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The effect of vitamin B12 level on fetal birth weight

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Abstract

Objective: Vitamin B12 is a co-enzyme necessary for lipid, protein, carbohydrate metabolism, erythropoiesis, DNA and RNA synthesis and homocysteine metabolism. In this study, we aimed to investigate the effect of serum vitamin B12 level on birth weight in pregnant women.

Methods: This cross-sectional clinical study included a total of 463 cases who referred to our clinic for the gestational follow-up between 28 and 32 weeks of gestation. Pregnant women who were vegetarian or had systemic disease which may cause vitamin B12 deficiency or those with the history of delivering baby with neural tube defect were excluded from the study. The cases underwent venous blood sampling and their vitamin B12 levels were determined in biochemistry laboratory by Beckman Coulter device. Normal ranges of vitamin B12 levels were considered to be between 145 and 912 pg/ml. Statistical analysis of the data obtained from the study was carried out by SPSS version 16.0. Conformity of the data to normal distribution was evaluated by Shapiro-Wilk test. The data showing normal distribution were analyzed by using parametric tests.

Results: Mean vitamin B12 levels of the cases was 219±202 pg/ml and 169 cases (36.5%) had vitamin B12 deficiency. In terms of birth weights, mean weight was 3298±482 g in cases with normal vitamin B12 levels while it was 3316±434 g in the cases with normal levels of vitamin B12 (p=0.288). When birth weights were distributed into the percentiles according to the weeks of gestation, it was seen that 39 cases (9.8%) were below 10th percentile, 333 cases (83.2%) were between 10th and 90th percentile, and 28 cases (7%) were above 90th percentile. According to these results, there was no significant difference between two groups in terms of birth weights.

Conclusion: According to the results of our study, there is statistically no significant effect of vitamin B12 level on birth weight and week of gestation.

Keywords: Gestation, vitamin B12 deficiency, birth weight.

Özet: Vitamin B12 düzeyinin fetal doğum ağırlığı üzerine etkisi


Sonuç: Çalışmanın sonuçlarına göre vitamin B12 düzeyinin doğum ağırlığı ve doğum haftası üzerinde istatistiksel olarak anlamli bir etkiye sahip çıkmamıştır.

Anahtar sözcükler: Gebelik, vitamin B12 eksikliği, doğum ağırlığı.
Introduction

Vitamin B12 is a co-enzyme necessary for lipid, protein, carbohydrate and homocysteine metabolisms, erythropoiesis, and DNA and RNA synthesis. Vitamin B12 has a significant role for cell division during pregnancy; it is synthesized in the liver and called as extrinsic factor. While it is effective in all cells, it is more active functionally in bone marrow, gastrointestinal system and central nervous system. It is a co-factor for the DNA synthesis in the bone marrow. In the deficiency of vitamin B12, depending on the insufficient DNA synthesis, erythroblasts cannot divide, they run into blood as megaloblasts and cause megaloblastic anemia.[1,2]

Vitamin B12 has a role in the reactions catalyzing the methionine synthesis from homocysteine. In this regard, B vitamins have a significant role in fetal growth, nutrition and development.[3-5] Anomalies that may occur in the metabolisms of methionine, homocysteine and cysteine cause poor obstetric outcomes such as placental dysfunction and preeclampsia.[6-9]

Although there are not much data about the physiological changes occurring in the vitamin B12 and vitamin B12 binding protein metabolism during pregnancy, it has been reported in some studies that biochemical vitamin B12 deficiency was observed in the third trimester at a rate of 35%.[9]

This study has been conducted to evaluate the changes that may be seen in the fetal birth weight in the deficiency of vitamin B12.

Methods

A total of 463 cases who referred for gestational follow-up between 28 and 32 weeks of gestation to the antenatal unit of gynecology and obstetrics clinic of a tertiary center between May 1, 2009 and September 21, 2009 were included in this study. The approval of local ethics board and written consent form of each patient were obtained for the study.

Age, pregnancy, delivery and abortion numbers, concurring chronic diseases, drug or smoking habits, and weeks of gestation according to their last menstrual period (LMP) of each case were investigated. Patients who were vegetarian, had a secondary disease that may cause vitamin B12 deficiency (thalassemia carrier, malabsorption syndromes, kidney diseases etc.) and history of delivering baby with neural tube defect were excluded from the study.

Vitamin B12 levels in serums obtained from fasting peripheral venous blood samples taken in the morning were analyzed by Beckman Coulter device (Beckman Coulter Inc., Pasadena, CA, USA) in the biochemistry laboratory. In order to determine vitamin B12 levels, the original kit of the device was used (Vitamin B12 access assay, Beckman Coulter Inc., Pasadena, CA, USA). Normal ranges of vitamin B12 levels were considered to be between 145 and 912 pg/ml.

Out of 463 cases included in the study, 400 patients delivered in our hospital. Of these 400 cases, delivery week and type, newborn body weight, 1-minute and 5-minute Apgar scores, and the presence of gestational complications observed during gestational follow-ups, preeclampsia, eclampsia, gestational diabetes mellitus (GDM), abruptio placentae, preterm labor, preterm premature rupture of membranes (PPROM), small for gestational age (SGA) and intrauterine growth retardation (IUGR) were recorded.

Classification of birth weights according to the gestational age was evaluated according to maturity and intrauterine growth curves defined by Hadlock (10). Accordingly, babies born with weights below 10th percentile according to gestational age were considered to be small for gestational age (SGA), those with weights between 10th and 90th percentile according to gestational age were considered to be appropriate for gestational age (AGA) and those with weights over 90th percentile were considered to be large for gestational age (LGA).[10]

Statistical Analysis

The statistical analyses of the data obtained from the study were performed by Statistical Package for Social Sciences version 16.0 (SPSS Inc., Chicago, IL, USA), the conformity of the data to normal distribution was evaluated by Shapiro Wilk test and the data showing normal distribution were analyzed by using parametric tests. The statistical analyses in the comparison between the groups were done by Student T test for mean values in data displaying continuity and by chi-square test in categorical variables. The relationship between vitamin B12 values and birth weight was analyzed by Pearson correlation test. The results were evaluated within 95% confidence interval. The value p<0.05 was considered statistically significant.
**Results**

Mean age of 463 cases included in the study was 26.1±5.1 (range: 17 to 40), the gravida was 1.92±1.10 (range: 0 to 6) and number of abortions was 1.31±0.67 (range: 1 to 4).

Mean vitamin B12 level of the cases was 219±202 pg/ml (range: 44 to 1516). Vitamin B12 level in 169 (36.5%) of the cases was lower than 145 pg/ml and they had vitamin B12 deficiency.

While 23 (5.0%) of the cases did not use any drug other than multivitamin including iron, 129 (27.9%) of them were using both multivitamin and antianemic preparation. The number of cases who were using only antianemic drug was 252 (54.4%). Fifty-nine (12.7%) cases were not using any preparation.

While B12 vitamin levels were normal in 129 (84.9%) of 152 cases using multivitamin, B12 vitamin levels were normal in 165 (53.1%) of 311 cases who were not using multivitamin. Vitamin B12 level was low in 46.9% of the cases not using multivitamin while it was low only in 15.1% of the cases using multivitamin. It was seen that vitamin B12 level of the cases using multivitamin was statistically and significantly higher (p<0.001) (Table 1).

Smoking habit during pregnancy was observed in 27 (5.8%) cases. While mean vitamin B12 level was 182±105 pg/ml in smoking cases, it was 221±205 pg/ml in non-smoking cases, and no significant difference was observed between the groups (p=0.331). Vitamin B12 levels were low in 14 (51.9%) smoking cases. Vitamin B12 levels were low in 155 (35.6%) of non-smoking cases. This difference was not statistically significant (p=0.088).

When vitamin B12 levels were analyzed according to the gravida, it was seen that 212 (45.8%) cases were primigravida. While mean vitamin B12 levels were 234±223 pg/ml in primigravida pregnant women, the levels were 206±181 pg/ml in multigravida pregnant women (p= 0.131). Vitamin B12 deficiency was found in 73 (34.4%) of primigravida pregnant women and in 96 (38.2%) of multigravida pregnant women (p=0.396).

In the study, 240 (51.8%) of the cases were nullipara and their mean vitamin B12 level was 228±212 pg/ml. For multipara pregnant women (parity ≥1), the mean vitamin B12 level was found as 209±190 pg/ml (p=0.319). While vitamin B12 deficiency was observed in 84 (35%) of nullipara pregnant women, this rate was 38.1% (n=85) for multipara pregnant women. No difference was observed between the groups in terms of vitamin B12 deficiency (p=0.486).

When we reviewed the records of 400 cases who delivered in our hospital, we observed that mean week of gestation at delivery was 39 weeks and ±1 week and 4 days (range: 32 weeks and 2 days – 42 weeks and 2 days), and birth weight was 3298±446 g (range:1470 to 4470 g). While 265 (66.2%) of the cases delivered vaginally, 135 (33.8%) of them were delivered by cesarean section. After delivery, 1-minute Apgar score of all newborns was 7 and above.

In cases with low vitamin B12 levels (n=148), mean week of gestation at delivery was 39 weeks and ±1 week and 4 days in cases with normal vitamin B12 levels (p = 0.451). In terms of birth weights, mean weight was 3298±482 g in cases with low vitamin B12 levels while it was 3316±434 g in the cases with normal levels of vitamin B12 (p=0.288).

When birth weights were distributed into the percentiles according to the weeks of gestation, it was seen that 39 cases (9.8%) were below 10th percentile, 333 cases (83.2%) were between 10th and 90th percentile, and 28 cases (7%) were above 90th percentile. While the baby in 18 (12.2%) of a total 148 cases with low vitamin B12 level was small for gestational age, the babies were SGA in 21 (8.3%) of the cases with normal vitamin B12 levels. There was no significant impact of vitamin B12 deficiency on birth weight percentiles (p=0.321) (Table 2).

| Table 1. Comparison of vitamin B12 levels in pregnant women who use and do not use multivitamin preparation. |
| --- | --- | --- | --- |
| Vitamin B12 level | Cases using multivitamin (n=152) | Cases not using multivitamin (n=311) | p value |
| Normal (n=294) | 129 (%84.9) | 165 (%53.1) | <0.01 |
| Low (n=169) | 23 (%15.1) | 146 (%46.9) |  |

| Table 2. Comparison of the groups according to vitamin B12 levels and birth weight percentiles. |
| --- | --- | --- | --- |
| Percentile | Vitamin B12 <145 pg/ml | Vitamin B12 ≥145 pg/ml | p value |
| <10% (n=39) | 18 (%12.2) | 21 (%8.3) |  |
| 10–90% (n=333) | 122 (%82.4) | 211 (%83.7) | 0.321 |
| >90% (n=28) | 8 (%5.4) | 20 (%17.9) |  |
Also, statistically no significant correlation was found between birth weight vitamin B12 levels. (Pearson correlation test: r=0.080; p=0.108) (Fig. 1).

Gestational complications were diagnosed in 39 (8.4%) cases. Among them, preterm labor and PPROM were found in 16 (3.5%) cases, preeclampsia and IUGR in 13 (2.8%) cases, constitutional SGA in 3 (0.6%) cases, GDM in 5 (1.1%) cases, and disorder in liver function tests in 2 (0.4%) cases. While gestational complication developed in 17 (11.5%) of the cases with low vitamin B12 levels, it was developed in 22 (8.7%) of the cases with normal vitamin B12 levels (p=0.370). In terms of complication rates, there was statistically no significance between the two groups.

In the review of 361 cases who had no complication during pregnancy and delivered after 37 weeks of gestation, it was found that SGA developed in 12 (9.2%) of 131 cases with vitamin B12 deficiency and in 16 (7%) of 230 cases with normal B12 levels (p=0.378). Birth weight was 3353±407 g in cases with vitamin B12 deficiency and 3351±396 g in cases with normal vitamin B12 levels (p=0.847) (Table 3).

