing that maternal hypothyroxinemia can lead to adverse fetal outcomes, no such effect is noted in any current publication (11). Since there are no established criteria for the diagnosis of isolated maternal hypothyroxinemia, it is not easy to detect the real incidence. In studies from areas without an iodine deficiency isolated hypothyroxinemia (IH) occurs in a frequency of 1.3-2.3% (12,13,14), whereas it occurs in a frequency of 25-30% in areas with a mild to moderate iodine deficiency (15,16). To date, there has been no study investigating the frequency of IH in Turkey. Thus, we planned to develop a study in order to determine the maternal-fetal effects of IH and the frequency of IH.

Materials and Methods

Patient Selection

We included 196 pregnant women aged 18 years and older who had no previous thyroid disease, had live singleton fetus, became pregnant spontaneously, were on their 4-12 weeks of pregnancy, and attended our gynecology and obstetric outpatient clinic for the first routine obstetric controls between 2009 and 2011. We obtained approval from the ethics committee. Written informed consent was obtained from all of patients in this study. Six patients did not complete the study due to abortion during the first trimester. All the subjects were euthyroid. Hypothyroidism was detected in three and hyperthyroidism was detected in 2 pregnant women, who were excluded from the study. Free T3 (fT3), fT4, TSH, anti-thyroid peroxidase antibody (anti-TPO), anti-thyroglobuline antibody (anti-TG), and urinary iodine measurements were performed in the remaining 185 pregnant women during the three trimesters. The delivery methods, gestational age and the weights of all infants were recorded.

Biochemical Analysis

The Abbott Architect 2000 device and chemiluminescent microparticle immunassay device was used to measure fT3, fT4 and TSH levels. Thyroid function tests were interpreted according to reference range that was determined for pregnants. Anti-TPO and anti-TG were studied with Roche Elecsys 2010 device and electrochemiluminescence immunoassay method. Subjects with serum fT4 values below the lower limit of the trimester-specific reference range and TSH concentrations within the trimester-specific reference range were diagnosed with IH (6,7). Since there are no FT4 reference levels available for pregnant women in Turkey, the manufacturer's recommended reference ranges were used in this study. Subjects with serum TSH concentration above the upper limit of the trimester-specific reference range (1st trimester: 0.1-2.5 mIU/L, 2nd trimester: 0.2-3.0 mIU/L and 3rd trimester: 0.3-3.0 mIU/L) with a normal free T4 were diagnosed with subclinical hypothyroidism (SH) (17). 24-hour urine was collected, the urinary iodine concentrations (UIC) was determined with a colorimetric method based on the Sandell-Kolthoff reaction as recommended by WHO and ICCIDD (18) using the spectrophotometric method (Shimatzu mini spectrophometer). A recent WHO/ICDIDD expert group defined epidemiological criteria for assessing iodine nutrition based on the median or range in UIC of pregnant women. Based on these ranges, iodine intake was accepted as follows: insufficient: UIC <150 μg/L; adequate: 150-249 μg/L; more than adequate: 250-499 μg/L; and excessive: >500 μg/L (18).

Statistical Analysis

The analysis used in the study was made via SPSS for Windows ver. 15.0 (Chicago, IL). We used The Kolmogorov-Smirnov test and the Shapiro-Wilk test for the analysis of convenience of the data for normal distribution, student's t-test and the Mann-Whitney test for the analysis of continuous variables, and Pearson's chi-Square and Fisher's exact tests for the analysis of categorical variables. The correlations between the continuous variables were evaluated with the Pearson and Spearman correlation tests. The variables that fitted the normal distribution were determined with average and standard deviations, and the variables not fitting the normal distribution were determined through the median and interquartile ranges. A p value of less than 0.05 was considered statistically significant.

Results

Study Population

The average age was 25.7±5.2 years (range 20-41). The clinical and biochemical features of our study population at presentation are reported in Table 1.