Discussion
In this study, we investigated to find the effects of vitamin B12 deficiency on fetal birth weight and obstetric outcomes. According to our findings, we observed no difference between the pregnant women groups with and without vitamin B12 deficiency in terms of birth weight and obstetric outcomes.

Vitamin B12 has a role in carbohydrate, lipid and protein metabolisms, DNA and RNA syntheses and in erythropoiesis. It is a co-factor necessary for cell division in pregnancy, and there are studies reporting that it is a significant element for fetal growth. The value of this vitamin during pregnancy should be at a normal level for both fetal health and anemia control.

It was seen by our findings that vitamin B12 level of the cases using multivitamin was statistically and significantly higher (p<0.001). There are studies in the literature reporting that the use of multivitamin does not affect maternal serum vitamin B12 levels. However, our findings correspond to the publications reporting opposite opinions. Ray suggested that the use of multivitamin increases maternal vitamin B12 levels; however, it has no effect on birth weight.

Although it is asserted that maternal vitamin B12 levels have a correlation with low birth weight and preterm labor, there are inconsistent data in the literature. A relationship is claimed between erythrocyte folate concentrations at >16 weeks of gestation and infants with preterm and SGA. It was determined that insufficient folate intake with diet and low folate levels at 28 weeks tripled preterm labor and low birth weight risks. Although vitamin B12 deficiency is not associated with poor obstetric outcomes, a positive correlation was found between maternal vitamin B6 level and birth weight of infant. In addition, an inverse correlation was found between cord blood vitamin B6 concentrations and preeclampsia which is a major risk factor for preterm labor. Also, the role of homocysteine which may affect obstetric outcomes was investigated and a correlation was found between preeclampsia, low birth weight, preterm labor, and homocysteine which increases as a result of genetic anomalies or

![Fig. 1. Correlation between vitamin B12 level and birth weight (Pearson correlation test: r=0.080; p=0.108).](image)

<table>
<thead>
<tr>
<th>Vitamin B12 level</th>
<th>SGA</th>
<th>Birth weight (gram)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low</td>
<td>12 (%9.2)</td>
<td>3353±407</td>
</tr>
<tr>
<td>Normal</td>
<td>16 (%7)</td>
<td>3351±396</td>
</tr>
<tr>
<td>p-value</td>
<td>0.378</td>
<td>0.847</td>
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</table>

Table 3. Vitamin B12 levels and mean birth weight and SGA prevalence in pregnancies terminated at term (n=361).
folate, vitamin B12 or vitamin B6 levels at suboptimal levels. In a recent study, it was suggested that maternal folate, vitamin B6 and vitamin B12 levels were not associated with low birth weight or SGA independently. In another study, it was argued that folate and vitamin B12 supplement during pregnancy would provide improvements in parameters such as birth weight, head circumference and height.

Although high homocysteine level was found to be associated with low birth weight, its correlation with vitamin B12 level could not be presented. Also, it was found that vitamin B12 levels were not different in pregnancies with IUGR and normal delivery. A study has been conducted to evaluate if maternal vitamin B12 level was an independent risk factor for increased IUGR frequency. In this study, serum vitamin B12 level was found significantly in direct proportion with vitamin B12 intake; however, no relationship was detected between vitamin B12 intake and IUGR. In women with low vitamin B6 and vitamin B12 levels and high homocysteine levels, a significant difference was found between DDA cases, SGA cases and the control group. At the same time, preterm labor was found to be associated with vitamin B6 and B12 levels. It was found that the risk of preterm labor was 60% less in those with >258 pmol/L vitamin B12 levels than those with lower levels.

Cross-sectional study setup and being unable to control all factors that may affect vitamin B12 levels metabolically are among the restrictions of our study. Also, we should not ignore the possibility of affecting findings with number of children, nutritional habits, and many socio-cultural, genetic and environmental parameters. In further studies, investigating parameters such as homocysteine, folate and vitamin B6 levels as well as vitamin B12 which are closely associated will help to interpret findings more healthily and reliably.

Conclusion

The results of our studies showed that maternal vitamin B12 deficiency had no effect on birth weight and delivery week. To clarify this matter, multi-centered, randomized and controlled studies to be conducted on wider series are required.

Conflicts of Interest: No conflicts declared.

References

Effects of maternal first trimester thyroid stimulant hormone levels on birth weights of fetuses born at term

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²Clinic of Gynecology and Obstetrics Tatvan State Hospital, Bitlis, Turkey
³Clinic of Gynecology and Obstetrics Patnos State Hospital, Ağrı, Turkey

Abstract

Objective: We aimed to investigate the relationship between first trimester maternal thyroid stimulant hormone (TSH) levels and fetal birth weight in pregnant women with TSH results within normal ranges.

Methods: A total of 193 patients meeting study criteria were separated into two groups according to their TSH levels found at first trimester as those between 0.4 and 2.5 mU/L, and those between 2.5 and 4.2 mU/L. There were 162 patients in the first group (Group 1) with TSH level between 0.4 and 2.5 mU/L, and 31 patients in the second group (Group 2) with TSH level between 2.5 and 4.2 mU/L. Birth weights were also categorized under three groups which were <2500 g, 2500–3500 g and >3500 g. These three fetal weight groups and two TSH groups established according to their first trimester measurements were compared.

Results: When both groups were compared in terms of demographic data and fetal weight, there was no significant difference between two groups in terms of the parameters analyzed. In both TSH groups, distribution percentages of the patients were found statistically similar according to fetal birth weights.

Conclusion: We found that normal TSH levels have no effect on fetal birth weight and that a further examination may not be required in terms of thyroid functions when TSH level is found within normal ranges at first trimester in terms of affecting fetal weight.

Keywords: Thyroid stimulant hormone, fetal birth weight, hypothyroidism.

Özet: Maternal ilk trimester tiroid stimülan hormon düzeylerinin miad›nda do€an fetüslerin do€um a€›rl›klar›na etkisi

Amaç: Normal s›n›rlarda saptanm›fl serum tiroid stimülan hormon (TSH) sonuçlar› olan gebelerde, ilk trimester maternal TSH düzeyi ile fetal do€um a€›rl›€› arasında iliflki olup olmad›€›n› araflt›r- may› amaçlad›k.

Yöntem: Çalışma şartlar›n› sağlayan toplam 193 hasta, birinci trimesterde saptanan TSH seviyesine göre 0.4–2.5 mU/L arasında olanlar ve 2.5–4.2 mU/L arasında olanlar olarak iki gruba ayrılıdı. Birinci gruba (Grup 1) TSH seviyesi 0.4–2.5 mU/L arasında olan 162 hasta, ikinci gruba (Grup 2) ise TSH seviyesi 2.5–4.2 mU/L arasında olan 31 hasta yer ald›. Do€um a€›rl›klar› da üç ayr› gruba ayrılıdı (<2500 g, 2500–3500 g ve >3500 g). Bu üç fetal a€›rl›€› gruba ile ilk trimester ölçümlerine göre oluflturulan iki TSH grubu karfl›-laflt›r›ld›.

Bulgular: Her iki grup demografik veriler ve fetal a€›rl›€› yönünden karfl›laflt›r›ld›€›nda bak›lan parametreler aç›s›ndan iki grup aras›nda anlaml› fark saptanmad›. Her iki TSH grubunda da üç ayrı gruba ayrıld› (<2500 g, 2500–3500 g ve >3500 g). Bu üç fetal a€›rl›€› grupu ile ilk trimester ölçümlemleri göre oluflturulan iki TSH grubu karfl›lafltrildi.

Sonuç: Normal TSH seviyelerinin fetal do€um a€›rl›€› etkisi olmadığı tespit edilerek fetal a€›rl›€› etkileri açısından ilk grup ile ilköncü trimesterde normal sınırlarla bir TSH tespit edildiğinde tiroid fonk- sionları açısından ileri bir tetkike gerek olmayabileceğini söyleye-biliriz.

Anahtar sözcükler: Tiroid stimülan hormon, fetal do€um a€›rl›€›, hipotiroidi.
Introduction

During pregnancy, significant changes occur in thyroid physiology and function. One of the most significant reasons is human chorionic gonadotrophin (hCG) within glycoprotein structure produced by placenta at first trimester. hCG increasing in serum is attached to TSH receptor in the thyroid cell membrane and causes T4 and T3 secretion to increase. Due to this thyrotropic activity of hCG, lower TSH levels are found in the first trimester of pregnancy compared to non-pregnant women. Despite some differences between different resources and clinics, normal reference range of TSH is generally accepted between 2.5 and 97.5 percentiles and given between 0.03 and 4.04 MU/L. Severe and sub-clinic hypothyroidism is the most frequent endocrine disorder, and its prevalence is reported as 2–5%. Hypothyroidism is reported with lower rate, and its prevalence is between 0.1% and 0.04%.

The incidence of thyroid dysfunction increased in the last decade and it was reported that this was associated with poor maternal and fetal outcomes. In different studies, there is a consensus that maternal thyroid hormones are effective on the fetal development. It is considered that severe maternal thyroid dysfunctions secondary to the suboptimal transplacental transition of maternal thyroid hormone are associated with low birth weights.

This brought up the discussion for scanning maternal thyroid hormones during pregnancy. There are different opinions on this matter. Although it is clear that certain maternal and fetal thyroid dysfunctions are associated with low birth weight, the effects of thyroid function tests within normal ranges on fetal development is still unclear. Therefore, we aimed in this study to investigate if there is any relationship between first trimester maternal TSH level and fetal birth weight in pregnant women who have no severe pregestational thyroid dysfunction, do not have any treatment for any thyroid dysfunction during pregnancy and have serum TSH results within normal ranges.

Methods

The patients who referred to our clinic and had their all follow-ups and deliveries in our clinic between January 2013 and January 2014 were included in our retrospective study. Those with multiple pregnancies, develop fetal preeclampsia and gestational diabetes during pregnancy and gave birth before 37 weeks of gestation were excluded from the study. In our study, we included both vaginal and cesarean deliveries. The deliveries of all our patients who had elective cesarean were done between 39 and 40 weeks of gestation. The data of 193 patients, who met all these criteria, had no thyroid dysfunction history and found to have TSH values within normal ranges in the first examination were included in the analysis. All data of the patients were obtained from electronic medical record system and patient file archives of the hospital.

In our clinic, maternal TSH levels are checked as a routine procedure in the first examination of patient. If abnormal values are found, free T3 and free T4 hormones are also checked, and patients are consulted with endocrinology department, if required. TSH values between 0.4 and 4.2 mU/L are considered normal in our clinic.

A total of 193 patients meeting study criteria were separated into two groups according to their TSH levels found at first trimester as those between 0.4 and 2.5 mU/L, and those between 2.5 and 4.2 mU/L. The cases were separated into three groups according to the fetal birth weight (<2500 g, 2500–3500 g and >3500 g), and they were compared according to their TSH levels as above.

The approval of Clinical Research Ethics Committee, Faculty of Medicine, Kahramanmaras Sütçü İmam University was obtained for our study.

Statistical Package for the Social Sciences (SPSS) version 21 (SPSS Inc., Chicago, IL, USA) was used for the analysis of the data. Parametric methods were used for the analysis of variables with normal distribution and non-parametric methods were used for the analysis of variables without normal distribution. For the comparison of demographic data between groups, Independent-Samples T test and Mann-Whitney U (Exact) test were used, and mean ± SD (standard deviation) was found by median ± IQR (Interquartile Range). In the comparison of the groups in terms of TSH and birth weight, Pearson Chi-Square Test (Exact), Fisher Exact Test (Exact) and Linear-by-Linear Association Test were used. Categorical data were expressed as n (number) and percentage (%). The data were analyzed via 95% confidence interval, and p value less than 0.05 was considered significant.
**Results**

The patients included in the study were separated into two different groups according to their TSH levels. There were 162 patients in the first group (Group 1) with TSH level between 0.4 and 2.5 mU/L, and 31 patients in the second group (Group 2) with TSH level between 2.5 and 4.2 mU/L.

The groups were compared in terms of age, gravida, parity, week of gestation, fetal birth weight and maternal hemoglobin (Hb) level, and no significant difference was found in terms of these parameters (Table 1). Since the patients who were at 42 weeks of gestation according to their last menstrual periods were delivered vaginally or by cesarean section, we had no pregnancy older than 42 weeks.

Later, the cases were distributed into three different groups according to their fetal birth weights (<2500 g, 2500–3500 g and >3500 g). The patients in these three groups were compared according to their TSH levels. In both TSH groups, distribution percentages of the patients were found similar according to fetal birth weights and no significant difference was observed (p=1) (Table 2).

**Discussion**

Maternal thyroid dysfunctions and especially hypothyroidism and autoimmune problems affect gestational outcomes and fetal development negatively. However, no program is implemented for screening women in reproductive period in terms of thyroid functions. There is still no consensus on this matter.\(^8\,\,9\)

While there are some differences among clinics, upper limit of TSH is 2.5 mU/L in the first trimester and 3 mU/L in the second trimester.\(^10\) In our study, TSH values between 0.4 and 4.2 mU/L in our clinic were considered normal.

In our study, we investigated the effects of TSH values being under or above 2.5 mU/L on gestational outcomes and birth weight in asymptomatic patients with TSH values within normal ranges and had no treatment for thyroid disorders. We found that maternal TSH levels did not affect fetal birth weight as long as they are within normal ranges.

Thyroid hormone concentration is one of the most effective biochemical markers to have a healthy fetal development.\(^11\) On the other hand, it has been shown in animal studies that thyroid hormones may have a direct role in fetal development and there may be abnormal skeletal development in those with thyroid hormone deficiency.\(^12,13\)

The relationship between maternal thyroid dysfunction during pregnancy and birth weight was investigated in a series of studies.\(^14,15\) In normal pregnancies, indirect effects of thyroid hormones on fetal growth were shown in previous studies as the low birth weight in babies of mothers with iodine deficiency in their diets compared to the babies of mothers who have sufficient iodine in their diets.\(^16\)

Most of the studies performed on thyroid dysfunctions during pregnancy were interested in the effects of sub-clinical or clinical hypothyroidism on gestational outcomes.\(^17\) In a study carried out for this purpose reported that mothers with hypothyroidism have the risk to deliver babies with low birth weight\(^18\) and to labor prematurely.\(^19,20\)

In some other studies investigating thyroid functions and birth weights analyzed free T4 (FT4) in

<table>
<thead>
<tr>
<th>Table 1. Comparison of demographic data of the groups with TSH levels between 0.4 and 2.5 mU/L and between 2.5 and 4.2 mU/L.</th>
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</thead>
<tbody>
<tr>
<td>TSH [0.4–4.2] (N=193)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Fetal birth weight*</td>
</tr>
<tr>
<td>Birth week**</td>
</tr>
<tr>
<td>Age*</td>
</tr>
<tr>
<td>Gravida (G)* **</td>
</tr>
<tr>
<td>Parity (P)* **</td>
</tr>
<tr>
<td>Maternal Hb at birth</td>
</tr>
</tbody>
</table>

Independent T test – Mann-Whitney U test (exact). *Mean±SD (standard deviation), **Median±IQR (interquartile range), Hb: Hemoglobin

<table>
<thead>
<tr>
<th>Table 2. TSH düzeyi 0.4–2.5 mU/L arasında ve 2.5–4.2 mU/L arasında olan grupların fetal doğum ağırlıklarının kilo gruplarına göre karşılaştırılması.</th>
</tr>
</thead>
<tbody>
<tr>
<td>TSH [0.4–4.2] (N=193)</td>
</tr>
<tr>
<td>---------------------------------------------------------------</td>
</tr>
<tr>
<td>Fetal birth weight</td>
</tr>
<tr>
<td>&lt;2500</td>
</tr>
<tr>
<td>[2500–3500]</td>
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<tr>
<td>&gt;3500</td>
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</table>

Pearson chi-square test (exact) – Fisher exact test (exact) – Linear-by-linear association test
maternal serum. The study of Shields et al. including 905 pregnant women investigated the relationship between FT4 levels and birth weight at 28 weeks of gestation and found negative correlation. In another similar study, Medici et al. found that high maternal FT4 levels at early weeks of gestation were associated with low birth weight.

In the studies investigating the effects of gestation-al thyroid functions on fetal and maternal outcomes, thyroid functions were checked in fetal cord blood in addition to maternal serum and their gestational outcomes and association with fetal development were investigated.

Medici et al. showed significant relationship between birth weight and FT4 levels checked in the fetal cord blood of normal healthy pregnant women. Also in this study, no significant relationship was found between fetal weight and FT3 or TSH results checked in cord blood. A positive correlation was found between birth weight and TSH levels in cord blood.

It can be argued in our study that why FT4 and FT3 were not evaluated together with TSH levels in our patients in terms of their association with fetal birth weight. However, as a routine procedure, FT3 and FT4 levels are not checked in our clinic in addition to TSH in the first examination. Yet, in patients found to have TSH levels outside the normal ranges, these tests were carried out for evaluation. Also, not considering heights and weights of mothers and fathers, BMI score of mother at the beginning of pregnancy, dietary habits of mother, smoking and alcohol use habits as the factors affecting fetal birth weight are the weakness of our study. In addition, TSH levels at other periods of pregnancy could be checked in terms of their effects on fetal birth weight; however, when TSH levels were found within normal ranges in the first examination, they were not checked again in our clinic during the other periods of pregnancy. Our study is not a study investigating maternal thyroid levels and poor perinatal outcomes but the first study investigating the relationship between fetal weight and maternal TSH levels within normal ranges as far as we know in the literature.

Conclusion
In conclusion, previous studies investigated and presented the abnormal serum TSH levels and thyroid dysfunctions requiring treatment on fetal birth weight. Our study investigated the effect of serum TSH levels on birth weight in patients with normal TSH values and had no thyroid dysfunction history. We found that TSH levels within normal ranges and at different levels have no effect on fetal birth weight and that a further examination is not required in terms of thyroid functions when TSH level is found within normal ranges at first trimester in terms of affecting fetal weight.

Acknowledgement
We would like to thank biostatistics specialist Hüseyin Candan who carried out statistical analyses of our study.

Conflicts of Interest: No conflicts declared.

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Effects of maternal first trimester thyroid stimulant hormone levels on birth weights of fetuses born at term


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Male fetus domination in total placenta previa cases

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Abstract

Objective: The aim of the study is to evaluate the effect of male gender in total placenta previa cases on maternal and perinatal outcomes.

Methods: Total placenta previa cases followed up at the Clinic of Gynecology and Obstetrics between January 2011 and June 2014 were examined retrospectively. All cases were categorized in two groups as male fetus (Group 1) and female fetus (Group 2). Numbers of male and female fetuses, demographic findings, surgical and perinatal outcomes were evaluated among the groups.

Results: 80 total placenta previa patients were included in the study. Out of all cases, 58 (72.5%) were male and 22 (27.5%) were female fetuses, and there was a significant difference between two groups (p=0.001). In male and female fetus groups, respectively, the mean parity was 2.6 and 2.2 (p=0.04), delivery week was 35.3 and 37.1 (p=0.004), mean birth weight was 2752 and 3096 g (p=0.03), number of delivery below 32 weeks was 10 (17%) and 0 (p=0.05), number of transfused patients was 20 (34.5%) and 2 (9%), mean transfusion of erythrocyte suspension was 0.9 and 0.3 (p=0.03) and operation durations in both groups were 70 and 59 minutes; in this regard, there was a significant difference between the groups (p=0.03).

Conclusion: In our study, a distinctive domination of male fetuses was observed in total placenta previa cases. Also, it was found that male fetuses increased poor gestational outcomes in placenta previa.

Keywords: Placenta previa, male fetus.

Özet: Total plasenta previa olgularında erkek fetüs hakimiyeti

Amaç: Çalışmanın amacı total plasenta previa olgularında erkek cinsiyetin maternal ve perinatal sonuçlarına etkisini değerlendirmektir.

Yöntem: Ocak 2011 ve Haziran 2014 tarihleri arasında Kadın Hastalıkları ve Doğum Kliniğinde takip edilen total plasenta previa olguları retrospektif olarak incelendi. Tüm olgular, erkek fetüs (Grup 1) ve kız fetüs (Grup 2) olmak üzere iki grup olarak incelendi. Erkek ve kız fetüs sayıları, demografik bulgular, cerrahi ve perinatal sonuçlar gruptar arasında değerlendirildi.

Bulgular: Çalışmamızda 80 total plasenta previa hastası dahil edildi. Tüm olguların 58'si (%72.5) erkek ve 22 (%27.5) kız fetüs olmak üzere iki grup arasında anlamlı fark izlendi (p<0.001). Erkek ve kiz fetüs gruplarında ortalama parite sırası ile 2.6 ve 2.2 (p=0.04), doğum haftası 35.3 ve 37.1 (p=0.003), ortalama bebek kiloları 2752 ve 3096 gram (p=0.03), 32 hafta altında doğum sayısı 10 (%17) ve 0 (p=0.05), transfüzyon yapılan hasta sayıları 20 (%3.45) ve 2 (%9) (p=0.02), ortalama eritrosit süspansiyonu transfüzyonu 0.9 ve 0.3 (p=0.03) ve her iki grupta operasyon süresi sırası ile 70 ve 59 dakika olarak aralarında anlamlı fark izlendi (p=0.03).

Sonuç: Çalışmamızda total plasenta previa olgularında belirgin erkek fetüs hakimiyeti saptandı. Ayrıca erkek fetüsüün plasenta previada kötü gebelik sonuçlarını artırdığı belirlendi.

Anahtar sözcükler: Plasenta previa, erkek fetüs.

Introduction

Placenta previa is a condition in which placenta reaches to internal cervical os or closes this orifice and it is a risk factor for maternal-fetal morbidity and mortality.[1-3]

The risk factors for placenta previa are reported as advanced maternal age, grand multiparity, recurring abortions, low socio-economic level, infertility treatments, previous curettage, Asherman’s syndrome, previous myomectomy, submucous myoma, smoking habit, previous uterine surgery, previous cesarean (C/S) and conception in a short time after cesarean.[4,5]

Placenta accreta is defined as the abnormal invasion of complete or full placenta into myometrium. There
are three groups according to the depth of the invasion: Accreta, increta, and percreta. Unless it is specifically stated, all these three groups are referred to as placenta accreta in practice. The risk factors of placenta accreta and placenta previa are same. The most significant risk factors for placenta accreta are placenta previa and previous cesarean.

In years, the increases in cesarean rates, previous cesarean numbers and maternal ages have caused an increase in the prevalence and aggressiveness of placenta previa and invasive placental diseases. In this way, significant changes appeared in the current practice. While uterine atony was the most frequent reason for postpartum hysterectomy, placenta previa/accreta has taken the first place today.

Therefore, placenta previa and accreta are investigated intensely today. In this study, we evaluated male fetus as one of the risk factors of placenta previa.

Methods

The files of the patients who referred to the Gynecology and Obstetrics Clinic of Kahramanmaras Sutcu Imam University between January 2011 and June 2014 were reviewed. The pregnant women found to have total placenta previa in our clinic were followed up. Ambulant follow-up was performed with 2 weeks of intervals for those who did not have bleeding and other additional complications. In case of bleeding, pregnant women hospitalized in risky pregnancy service and monitored. Bleedings were categorized as mild and severe according to the blood pressure and pulse, hemoglobin level, fetal well-being and bleeding pad follow-up of the pregnant women. Mild bleedings were followed up. In case of severe bleeding, pregnancy was terminated through cesarean section. The cesarean procedure was carried out electively at 36 weeks of gestation in pregnant women without bleeding.