IH was detected in 72 pregnant patients out of 185 (38%). When the evaluation was performed for each trimester individually, no patients with IH were detected during the first trimester. At the second trimester, 59 pregnant patients out of 185 (32%), and at the third trimester, 50 pregnant patients out of 185 (27%) were noted to have IH (Figure 1). Thirteen (26%) patients detected in the third trimester had new-onset IH, whereas IH was present even during the second trimester in 37 (74%) patients.

Treatment was not administered to the patients with IH. The comparison of laboratory parameters of the patients with or without IH and other features are given in Table 2.

There was no relationship of fT4 levels (0.94 cut-off rate) with delivery method (vaginal or cesarean), infant birth weight, and

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complications during the first trimester (p=0.337, 0.588, 0.386, respectively).

There was no significant relationship of fT4 levels (0.75 cut-off rate) with delivery method (vaginal or cesarean), infant birth weight, and complications during the second trimester (p=0.855, 0.390, 0.551, respectively).

No significant relationship of fT4 levels (0.65 cut-off rate) with delivery method, and complications at the third trimester was found (p=0.653 and 1.000, respectively). During the third trimester, the birth weights of infants with IH were higher (3200 vs 3600) (p=0.029).

While the UIC in 59.5% of pregnant patients were less than 150 mcg/l during the first trimester, these levels were lower in 51.7% of pregnant patients during the second trimester. In the third trimester, 60% of pregnant patients were noted to have lower urinary iodine levels.

In all trimesters, no relationship was detected between fT4 and UIC (p=0.469, p=0.897 and p=0.223 for the first, second and third trimesters, respectively). Additionally, no relationship was detected between TSH levels and UIC during any of the trimesters (p=0.303, p=0.561 and p=0.333 for the first, second and third trimesters, respectively).

During the second trimester, SH was detected in 9 (4.9%) pregnant patients and in 6 (3.2%) patients during the third trimester, and 1-thyroxin replacement was started accordingly. Anti-TPO and anti-TG levels were positive in three patients with SH during the second trimester and in 3 patients with SH during the third trimester.

50% of 50 patients with IH returned for their postpartum visits, and their thyroid function was noted to have returned to normal.

Discussion

Although the underlying cause of IH is not fully understood, iodine deficiency during pregnancy appears to be a responsible factor. Different rates of IH incidence are reported in different studies depending on the sufficiency of iodine in the geographic locations in which the studies are performed. While the frequency of IH in iodine-sufficient ares has been reported to be between 1.3% (12) and 2.3% (13), this rate has been recorded between 25-30% in areas of mild-to-moderate iodine deficiency. Indeed, in conditions
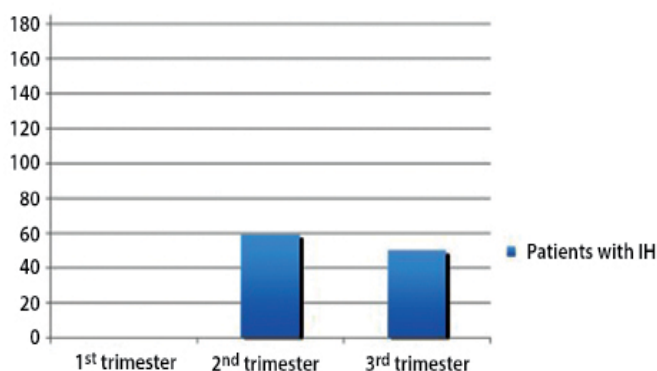
of mild-moderate iodine deficiency, thyroid stimulation by hCG, which occurs over the 1st trimester, leads to the preferential output of T3 over T4. In these women, T4 secretion soon becomes inappropriately low relative to the increasing T4-binding globulin (TBG) concentrations. This leads to the progressive desaturation of TBG by T4, ultimately resulting in steadily declining fT4 concentrations (6,19). In iodine- sufficient areas, the cause of IH is not fully understood, however, pregnant patients with IH in these areas may be consuming less iodine (below the recommended 250 µg/day) than required for normal thyroid function and production of thyroid hormones. In this study, we detected IH in 38% of pregnant patients in our region, and 59.5% (urinary iodine <150 mcg/L) of them were suffering from iodine deficiency. At the beginning of the study, the median UIC was 117.5 mcg/L. In Turkey, after salt iodization, the median UIC increased to 87 µg/L in 2002 and to 117 µg/L in 2004 (20). In 2007, the median UIC in school-age children reached 130 µg/L, suggesting sufficient iodine intake in the general population (21). These follow-up monitoring studies demonstrated that iodine deficiency was eliminated in most urban areas, including Ankara, the capital city of Turkey. However, iodine status among pregnant women is a still debated issue in our country. A study conducted in Ankara has shown that the median UIC in pregnant women was 80.5 µg/L (22). In another study with first-trimester pregnant women, almost half of the subjects were below the WHO, United Nations Children's Fund, and International Council for the Control of Iodine Deficiency Disorders lower median reference limits of 150 µg/L (23). Despite mandatory iodination, the fact that the iodine deficiency rate is still high in our region can explain high frequency of IH. In the group with IH, although iodine deficiency was higher, the difference was not statistically significant. This suggests that iodine deficiency is not the only element in IH pathogenesis. When the evaluation was made separately for each trimester, we did

Figure 1. IH rate for every trimester through the pregnancy

Table 1. The clinical and biochemical features at presentation	
	Median (Interquartile range) OR n (%)
Age (years)	25 (6.50)
Height (cm)	161.28±5.57*
Weight (kg)	61.50 (15.50)
Smoking rate	33 (17.83%)
Abortus story	20 (10.81%)
sT3 (2.5-3.9 pg/mL)	3.28±0.37*
sT4 (0.61-1.2 ng/dL)	0.91±0.14*
TSH (0.34-4.25 µIU/mL)	0.81 (1.03)
TPO (0-9 IU/mL)	0.80 (1.00)
UIC (mcg/L)	117.50 (64.50)
Delivery method (C/S)	74 (40.0%)
Abortus	6 (4.0%)
Complication	8 (5.5%)
Infant weight (gr)	3238.82±503.00*
*Data stated with an average ± standard deviation (that fit normal distribution) height, fT3, fT4, infant weight. UIC: Urinary iodine concentrations	

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not have any patient with IH detected at the first trimester. During the second trimester, IH was detected in 59 of 185 patients (32%), and in 50 of 185 patients (27%) in their third trimester. While 13 (26%) patients detected at the last trimester had new onset IH, in 37 (74%) patients, IH was present even in the 2nd trimester. Same as our results, in a study by Moleti et al. (16), IH was detected in 25% of pregnant patients in an iodine-deficient region and the frequency of IH was highest in the second trimester, and was lower (3.2%) in the early weeks of pregnancy.

In our study, anti-TPO was detected in 40% of the pregnant patients with subclinical hypothyroidism. This result supports the notion that SH can occur due to autoimmune thyroiditis, which often causes progressive thyroid failure (24). Anti TPO levels in our patients with IH were similar to that in normal pregnant patients in compliance with the previous studies (16,24). These results suggest that autoimmune thyroiditis does not play a role in the pathogenesis of IH. According to the recent ATA guidelines proposals, treatment is not recommended (25), Current ETA guideline does not recommend any therapy in the 2nd and 3rd trimesters for IH cases (26), and thus, in our study, treatment was not administered to patients with IH. WHO, ATA and ETA guidelines recommend 250 mcg daily intake of iodine for pregnant women (18,25,26). In studies from some mild and moderate iodine-deficient European countries, it was observed that iodine supplementation for pregnant women did not prevent

decrement in fT4 (27,28). In such places as our region, with oral intake, a total amount must be 250 mcg/day. Thus, 100-150 mcg/day iodine supplementation should be given. Therefore, it should be emphasized that the goal of iodine supplementation should not be the inhibition of fT4 drop, it should be given for the increased requirement in pregnancy, to suppress enlargement of mother's thyroid gland and to prevent iodine deficiency disorders in babies.