All cases with total placenta previa were evaluated for placenta accreta by ultrasonography before the operation. Patients suspected to have placenta accreta were referred to urology and cardiovascular surgery clinics before the operation. Before the date of planned cesarean operation, we contacted our blood center to inform the blood type of the patient and made them keep available 4 units of erythrocyte suspension and 2 units of fresh frozen plasma in order to use if necessary.

In the ultrasonography, it was entered to the abdomen through infra-umbilical median incision in pregnant women with placenta accreta risk. Pfannenstiel incision was performed in all other pregnant women. Before the uterine incision, the presence of placenta accreta finding on the uterine wall was investigated. The placenta previa cases having placenta accreta risk and filling anterior wall of uterus inferior segment were delivered by classical incision. In remaining pregnant women, placenta termination limit was determined ultrasonographically before the cesarean procedure and uterine incision was carried out transversely 1–2 cm above this limit. Also, in ultrasonography at gestational follow-ups or during operation, hysterectomy was performed without separating placenta in pregnant women with placental invasion anomaly. Placenta was separated in pregnant women who had no indication for placenta invasion anomaly. Difficult separation and fragmentation of placenta was considered as an indication of invasion.

Bleeding was tried to stop by separate sutures, compression sutures, and uterine and hypogastric arter ligation. Also, when necessary, Foley catheter was applied to the cavity for hemostasis purpose. Emergency hysterectomy was carried out in patients with ongoing bleeding. All postoperative patients were monitored in the intense care unit.

These cases were grouped according to the baby gender (Group 1, male baby; Group 2, female baby). It was investigated if there was a significant difference between these groups in terms of numbers, demographic findings, operation and perinatal outcomes.

Statistical Analysis

Analysis of the data was done by using SPSS (Statistical Package for the Social Sciences version 19 software; IBM, Armonk, NY, USA). P≤0.05 was considered statistically significant. To compare the rates, hi-square (χ²), Yates’ correction of χ², and Fisher’s exact tests were used. Variance analysis (F test) was used to compare the mean values of two or more groups.

Results

80 total placenta previa patients were included in the study. In all cases, there was statistically a significant difference between the groups as 58 (72.5%) male fetuses and 22 (27.5%) female fetuses (p<0.000) (Table 1).

Between two groups, there was no significant difference in terms of mean age, gravida and number of patients with previous C/S.
Mean parity was found as 2.6 and 2.2 in male and female fetus groups, respectively (p=0.04) (Table 1).

There was also no significant difference between the groups in terms of emergency C/S, elective C/S and general/spinal anesthesia types. Delivery week was found as 35.3 and 37.1 in two groups, respectively (p=0.003). Mean birth weight was 2752 and 3096 g, respectively (p=0.03). While delivery below 32 weeks of gestation was seen in 10 (17%) patients who delivered male fetuses, no such delivery was seen in patients who delivered female fetuses (p=0.05). C/S hysterectomy, placenta accreta and surgical complications were similar in both groups.

The number of patients who underwent erythrocyte suspension (ES) transfusion was 20 (34.5%) and 2 (9%), respectively (p=0.02). Mean ES transfusion amount was 0.9 and 0.3 unit in two groups, respectively (p=0.03).

Operation durations in both groups were 59 and 70 minutes, respectively, and there was a significant difference (p=0.03). In both groups, hospitalization durations and postoperative baby Apgar scores were similar.

Discussion

In the literature, there are studies showing that male fetus is a risk factor for placenta previa. In 6 studies performed in the past reported that male gender caused a slight risk increase in placenta previa.[10-15] Demissie et al. found in their study carried out in 1999 that male/female rate was 1.05 in 445,270 deliveries without placenta previa while it was significantly high as 1.19 in 2685 deliveries with placenta previa (p<0.001). By adding previous 6 studies to this study, male/female rate was reported as 1.14 in placenta previa cases.[16] Wen et al. evaluated 433,031 deliveries and found male/female rate as 1.04 while it was 1.19 in placenta previa cases (p=0.02).[17] Rosenberg et al. compared 184,705 cases without placenta previa to 771 placenta previa cases (p<0.02). However, all placenta previa patients including mild placenta previa cases such as partial and inferior segment were included in these studies. We did not find any study evaluating male/female rate only in total placenta previa patients.

In our study that we performed on pregnant women with total placenta previa, we found high level of male gender dominance (p<0.000, RR:2.63) (Table 1). We believe that there are two reasons for high level of male gender dominance compared to previous studies:

1. In our study, unlike previous studies, we evaluated only the cases with total placenta previa. If male fetus is a risk factor in placenta previa, it will certainly be more distinct in total placenta previa which is completely clinical.

2. In our study, we observed that male fetus increased poor gestational outcomes. Mean gestational week at delivery and birth weight were found lower in male fetuses. Also, deliveries below 32 weeks of gestation were at the statistical significance threshold (p=0.05). Also, the number of patients who received transfusion, mean amount of transfusion and operation durations were higher in male fetuses. The number of patients who delivered below 32 weeks of gestation was higher in male fetuses; however, the difference was on significance threshold (p=0.05) (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male fetus (s=58)</th>
<th>Female fetus (s=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number</td>
<td>58</td>
<td>22</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>30.6±4.7</td>
<td>30.9±7.1</td>
<td>t=-0.2</td>
</tr>
<tr>
<td>Parity</td>
<td>2.6±0.8</td>
<td>2.2±0.8</td>
<td>t=2</td>
</tr>
<tr>
<td>Gravidity</td>
<td>3.8±1.5</td>
<td>3.6±1.8</td>
<td>t=0.4</td>
</tr>
<tr>
<td>Previous C/S</td>
<td>46 (79.3%)</td>
<td>18 (81.8%)</td>
<td>x²=0.06</td>
</tr>
</tbody>
</table>

Table 1. Comparison of the demographic characteristics of male and female fetuses in placenta previa.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Male fetus (s=58)</th>
<th>Female fetus (s=22)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Emergency cesarean</td>
<td>36 (62%)</td>
<td>12 (54.5%)</td>
<td>x²=0.4</td>
</tr>
<tr>
<td>Elective cesarean</td>
<td>22 (38%)</td>
<td>10 (45.4%)</td>
<td>x²=0.4</td>
</tr>
<tr>
<td>Anesthesia type</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>General anesthesia</td>
<td>46 (79.3%)</td>
<td>18 (81.1%)</td>
<td>Fischer test</td>
</tr>
<tr>
<td>Spinal anesthesia</td>
<td>12 (20.9%)</td>
<td>4 (18.1%)</td>
<td>Fischer test</td>
</tr>
<tr>
<td>Delivery week</td>
<td>35.3±3.2</td>
<td>3.1±1.1</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Birth week</td>
<td>2752.3±685</td>
<td>3096.4±491.8</td>
<td>t=2.1</td>
</tr>
<tr>
<td>Delivery at &lt;32 weeks of gestation</td>
<td>10 (17.2%)</td>
<td>0</td>
<td>t=2.1</td>
</tr>
<tr>
<td>Cesarean hysterectomy</td>
<td>9 (15.5%)</td>
<td>1 (4.5%)</td>
<td>x²=2.2</td>
</tr>
<tr>
<td>Placenta accreta</td>
<td>9 (15.5%)</td>
<td>1 (4.5%)</td>
<td>x²=2.2</td>
</tr>
<tr>
<td>Bladder injury</td>
<td>2 (3.4%)</td>
<td>0</td>
<td>x²=0.7</td>
</tr>
<tr>
<td>Number of patients who underwent ES transfusion</td>
<td>20 (34.5%)</td>
<td>2 (9%)</td>
<td>x²=5.2</td>
</tr>
<tr>
<td>Mean ES transfusion</td>
<td>0.9±1.5</td>
<td>0.3±0.9</td>
<td>p=0.03</td>
</tr>
<tr>
<td>Operation duration (min)</td>
<td>59±17.7</td>
<td>70.7±22.3</td>
<td>p=0.039</td>
</tr>
<tr>
<td>Hospitalization (day)</td>
<td>3.3±1.5</td>
<td>3.9±1.7</td>
<td>p=0.196</td>
</tr>
<tr>
<td>1-minute Apgar score</td>
<td>7.9±1.3</td>
<td>7.7±1.7</td>
<td>t=0.4</td>
</tr>
<tr>
<td>5-minute Apgar score</td>
<td>9.3±0.6</td>
<td>8.9±1.6</td>
<td>t=1.2</td>
</tr>
</tbody>
</table>

Table 2. Comparison of the gestational outcomes of male and female fetuses in placenta previa.

ES: Erythrocyte suspension
In conclusion, male fetus increases poor gestational outcomes in placenta previa. In fact, the incidence, risk factors and complications of placenta previa have increased within years:

- **Advanced maternal age**: Pregnancy above 35-year-old has increased from 5% to 13% between 1970 and 2000 in the USA, and the mean age of being mother for the first time increased from 21.4 to 25 between 1970 and 2006.\(^{[19]}\)

- **Increases in cesarean rates**: While cesarean rate in developed countries was 18.6% in 1992, it increased to 27.7% in 2007.\(^{[20]}\) The increase in undeveloped countries has a higher rate. Previous C/S rate has increased 65% over the years.\(^{[21]}\)

- **Increase of placenta previa cases**: Faiz et al. found in their study that placenta previa cases increased within 22 years from 1976 to 1997.\(^{[22]}\)

- **Increase of placenta accreta cases**: Placenta invasion anomaly was first defined in 1930, and it was a rare disease before these years.\(^{[23]}\) Its incidence reached 1/2500 with a 10-time increase within last five decades.\(^{[24]}\) Recently, its incidence is reported up to 3/1000.\(^{[25]}\)

- **Increase in peripartum hysterectomy cases**: In the study of Bodelon et al., it was reported that the incidence of hysterectomy which was carried out within peripartum first 30 days increased to 0.82/1000 deliveries in 2006 from 0.25/1000 in 1987 (p<0.001).\(^{[26]}\)

These results show that placental implantation and invasion anomalies progress more aggressively over the years. We believe that male fetus dominance has become clear over the years depending on the more aggressiveness of placental implantation and invasion anomalies. However, the number of cases in our study is insufficient.

In the literature, we did not found any study investigating the effect of male fetus on perinatal outcomes in placenta previa. In their study, Wen et al. found no significant difference between fetal genders in placenta previa and birth weights and delivery weeks.\(^{[27]}\) We concluded in our study that male fetus is a risk factor for total placenta previa and it increases poor gestational outcomes. Wider case series are needed to investigate on this matter.

**Conclusion**

In conclusion, we observed male fetus dominance in placenta previa. Also, we determined that male fetuses increased poor gestational outcomes in placenta previa. We believe that this depends on the aggressiveness of placentinal implantation and invasion anomalies over the years.

**Conflicts of Interest**: No conflicts declared

**References**


Ultrasound fetal weight estimation in twin pregnancy

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Faculty of Medicine University Tunis El Manar, Tunis, Tunisia

Abstract

Objective: To assess the performance of ultrasound in twin’s fetal weight estimation (FWE), screening of low birth weight (LBW) and twin’s weight discordance (TWD).

Methods: A prospective study including fifty twin pregnancies was carried out. Each patient underwent an ultrasonography with estimated fetal weight (EFW) up to 4 days before delivery. We calculated the median absolute difference (MAD) and the median absolute percentage error (MAPE) between EFW and birth weight (BW). The correlation and the concordance were also assessed. Finally, we calculated the sensitivity (Se), specificity (Sp), the positive predictive value (PPV) and the negative predictive value (NPV) of ultrasound in the diagnosis of the LBW and TWD.