The levels of fT4 in patients with IH were significantly lower when compared to the group without IH during the first and the second trimesters, while TSH levels were significantly higher. The difference between these groups disappeared during the third trimester. As noted from previous studies, the need for iodine during pregnancy increases significantly. In patients from regions of iodine deficiency, fT4 levels decrease later in gestation and TSH levels increase. We assume that the reason for the decrease in fT4 levels that are within the normal range in the group without IH and disappearance of the difference between the groups is due to the deficiency of iodine in our region.

Demographic data of patients with and without IH were similar. No obstetric complication occurred in patients with IH, and their cesarean section rates were similar to that of the group without IH. Supporting the results of a previous study, there was not any relationship between IH and excessive adverse pregnancy outcome (24). During the first and the second trimester, no relationship was detected between T4 levels and infant birth weights, but during the third trimester, birth weight of patients with IH was higher. Pre-pregnancy weight of patients with IH was greater than that of patients without IH, but this difference was not statistically significant. The difference in infant weights may be related to the different pre-pregnancy weights of the mothers. The Endocrine Society (17) and the latest ATA (25) guidelines propose a thyroid function test in pregnancy, with the aim of identifying high-risk pregnant women. However, no recommendation is available for follow-up during late pregnancy.

It has been reported that pregnant women can have subclinical or apparent hypothyroidism although their thyroid function tests are normal at the beginning of the pregnancy and, hypothyroidism can be underdiagnosed in 40% of pregnant women when thyroid function tests are performed only in the early gestational weeks (16). Supporting these findings, in our study, we found SH in 15 pregnant women whose thyroid function tests that were done in the first trimester were normal. We assume that large population studies are needed in order to evaluate whether there is a need for thyroid function tests during pregnancy in women living in regions where iodine deficiency is still a problem.

In conclusion, in our study, we found out that IH is not related with adverse obstetric outcomes. In the second or three trimesters, we did not encounter any pregnancy complications in patients with IH. Our findings support the updated guidelines which suggest that providing therapy to patients with IH is not required (25).

Conflicts of Interest

There are no conflicts of interest.

Table 2. Demographic and hormone analysis outcomes of patients with and without isolated hypothyroxinemia (IH)

	With IH n=72	Without IH n=113	p-rates
Age (years)	27.0±3.9	25.5±5.4	0.168
Height (cm)	161.1±5.7	160.2±5.1	0.538
Weight (kg)	64.7±10.2	62.0±11.2	0.374
Smoking rate	11 (15.3%)	22 (19.5%)	0.729
Abortus story	7 (9.7%)	13 (11.5%)	0.837
fT3 (pg/mL) (1)	3.3±0.35	3.2±0.33	0.414
fT3 (pg/mL) (2)	2.68±0.5	2.86±0.3	0.111
fT3 (pg/mL) (3)	2.7±0.17	2.8±0.16	0.163
fT4 (ng/dL) (1)	0.83±0.11	0.93±0.13	0.006
fT4 (ng/dL) (2)	0.55±0.04	0.73±0.89	0.000
fT4 (ng/dL) (3)	0.68±0.14	0.67±0.12	0.886
TSH (µIU/mL) (1)	1.7±1.5	0.97±0.8	0.000
TSH (µIU/mL) (2)	2.4±1.39	1.4±0.85	0.008
TSH (µIU/mL) (3)	1.86±0.95	1.4±0.72	0.431
Anti TPO + (%)	5.3	10	0.294
Iodine deficiency (%) (1)	60	49.3	0.562
Iodine deficiency (%) (2)	56	47.2	0.754
Iodine deficiency (%) (3)	59	48.2	0.658
Delivery method (C/S)	32 (44.4%)	42 (37.1%)	0.400
Abortus	0	6 (5.3%)	0.269
Complications	0	8 (7.1%)	0.188

(1), (2), (3) respectively 1st trimester, 2nd trimester, 3rd trimester

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