Results: The MAD was equivalent for both twins. The MAPE was 7.7% [range: 0 to 32] for T1 and 8.2% [range: 0 to 27] for T2. The proportion of estimates beyond 10% of actual BW was 38% for T1. We have noted a significant correlation between EFW and BW for the both twins (R1=0.87; R2=0.89). In case of LBW, ultrasound had a se, sp, PPV and NPV respectively 90.32%, 76.82%, 80% and 87%. Ultrasound’s performance in the diagnosis of TWD varied depending on the adopted threshold. Chiorionicity, presentation and gestational age did not have any influence in the performance of FWE.

Conclusion: The Ultrasound is essential in the diagnosis and management of perinatal complications common in twins. Its performance is satisfactory in EFW and depends on the threshold adopted for the diagnosis of TWD.

Keywords: Ultrasound, twin pregnancy, estimated fetal weight, weight discordance, low birth weight.

Özet: ikiz gebelikte ultrason fetal ağırlık tahmini

Amaç: İkizlerin fetal ağırlık tahmininde (FWE), düşük doğum ağırlığının (LBW) ve ikizlerin ağırlık uyumsuzluğunun (TWD) tanımasında ultrason performansının değerlendirilmesi.

Yöntem: Elli beş gebemen dâhil edildiği prospektif bir çalışma gerçekleştirildi. Her bir hastaya, doğumdanhort gün önceki kadar tahmini fetal ağırlık (EFW) için ultrasonografi uygulandı. Tahmini fetal ağırlık ile doğum ağırlığı (BW) arasındaki medyan mutlak farklılığı (MAD) ve medyan mutlak yüzde hatasını (MAPE) hesaplandı. Korelasyon ve kordondan da ayrıca değerlendirildi. Son olarak, düşük doğum ağırlığı ve ikizlerin ağırlık uyumsuzluğuna parsiz ultrasonun hassasiyetini (Se), özgüllüğünü (Sp), pozitif prediktif değeri (PPV) ve negatif prediktif değeri (NPV) hesaplandı.

Bulgular: Medyan mutlak farklılık, her iki ikiz için de eşdeğerdi. Medyan mutlak yüzde hatasını, T1 için %7.7 [aralık: 0–32] ve T2 için %8.2 idi [aralık: 0–27]. Gerçek doğum ağırlığının %10'undan fazla tahminleri oranı, T1 için %38'di. Her iki ikiz için de tahmini fetal ağırlık ve doğum kilosu arasında anlamlı bir korelasyon tespit ettiğim (R1=0.87; R2=0.89). Düşük doğum ağırlığında, ultrasonun hassasiyeti, özgüllüğü, pozitif prediktif değeri ve negatif prediktif değeri, sırasıyla %90.32, %76.82, %80 ve %87 idi. İkizlerin ağırlık uyumsuzluğu tansında ultrason performansı, kabul edilen eşik değeri bağlı olarak değişmiştir. Koryonitise, prezentasyon ve gebelik yaş, fetal ağırlık tahmininde hiçbir etkiye sahip değildir.

Sonuç: Ultrason, ikizlerde yaygın olan perinatal komplikasyonların tanısı ve yönetiminde hayatı önemli bir şapıdır. Ultrason, tahmini fetal ağırlığın için kabul edilebilir bir performans sergilemektedir ve ikizlerin ağırlık uyumsuzluğu tansında kabul edilen eşik değere bağlıdır.

Anahtar sözcükler: Ultrason, ikiz gebelik, tahmini fetal ağırlık, ağırlık uyumsuzluğu, düşük doğum ağırlığı.
Introduction

Multiple pregnancies are constantly increasing due to the frequent use of assisted reproductive techniques. Twin pregnancies have a higher risk compared to singleton pregnancies: their mortality rate is six times higher than singletons. Neonatal morbidity is also increased. These kinds of pregnancies lead to many complications and above all prematurity and intrauterine growth retardation (IUGR). Moreover, twin growth discordance (TGD) is a specific complication of these pregnancies. Thus, ultrasound monitoring seems to be important for the management of these pregnancies. For example, fetal weight estimation (FWE) allows detecting and monitoring fetal growth disorders. It also makes it possible to predict any necessary neonatal care in case of preterm delivery. Therefore, the accuracy of FWE is essential to good obstetrical management. However, the literature is poor concerning the validity of sonographic prediction of the fetal weight and the fetal weight discordance in twin pregnancies.

The aim of our study was to evaluate the performance of ultrasound in estimating the fetal weight in twin pregnancies, the diagnosis of TGD and prenatal diagnosis of low birth weight (LBW). We also studied the effects of different maternal and fetal related factors on this prediction.

Methods

Each patient underwent an ultrasound (US) exam with FWE up to 4 days before delivery. The US exam was performed using an ULTRASONIX, SONIX OP ultrasound machine (Ultrasonix Medical Corporation, Richmond, BC, Canada), with a curvilinear abdominal probe 3.5 MHz. The EFW was calculated using Hadlock formula:[3] Log 10 EFW = 1.3596-0.00386AC*FL+0.0064HC+0.00061BDP*AC+0.0424AC+0.174FL. Weight differences between twin fetuses were calculated as follows: (The weight of the largest twin – the weight of the smallest twin) / weight of the largest twin. This difference was calculated throughout pregnancy and upon delivery.

TGD was defined as a weight difference between twins of 20% and above.[4] The causes of twins’ weight discordance (TWD) have not been studied.

Low birth weight (LBW) was defined by a birth weight (BW) below 2500 g.[5] In the literature, this value is known to increase the risk of morbidity and neonatal mortality significantly.[5] Oligohydramnios was defined by each twin’s single deepest pocket <20 mm. In the literature, this measurement method appears to be the most appropriate in twin pregnancies.[6] Maternal obesity was defined as a body mass index (BMI) ≥35 kg/m² the day of delivery.[5] The following details were recorded:

- Age, parity, height, weight and BMI the day of delivery.
- The gestational age, chorionicity, fetal presentation, EFW for the first twin (EFW T1) and the second twin (EFW T2), each twin’s single deepest pocket.

At birth, we also recorded the BW of the first twin (BW T1) and the second twin (BW T2). The EFW was compared to the actual BW. Data was recorded on a standard spreadsheet (Microsoft Excel; Microsoft Corporation, Redmond, WA, USA). Descriptive parameters are expressed as median [1st, 3rd quartiles]. Frequencies are presented as percentages.

The analysis was performed in several ways: percentage error was calculated by subtracting the actual BW from the EFW and then dividing the difference by the actual BW and multiplying by 100. The median absolute percentage error (MAPE), expressing the systematic error, was calculated from the percentage error. Absolute percentage error and median absolute percentage error (MAPE) were calculated the same way by using the absolute value of the difference between the EFW and the actual BW. The proportion of estimates within 10% of the actual BW was also calculated.

Correlation between BW and ultrasound EFW was demonstrated using the Pearson coefficient and agreement between these two measurements was assessed using Bland and Altman’s plots.[8]

Statistical analysis was performed using XLSTAT 2014.4.09 (Addinsoft, New York, NY, USA); p<0.05 was considered statistically significant.

Percentage errors were compared using the Student’s t test in reference to maternal body mass index (BMI), chorionicity, gestational age, fetal presentation. We calculated the sensitivity, specificity, negative predictive value (NPV) and positive predictive value (PPV) of EFW to detect TGD.
Results

During the study, we managed 2170 deliveries in our unit. Fifty patients met the inclusion criteria and a total of 100 fetuses were studied. Mean maternal age was 32 [range: 28 to 36] years. Mean BMI was 33.81 [range: 27 to 40] kg/m². Twenty eight patients (56%) had BMI >35 kg/m². Mean gestational age at delivery was 37 [range: 35 to 37] weeks. Time elapsed between sonography and delivery was 2.27 [range: 0 to 4] days. Forty patients delivered in our department, the other 10 patients delivered in a private clinic. Overall, there were 41 dichorionic diamniotic pregnancies (82%), and no case of monoamniotic pregnancies. Table 1 details the results of comparison between EFW and actual BW for each twin.

Median absolute difference (MAD) was 155 g [range: 72 to 337.5] for T1 and 150 g [range: 100 to 266.5] for T2. The MAPE was 7.7% [range: 2.5 to 14.76] for T1 and 7.55% [range: 3.37 to 11.85] for T2 (p=0.8). Finally, the proportion of estimates beyond 10% of the actual BW was 38% for T1 and 34% for T2 (p=0.082). Thus, there was no significant difference in fetal weight estimation’s performance between twins. We found a strong and significant correlation between EFW and BW for both fetuses. In fact, the correlation indexes were respectively R1=0.87 for T1 and R2=0.89 for T2.

The linear regression analysis calculates the BW with the following formulas: for Twin 1 BW T1= 415.57+0.846*EFW T1, for Twin 2 BW T2= 65.68+0.963*EFW T2 (Fig. 1).

Bland-Altman analysis for these variables is shown in Fig. 2. For T1, bias was 39.4 g (95% limits of agreement -580 g to +650 g). For T2, bias was 19.4 g (95% limits of agreement -550 g to +550). None of the parameters studied; obesity, term, chorionicity or presentation, has significantly hampered the performance of the ultrasound examination (Table 2). T1 weighed less than 2500 g in 28 cases (56%). LBW was more fre-

Table 1. Differences between the birth weight (BW) and the estimated fetal weight (EFW) for both twins.

<table>
<thead>
<tr>
<th></th>
<th>1. twin</th>
<th>2. twin</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absolute difference (g)</td>
<td>155 [72–337.5]</td>
<td>150 [100–266.5]</td>
<td>0.50</td>
</tr>
<tr>
<td>Median absolute percentage (%) error</td>
<td>7.7 [2.5–14.76]</td>
<td>7.55 [3.37–11.85]</td>
<td>0.80</td>
</tr>
<tr>
<td>The proportion of estimates 10% of the actual BW</td>
<td>19 (%38)</td>
<td>17 (%34)</td>
<td>0.82</td>
</tr>
</tbody>
</table>

Fig. 1. Correlation between EFW and BW using Pearson linear regression. BW T1: first twin birth weight; BW T2: second twin birth weight; EFW T1: first twin estimated fetal weight; EFW T2: second twin estimated fetal weight.
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1. Discussion

Actually, twin pregnancies represent 3% of live births. These pregnancies have a high neonatal risk; prematurity and LBW. Moreover, TWD is a particular situation that should be taken into account in obstetrical decisions. Thus, the accuracy of ultrasound FWE in twins is essential for obstetrical management. Our study is still mainly limited by the small number of cases, however, this can be explained by the difficulty of recruiting during one year more cases meeting the strict inclusion criteria and scheduling a specialized US examination up to four days before delivery. Our results can be improved by a larger multicentric study involving more sonographers. We found good results concerning EFW in both twins with a MAD of 150–155 g [T1-T2]. Besides, the MAPE was 7.5–7.7% [T1-T2]. Thus, we can conclude that the performance of ultrasound in EFW in twin pregnancies is similar to singletons. This latter has been widely studied in the literature and the various publications attribute a MAPE ranging from 6 to 10%. These results are similar to those of Ivars et al. with a MAD of 110–127 g [T1-T2] and a MAPE of 5.41–5.64% [T1-T2]. Nevertheless, the proportion of estimates beyond 10% of the actual BW was lower: 25% compared to 34% in our study. This seems paradoxical, especially as, in our study, the delay between US exam and delivery was lower (2.27 days vs. 7 days). Additionally, similar results are reported by Danon et al., in their retrospective study over 278 twin pregnancies, with an interval of three days between US estimation and delivery. The proportion of estimates beyond 10% of the actual BW is 33.6%.

Fig. 2. Agreement analysis using Bland and Altman plots. BW: birth weight; EFW: estimated fetal weight; T1: first twin; T2: second twin.
We have found a strong correlation between EFWs and BWs. Similar conclusion is reported in literature.\textsuperscript{[9]} The linear regression technique with the calculation of a correlation coefficient searches the existence of a linear relationship between the two values; it may be present in spite of a poor concordance between the two values. In order to estimate the best match between the two values, we performed a concordance study using Bland and Altman’s method. The same method was used by Ivars et al.\textsuperscript{[9]} In their work, the bias was +35 g for T1 and -23 g for T2. These results are similar to ours with a bias of +39.4 g for T1 and 19.4 g for T2. However, in our study, the limits of agreement were quite large so we have to improve these results.

Hadlock’s formula used in our study is mainly used for singletons,\textsuperscript{[3]} this subject has been discussed by many authors. For example, Ong et al.\textsuperscript{[10]} compared several mathematical formulas EFW in twin pregnancies and did not find significant differences. Diaz-Garcia et al.\textsuperscript{[11]} compared several formulas and found that Hadlock 2 was the most effective with the best proportion of estimates within 10\% of the actual BW and a better prediction of TWD. As a conclusion, Hadlock formula would be a valid method for EFW in twin pregnancies.

Twin’s weight discordance is considered to be moderate when it ranges from 25 to 30\% and severe when it exceeds 30\%.\textsuperscript{[4]} This specific situation to multiple pregnancies is associated with high risk of morbidity and perinatal mortality\textsuperscript{[12,13]} requiring monthly ultrasound monitoring to detect any growth abnormal-

\begin{table}[h]
\centering
\caption{Effects of different maternal and fetal related factors on ultrasound fetal weight estimations.}
\begin{tabular}{|c|c|c|}
\hline
\textbf{Maternal obesity} & 1. ikiz & 2. ikiz \\
\hline
Obese: >35 kg/m\textsuperscript{2} & 28 & 28 \\
250 g [100;450] & 150 g [100; 251.5] & \\
No obese: <35 kg/m\textsuperscript{2} & 22 & 22 \\
154 g [50;250] & 190 g [75; 300] & \\
p=0.12 & p=0.08 & \\
\hline
\textbf{Gestational age: >32 weeks} & 46 & 46 \\
150 g [100; 266.5] & 154 g [72; 300] & \\
p=0.25 & & \\
\hline
\textbf{Gestational age: <32 weeks} & 4 & 4 \\
100 g [75; 150] & 200 g [100; 310] & \\
p=0.5 & p=0.38 & \\
\hline
\textbf{Chorionicity} & & \\
Dichorionic-diamniotic & 41 & 41 \\
150 g [50; 300] & 150 g [75; 200] & \\
p=0.26 & p=0.27 & \\
Monochorionic-diamniotic & 9 & 9 \\
287 g [140.5; 455] & 150 g [100 ;184] & \\
\hline
\textbf{Fetal presentation} & & \\
Cephalic (C) & 30 & 21 \\
147 g [85; 327] & 152 g [90; 254] & \\
19 & 17 & \\
136 g [78; 300.5] & 126 g [100; 258.2] & \\
Transverse (T) & 1 & 1 \\
156 g & 138 g [120; 266] & \\
C-B; p=0.21 & C-B; p=0.16 &  \\
C-T; p=0.48 & C-T; p=0.23 & \\
B-T; p=0.47 & B-T; p=0.28 & \\
\hline
\end{tabular}
\end{table}

\begin{table}[h]
\centering
\caption{Performance of ultrasound in prenatal diagnosis of twin’s weight discordance according to the adopted threshold.}
\begin{tabular}{|c|c|c|c|c|}
\hline
\textbf{Threshold} & \textbf{Sensitivity} & \textbf{Specificity} & \textbf{PPV} & \textbf{NPV} \\
\hline
\textsuperscript{≥}20\% & 76.9\% & 81.8\% & 62\% & 93.5\% \\
\textsuperscript{≥}25\% & 81.5\% & 89.2\% & 74\% & 95.4\% \\
\hline
\end{tabular}
\end{table}
ities in time and consequently adapt obstetrical management. For example, almost all obstetrical teams recommend cesarean section since TWD is higher than 30% or in case of severe IUGR. The prevalence of TWD varies according to the definition adopted; it is found in 10–29% of twin pregnancies. In literature, the threshold adopted to define twins discordance ranges from 10 to 40%, but 20% is the threshold commonly used. \(^{10}\)

Ultrasound is the gold standard exam in prenatal screening of TWD. Its performance depends on the adopted threshold. Thus, Mottet et al., in a series of 67 twin pregnancies found that the sensitivity of ultrasound is 80% for the detection of severe discordance (threshold ≥35%) and it decreases to 41% in case of moderate discordance (threshold ≥25%) and decreases to 20% in case of slight discordance (threshold ≥20%). \(^{12}\) We report similar findings and we found that the performance of ultrasound decreases for a threshold of 20%. However, we found a higher sensitivity (>70%) in each used threshold. These results should be confirmed by a larger number of cases. Several groups have proposed other methods to improve sonographic prenatal diagnosis of TWD. For example, Erkkola et al. used the cephalic circumference but the PPV was low. Other authors have used the abdominal circumference (AC). They found the same sensitivity as using EFW. Storlazzi et al. have used other parameters to define the discrepancy as a difference of BIP >6 mm; a difference of CA >20 mm; femur length >5 mm. But the best predictive value was found using EFW. Finally, and because of these low PPV, other studies proposed to associate biometric parameters to fetal Doppler to improve the performance of Us in the diagnosis of TWD and to better target fetuses at risk. \(^{17,18}\)

In the other side, the NPV of ultrasound in screening TWD is excellent. \(^{11}\) This could lead to the identification of twin pregnancies at lower risk and thus avoid excessive monitoring. LBW is the leading cause of infant mortality in the world. Approximately 40% of twins are born before 37 weeks and 20 to 30% are small for gestational age. Thus, prematurity and IUGR increase the incidence of LBW to 50–60%. In this work, Us was relevant to predict LBW with a PPV 85% and a NPV 90%. These results should be confirmed in a larger series especially since in the literature, low PPV is often reported as 22–47%. \(^{20,20}\)

Considering maternal and fetal factors that may affect the performance of ultrasound EFW, we studied: maternal obesity, chorionicity and fetal presentation. We concluded that any factor had a significant impact. Literature data are controversial. For example, about maternal obesity, some studies conclude that obesity leads to an overestimation of EFW. Other authors do not find significant differences between obese and non-obese patients. Finally, Ivars et al. concluded that maternal obesity increases the performance of ultrasound. This may seem surprising; obesity being experienced in our daily practice as a difficulty. These conflicting results may be explained by differences in BW in obese and non-obese patients, or by using a more powerful ultrasound machine or sonographer’s experience. A study measuring the time required to perform a twin’s weight estimation in case of maternal obesity may improve our conclusion.

The chorionicity should be determined during the first trimester ultrasound, because this will determine the subsequent monitoring. For Ivars et al., chorionicity does not affect EFWs. On the other hand, and according to the same team, the term was found as a factor positively influencing EFW (p=0.012) before 32 weeks. Finally, in literature, fetal presentation is not known to affect the performance of the US estimations. \(^{23}\)

**Conclusion**

Ultrasound is essential in the diagnosis and management of perinatal complications common in twins. Its performance in the estimation of fetal weight is satisfactory; it allows anticipation and better management of neonatal premature births. However, its performance in the diagnosis of growth discordance is limited in terms of positive predictive value. On the other hand, the negative predictive value is excellent. This could lead to the identification of twin pregnancies at lower risk and thus prevent excessive obstetrical care.

**Conflicts of Interest:** No conflicts declared.

**References**


The incidence of thyroid dysfunction in pregnant women

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2Gynecology and Obstetrics Clinic Haseki Training and Research Hospital, Istanbul, Turkey

Abstract

Objective: Despite the different data presented in the literature, there is no satisfactory data for the incidence of thyroid dysfunction during pregnancy in Turkey where iodine deficiency is prevalent. In this study, we aimed to present the incidence of thyroid dysfunction during pregnancy.

Methods: A total of 1876 pregnant women, whose thyroid stimulating hormone (TSH) and free T4 values were checked, were included in the study. Weeks of gestations, TSH and free T4 serum levels according to the last menstrual date and ultrasonography were retrospectively screened from the archive of our hospital. TSH reference ranges were accepted as 0.1–2.5 mU/l in the first trimester, 0.2–3.0 mU/l in the second trimester and 0.3–3.0 mU/l in the third trimester. The patients with high TSH value special to the trimester and low free T4 value were considered to have overt hypothyroidism, those with low TSH value and high free T4 value were considered to have overt hyperthyroidism, and the cases with abnormal TSH value but normal free T4 value were considered to have subclinical thyroid dysfunction.

Results: Mean age of the pregnant women included in the study was 29.14±5.84 years. While 65.4% (n=1227) of the cases were in their first trimester, 21.1% (n=395) of them were in the second trimester, and 13.5% (n=254) of them were in the third trimester. Hyperthyroidism was found in 5.38% (n=101) of the pregnant women; while 1.22% (n=23) of them had overt hyperthyroidism, 4.16% (n=78) of them had subclinical hyperthyroidism. Of the cases, 15.88% (n=298) had hypothyroidism where 10.18% (n=191) of them had overt hypothyroidism and 5.70% (n=107) of them had subclinical hypothyroidism.

Conclusion: In the pregnant women included in the study, we observed a high rate of hypothyroidism since TSH upper limit was possibly decreased in the first trimester and we were in a risky region for iodine deficiency.

Keywords: Pregnancy, hypothyroidism, hyperthyroidism.
The incidence of thyroid dysfunction in pregnant women

**Introduction**

Thyroid function tests of the pregnant women have different values than normal women. This has caused to establish new reference ranges unique to pregnancy and ideal trimester. The studies published in mostly western countries and supported by both American Thyroid Association (ATA) and American Endocrine Society (AES) recommend TSH reference range as 0.1–2.5 mU/l in the first trimester, 0.2–3.0 mU/l in the second trimester and 0.3–3.0–3.5 mU/l in the third trimester.\(^1\) The most common tests to evaluate thyroid function are thyroid stimulating hormone (TSH) and free thyroxine (fT4)\(^6,7\).

Although hypothyroidism is reported as 2–4% and hyperthyroidism as 0.1–0.4% in the general literature, upper limit of the TSH is accepted as 5 mIU/L in the literature.\(^8\) Also, our country is still a region for iodine deficiency.\(^9\) Therefore, thyroid dysfunction rate is expected to be higher than western literature. In Turkey, there is no satisfactory data obtained by using this reference range recommended for TSH level.

In our study, we aimed to determine the incidence of thyroid dysfunction through TSH and fT4 levels of the pregnant women in our study group by considering TSH reference range, which have been accepted in recent years, as 0.1–2.5 mU/l in the first trimester, 0.2–3.0 mU/l in the second trimester and 0.3–3.0 mU/l in the third trimester.

**Methods**

By obtaining the approval of Ethics Board of İstanbul Training and Research Hospital (İTRH), 1876 singleton pregnant women, who admitted to the Pregnancy Clinic of İTRH Gynecology and Obstetrics Department between January 1st, 2010 and January 1st, 2014 and whose TSH and fT4 values were checked, were included into our study. Ages of pregnant women, weeks of gestation according to the ultrasound, and TSH and fT4 levels were retrospectively screened from the archive of our hospital. Anamnesis and clinical evaluation were ignored. TSH and fT4 levels were analyzed with original kits in the Advia Centaur XP immunoassay device (Siemens Healthcare, Malvern, PA, USA) working with chemiluminescence method in the same laboratory. The data of the pregnant women were analyzed by using Microsoft Excel Office 2011 (Microsoft Corporation, Redmond, WA, USA). Of the pregnant women, mean ages, weeks of gestation, and hypothyroidism and hyperthyroidism rates unique to the trimesters were calculated.

Normal reference range for TSH was accepted as 0.1–2.5 mIU/L in the first trimester, 0.2–3.0 mIU/L in the second trimester and 0.3–3.0 mIU/L in the third trimester. Pregnant women whose TSH levels were over 2.5 mIU/L in the first trimester, over 3 mIU/L in the second and third trimesters were considered to have hypothyroidism. fT4 normal levels were considered as 0.93–1.7 mIU/L. The pregnant women whose TSH levels were above 2.5 mIU/L in the first trimester and over 3 mIU/L in the second and third trimesters but within normal ranges for fT4 were considered to have subclinical hypothyroidism while those with fT4 below 0.93 according to lower limit of laboratory were considered to have overt hypothyroidism.

The pregnant women with TSH levels below 0.1 mIU/L in the first trimester, below 0.2 mIU/L in the second trimester and below 0.3 mIU/L in the third trimester were considered to have hyperthyroidism. Among these pregnant women, those within normal ranges of fT4 were considered to have subclinical hyperthyroidism and those with fT4 levels above 1.7 mIU/L according to the upper limit of laboratory were considered to have overt hyperthyroidism.

**Results**

Mean age of the pregnant women included in the study was found as 29.14±5.84 (range: 15 to 48) years. Mean week of gestation was 13.95±9.28 and median week of gestation was 10 (range: 5 to 40). While 65.4% (n=1227) of the cases were in their first trimester, 21.1% (n=395) of them were in the second trimester, and 13.5% (n=254) of them were in the third trimester. Mean TSH value was 1.71±2.20 mIU/L and mean fT4 value was 1.05±0.23 mIU/L in all pregnant women. When grouped according to the trimesters, mean TSH value was 1.57±2.25 mIU/L and mean fT4 value was 1.10±0.24 mIU/L in the first trimester, mean TSH value was 1.87±0.68 mIU/L and mean fT4 value was 0.99±1.83 mIU/L in the second trimester, and mean TSH value was 2.15±2.53 mIU/L and mean fT4 value was 0.93±0.13 mIU/L in the third trimester.

Hyperthyroidism was found in 5.38% (n=101) of the pregnant women; while 1.22% (n=23) of them had overt
hyperthyroidism, 4.16% (n=78) of them had subclinical hyperthyroidism. Hypothyroidism rate was 15.88% (n=298), and overt hypothyroidism was found in 10.18% (n=191) of them and subclinical hypothyroidism in 5.7% (n=107) of them.

The rates for hyperthyroidism, overt hyperthyroidism and subclinical hyperthyroidism of the pregnant women in the first trimester were 7.09%, 1.71% and 5.38%, respectively. The rates for hyperthyroidism, overt hypothyroidism and subclinical hypothyroidism in the first trimester were 15.64%, 10.92% and 4.72%, respectively.

During the second trimester, 3.03% of the pregnant women had hyperthyroidism and 16.70% of them had hypothyroidism.

During the third trimester, 0.78% of the pregnant women had hyperthyroidism and 15.74% of them had hypothyroidism. The rates of thyroid dysfunction in all pregnant and all 3 trimesters are given in the Table 1.

Discussion
Thyroid dysfunction is among the most common endocrine problems seen in the pregnant women. In early pregnancy, maternal thyroid functions are affected by the increase in thyroid binding globulin (TBG), stimulation of TSH receptors via human chorionic gonadotropin (hCG) and changes in iodine metabolism.\(^6\) Serum total T4 and T3 production increases in the first half of pregnancy; draws a curve around week 20 and reaches a pregestational period when it reaches a particular stable period. TBG increase causes an increase in total T4 and T3 levels about 1.5 times. Serum fT4 and fT3 levels increase slightly within normal ranges in the beginning; however, as the weeks of gestation progress, they gradually decrease by staying within normal ranges especially in the first and second trimesters. Serum fT4 and fT3 are independent biological active forms and 0.03% of total T4 and 0.3% of total T3 are in free forms.\(^7\)

Due to the increase in the production of thyroid hormone, increase of iodine intake about 1.3-1.5 times and transition of iodine from mother to fetus, iodine need during pregnancy increases about 50% and daily intake requirement reaches 250 µg.\(^8\) Normal thyroid gland can meet the hormone needs increased during pregnancy and keeps thyroid hormone levels within normal ranges. However, in cases with obvious thyroid pathology, thyroid hormone production cannot be increased and therefore hypothyroidism may occur in pregnant woman.\(^9\)

In the first trimester, fetal neurodevelopment is provided by maternal thyroid hormones transferred through placenta.\(^10\)

It is known that the redundancy or scarcity of maternal thyroid hormone affects fetus and gestational outcomes of mother at each phase of the pregnancy.\(^6,11,12\) Maternal hypothyroidism is the most common thyroid dysfunction seen during pregnancy and it is associated with fetal loss, hypertension related with gestation, preterm labor, ablatio placentae and decreased intellectual function in baby.\(^11,14\) These adverse outcomes are associated with overt hypothyroidism (increased serum TSH and decreased fT4) seen in 0.2% of the pregnancies and subclinical hypothyroidism (increased TSH, normal fT4) seen in 2.3% of the pregnancies.\(^11,14\) Overt hyperthyroidism is rarer and seen in 0.2% of the cases. It is associated with intrauterine growth restriction, preeclampsia and preterm labor for mother and fetus.\(^11\) Subclinical hyperthyroidism (decreased TSH, normal fT4) is seen in 1.7% of the cases and it is not associated with poor gestational outcomes.\(^13\) Although fT4 and fT3 are usually found at a high rate together in hyperthyroidism cases, T3 concentration alone can be found high in a group of hyperthyroidism cases seen rarely which is called T3 toxicosis.

In the first trimester, the case known as gestational thyrotoxicosis or temporary gestational hyperthyroidism develops depending on the hCG secretion with high titration stimulating thyroid TSH receptors. It should be suspected in women who refer for the complaints of nausea and vomiting in the first weeks after temporary hyperthyroidism conception associat-

**Table 1.** Percentages (%) of thyroid dysfunction in all pregnant and all three trimesters.

<table>
<thead>
<tr>
<th></th>
<th>All pregnant women</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hyperthyroidism</td>
<td>5.38</td>
<td>7.09</td>
<td>3.03</td>
<td>0.78</td>
</tr>
<tr>
<td>Overt hyperthyroid</td>
<td>1.22</td>
<td>1.71</td>
<td>0.50</td>
<td>0</td>
</tr>
<tr>
<td>Subclinical hyperthyroid</td>
<td>4.16</td>
<td>5.38</td>
<td>2.53</td>
<td>0.78</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>15.88</td>
<td>15.64</td>
<td>16.70</td>
<td>15.74</td>
</tr>
<tr>
<td>Overt hypothyroid</td>
<td>10.18</td>
<td>10.92</td>
<td>8.10</td>
<td>9.84</td>
</tr>
<tr>
<td>Subclinical hypothyroid</td>
<td>5.70</td>
<td>4.72</td>
<td>8.60</td>
<td>5.90</td>
</tr>
</tbody>
</table>
ed with hyperemesis gravidarum and have thyroid function tests consistent with hyperthyroidism. In this study, we found hyperthyroidism in 7.1% of the cases in the first trimester, 3.0% of the cases in the second trimester and in 0.8% of the cases in the third trimester. We believe that the reason for the high rate found in first trimester compared to other trimesters and the literature is ruling out the cases with temporary hyperthyroidism associated with gestational thyrotoxicosis and hyperemesis gravidarum and association of autoimmune hyperthyroidism with remission in the second and third trimesters.

If mother has severe iodine deficiency during pregnancy, fetus develops hypothyroxinemia and fetal goiter. In severe iodine deficiency, IQ level decreases 13.5 points compared to normal level. If daily iodine intake decreases below 100 µg during pregnancy, it can be defined as iodine deficiency. Turkey is a region for iodine deficiency. In Turkey, the regions with severe and moderate iodine deficiency are more than the regions with slight insufficient and normal iodine concentrations. In Istanbul, iodine deficiency was reported as 46.2%. In the USA, moderate iodine deficiency was reported in 7% of the women in fertility period. The rates in Turkey are higher than the rate reported in the USA.

Although the hypothyroidism incidence is reported as 0.3-2.5% in the literature, it is based on the study of Klein et al. carried out in 1991 where they considered TSH level above 6 mU/L as hypothyroidism. ATA defined a specific trimester TSH upper limit in 2011, the limit was changed as 2.5 mU/L for the first trimester and it was accepted internationally.

Temur et al. from Turkey determined the upper limit of TSH as 5.6 mU/L in their studies including first and second trimesters, and found hypothyroidism incidence as 3.6%. Although their rate was lower than the rate of our study, they found no difference in terms of thyroid dysfunction between pregnant women who had and had not risk factor of thyroid disease, and they emphasized to screen all pregnant women for that reason.

Remarkably, in a study including 4800 pregnant women, subclinical hypothyroidism prevalence was 27.8% when TSH upper limit was accepted as 2.5 mIU/L but the prevalence was 4.0% when this limit was accepted as 4.87 mIU/L. In our study, we established the upper limit of TSH as 2.5 mIU/L and 15.9% of the pregnant women had hypothyroidism in all trimesters; 10.2% of them had overt hypothyroidism and 5.7% of them had subclinical hypothyroidism. When we evaluated the pregnant women only in the first trimester, 15.6% of them had hypothyroidism. In the studies published in Turkey, hypothyroidism was reported as 2.8% and 1.6%; we believe that the high rate of hypothyroidism in our study may be associated with changing the upper limit of TSH.

Although there is a consensus that thyroid dysfunction screening should be done to high-risk women who are symptomatic or have history of thyroid disease history, type 2 diabetes or other autoimmune diseases and who have high risk for thyroid diseases associated subclinical thyroid diseases, we believe that all pregnant women should be screened as a routine practice in terms of thyroid dysfunction due to the high rate.

Our study was retrospective and therefore had some limitations. We could not access the data of pregnant women who had thyroid dysfunction previously and referred to our hospital. It seems that our higher rate of thyroid dysfunction than the rates reported in the literature is affected by these limitations. It is an expected result to have higher results in countries with iodine deficiency as our country.

Conclusion
In our study region, we found a high rate of thyroid dysfunction incidence. In this study, high rate of hypothyroidism as 15% may result from changing upper limit of TSH to 2.5 mIU/L in the first trimester and to 3 mIU/L in the second and third trimesters. Also, having a study region with iodine deficiency and the pregnant women referred to our hospital due to a previous thyroid disease might increase this rate.

Conflicts of Interest: No conflicts declared.

References


Velamentous cord insertion and birth weight discordance in monochorionic twin pregnancy: a case report

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Abstract

Objective: The aim is to discuss the impact of non-central placental cord insertion on birth weight discordance in twin pregnancies.

Case: Thirty-year-old patient with gravida 2 and parity 1 referred to our clinic when she was found to be monochorionic diamniotic twin pregnant. Upon the determination of crown-rump length (CRL) discordance between both fetuses in the first trimester screening test carried out at twelve weeks of gestation, the patient was taken under close follow-up. Marginal insertion was found in the cord of one of the fetuses in the ultrasonographic examination performed due to the slight increase of discordance between the fetuses at 16 weeks of gestation. The case showing intrauterine growth retardation (IUGR) as of the 24 weeks of gestation was monitored closely via biophysical scoring and Doppler parameters. The patient was delivered by cesarean section due to the decrease in biophysical score and the determination of reverse flow in umbilical artery of the fetus found to have marginal cord insertion and IUGR at 30 weeks and 4 days of gestation.

Conclusion: Non-central placental cord insertion contributes to the birth weight discordance in monochorionic twin pregnancies. Sonographic determination of the location of placental cord insertion can be assessed as the criteria in antenatal evaluation of twin pregnancies. Also, we believe that a careful determination of umbilical cord insertions is useful together with close follow-up of the fetuses when twin discordance is found in first trimester monochorionic pregnancies.

Keywords: Twin discordance, monochorionic pregnancies, velamentous cord insertion.

Özet: Monokoryonik ikiz gebelikte velamentöz kord insersiyonu ve doğum ağırlığı diskordansı: Olgu sunumu

Amaç: İkiz gebeliklerde, santral olmayan plasental kordon insersiyonunun doğum ağırlığı diskordansına olan etkisinin tartıflanması amaçlanmıştır.

Olgu: Otuz yaşındaki, gravida 2, parite 1 olan hasta monokoryonik diamniyotik ikiz gebelik saptanmas› üzerine klini€imize baflvurdu. On ikinci haftada yapılan ilk trimester tarama s›ras›nda her iki fetüs aras›nda bafl-popo mesafesi (CRL) diskordans› saptanmas› üze-rine hasta yak›n takibe al›nd›. On alt›nc› gebelik haftas›nda fetüsler aras›ndaki diskordans›n az miktarda artarak devam etmesi üze-rine yapılan ultrasonografik incelemede fetüslerden birinin kordo-nunda marjinal insersiyon saptand›. Yirmi dördüncü haftadan iti-baren intrauterin gelişme gerili€i (IUGR) bulgular› gösteren olgu biyofizik skorlama ve Doppler parametreleri ile takibe al›nd›. Otuz hafta dürt günlük gebelik mevcutken marjinal kord insersiyonu ve IUGR saptanan fetüste umbilikal arterde ters ak›m saptanmas› ve Biyofizik skorda bozulma nedeniley hasta sezaryen ile do-€urtuldu.

Sonuç: Non-central placental cord insertion contributes to the birth weight discordance in monochorionic twin pregnancies. Plasental cord insertion in monozygotic twins can be assessed as a criterion for antenatal evaluation. Also, we believe that careful determination of umbilical cord insertions is useful together with close follow-up of the fetuses when twin discordance is found in first trimester monochorionic pregnancies.

Keywords: Twin discordance, monochorionic pregnancies, velamentous cord insertion.

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Introduction

Increased morbidity and mortality are seen in all perinatal complications of twin pregnancies except preeclampsia and macrosomia. As in other complications, compared to the dichorionic twin pregnancies, intertwin weight discordance in monochorionic twin pregnancies is observed more frequently. The studies carried out until today have shown that intertwin birth weight discordance is associated with increased morbidity and mortality.

The location of placental umbilical cord insertion is a factor contributing perinatal morbidity in singleton and twin pregnancies. Marginal cord insertion observed in 7% of singleton pregnancies is more frequent in twin pregnancies. In monochorionic twin pregnancies, this rate is distinctly higher. In this case report, we aimed to present the monochorionic twin pregnancy case with marginal cord insertion in one of the fetuses resulting with intrauterine growth retardation and to discuss its management.

Case Report

Thirty-year-old patient with gravida 2 and parity 1 referred to our clinic when she was found to be monochorionic diamniotic twin pregnant in another clinic. In the first examination, monochorionic diamniotic twin pregnancy was determined. The pregnancy was measured as 12 weeks and 6 days according to the last menstrual period, and crown-rump length (CRL) was 54.3 mm (12 weeks) and nuchal translucency (NT) was 1.1 mm in the right fetus while CRL was 69.7 mm (13 weeks and 1 day) and NT was 1.2 mm in the left fetus. This one week difference in the measurements of fetuses was thought to be associated with early-onset twin-to-twin transfusion syndrome (TTTS) which is reported in the literature and can be seen in monochorionic pregnancies, and the patient was taken under close follow-up. In the next follow-ups of the patient, the discordance between fetuses as of 14 weeks of gestation became more distinctive. The patient was applied amniocentesis at 16 weeks of gestation. While no fetal anomaly was determined in the ultrasonographic examination, it was found that the cord of right fetus was entering into the placenta marginally, and this condition was considered as the reason of IUGR in this fetus (Fig. 1). Upon the normal result of karyotype analysis, the patient was taken under ultrasonographic follow-up with two weeks of intervals. Beginning from 24 weeks of gestation, the patient was followed up with color Doppler. At 28 weeks of gestation, end-diastolic flow loss occurred in the umbilical artery of right fetus. At this stage, two doses of corticosteroid (betamethazone 12 mg with 24h interval) were administered to the patient to increase fetal lung maturation and weekly follow-ups were maintained. In the ultrasonography carried out at 30 weeks of gestation, the measurements of the fetus with central-located cord insertion were found consistent with 29 weeks of gestation, and estimated fetal weight was 1341g. The measurements of the fetus with marginal insertion were consistent with 26 weeks of gestation and estimated fetal weight was measured as 834 g. In the Doppler examina-

![Fig. 1. Marginal cord insertion into the placenta on the right fetus (arrow).](image1)

![Fig. 2. Reverse flow in umbilical artery shown in ultrasonographic examination.](image2)
tion, the delivery was decided due to the observation of poor biophysical score and reverse flow in umbilical artery of this fetus (Fig. 2). Babies which were 1140 g and 736 g were delivered by cesarean section with 1-minute and 5-minute Apgar scores as 3; then, they were intubated and taken into newborn intense care unit. Marginal insertion was observed in the cord of the smaller fetus (Fig. 3). The babies were discharged after newborn intense care follow-up without any complication.

Discussion

Twin pregnancies are associated with increasing perinatal morbidity rates.\(^1\) While growth discordance causes poor outcomes, these cases are the patients that should be considered as the high-risk group.\(^4\) In twin pregnancies, there are many reasons causing discordance and varying according to chorionicity.

The studies show that unequal placental share and umbilical cord insertion anomalies in monochorionic twin pregnancies cause growth discordance. This rate is lower in dichorionic twins compared to monochorionic twins.\(^8\) It was found in the study carried out on the placentas of 60 monochorionic twin pregnancies that either the existence of velamentous or marginal insertion significantly increases weight discordance.\(^6\) There are studies in the literature investigating the accuracy of determining cord insertion sonographically in singleton and twin pregnancies. In a study carried out by Di Salvo et al. on singleton and twin pregnancies, it was proved that cord insertion was determined accurately in the ultrasonography examination by histopathological studies performed on 49 out of 54 pregnancies later.\(^7\)

In twin pregnancies, CRL discordance is a non-rare condition which can be observed depending on the different genetic potential or unequal placental share. Besides, there are studies in the literature showing that CRL discordance at early weeks is associated with pregnancy loss, chromosomal anomalies or structural malformations.\(^8,9\) In the systematic review of D’Antonio et al., it was reported that the increase of CRL discordance at 11–14 weeks of gestation is associated with intrauterine loss risk. Accordingly, when CRL discordance exceeds 50%, intrauterine mortality of one of the fetuses reaches to 100%.\(^8\) Also, there is an increase in preterm labor and the risk of IUGR. In addition, increases in diaphragmatic hernia, ventriculomegaly, schizencephaly, aortic atresia and sacral agenesis were reported in fetuses with CRL discordance at first trimester.\(^9\)

While it was expressed that predictive value of CRL discordance is weak for poor perinatal outcome, it was reported that the rate of perinatal loss doubles when monochorionicity is determined. There are studies showing that CRL discordance at an early period such as first trimester can be a predictor to determine weight discordance.\(^9\) As a result of these studies, when chromosomal and structural anomalies are ruled out, it has been shown that CRL discordance has a weak relationship with poor perinatal results. Also, it has been highlighted that this association is not useful to estimate poor outcomes that may develop after 14 weeks of gestation in monochorionic and dichorionic pregnancies.\(^9\)

Antenatal observation is significant in twin pregnancies in terms of increased risks. In this report, fetal weight evaluation has a 20% margin of error. The factors that may cause weight discordance including the location of placental cord insertion should be investigated in these cases.

Conclusion

Marginal cord insertion is a condition that may cause first trimester CRL discordance, estimated fetal weight discordance and intrauterine growth retardation in
monochorionic twin pregnancies. Insertion location of the cord in twin pregnancies can be a parameter to determine during antenatal period in terms of gestational follow-up.

Conflicts of Interest: No conflicts declared.

References

An unexpected temporary fetal acid reason: rupture of fetal ovarian cyst

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Abstract

Objective: To discuss the relationship between isolated fetal acid cases and fetal ovarian cysts.
Case: We presented an isolated fetal acid case developing the rupture of fetal ovarian cyst.
Conclusion: Fetal hydrops may occur depending on the systemic or local pathological processes. With this case, we concluded that the rupture of fetal ovarian cyst may be the reason of isolated fetal acid.
Keywords: Fetal acid, fetal ovarian cyst, rupture of fetal ovarian cyst.

Introduction

Fetal acid can be accepted as the indication of fetal hydrops and it may develop as a response to various etiological factors. With the wide use of Rh immunoglobulin recently, non-immune hydrops cases are seen more frequently than immune hydrops cases. Due to many different fetal reasons, fetal acid may developed as an isolated way independent from other serosal cavities and subcutaneous tissue. The reasons of isolated primary fetal acid are not clear. Although some of them regress spontaneously, the condition progresses towards fetal hydrops in many cases. Ovarian cysts are the abdominal cystic masses observed frequently in female newborns. They are generally not symptomatic and disappear spontaneously. Together with the wide use of ultrasonography, ovarian cysts are diagnosed more often both in fetuses and newborns. These formations are followed up and monitored since they are usually asymptomatic and have no clinical significance. In this report, we have presented a case with the rupture of fetal ovarian cyst which is a rare and unexpected condition for fetal acid.

Case Report

Thirty-four-year-old patient (gravida 2, parity 0) with a pregnancy loss at early period referred to our clinic at 32 weeks of gestation due to fetal intraabdominal cystic formation. Her pregnancy progressed normal until this week and no pathology was found in the follow-up. There was no concomitant apparent disease in her anamnesis. During the pregnancy, she attended all pre-
natal visits and no abnormal finding was established. In her ultrasonography at 32 weeks of gestation, the fetal biometry was consistent with gestational age, and amniotic fluid volume was normal. Her blood pressure and fetal movements were normal. In the ultrasonography, 15 mm round cystic formation was found in the left inferior fetal abdomen (Fig. 1). Cystic formation was independent from fetal kidneys and bladder. Pericystic or intracystic vascularity was not observed in the Doppler ultrasonography. Bilateral fetal kidneys and intestines were in normal structures. Since the fetus was female, had a round anechoic structure and not associated with urinary and gastrointestinal structures, ovarian origin was suspected first. Therefore, re-evaluation was made for maternal diabetes screening and thyroid functions, and the results were normal. The patient was asked to come for a check 2 weeks later. In the ultrasonography carried out at 34 weeks of gestation, fetal biometric measurements were consistent with gestational age and amniotic fluid was within normal ranges. Only abdominal circumference was measured as bigger than gestational age, and it was found as consistent with 9th percentile. There was diffusive free fluid in the fetal abdomen (Fig. 2). It was seen that the cystic formation in the left ovary regressed and its diameter was measured as 14 mm (Fig. 3). It seemed that the intestines were floating in the free fluid. No effusion was observed in the thorax and there was no edema in the subcutaneous tissue; therefore, it was defined as isolated primary fetal acid and further evaluation was performed for hydrops fetalis. Full blood count, HbA1c, VDRL and TORCH screenings, Parvovirus B-19 screening, indirect coombs test and anti-cardiolipin IgM-IgG screenings were carried out. Peak systolic velocity of middle cerebral artery was found 55 cm/sec (1.12 MOM) and it was not predictive for fetal anemia. As it may be the indication for fetal hydrops, fetal karyotyping by cordocentesis was recommended; however, the patient did not accept karyotyping. Fetal cardiac examination was evaluated as normal, and all screening procedures were resulted normal. The patient was asked to come for a check 2 weeks later. Ultrasonography made at 36 weeks of gestation showed normal results. The free fluid in the fetal abdomen was completely regressed and ovarian cystic formation disappeared. At 40 weeks of gestation, the patient delivered a healthy 3400 g baby. No abnormal formation was found in the postnatal ultrasonography of the baby.
Discussion
Hydrops fetalis is defined as pathological effusion in soft tissues and at least two serosal cavities due to immune or non-immune reasons. While placental edema and subcutaneous edema accompany the condition, pericardial, pleural fluid collection or acid-like pathological fluid collection accompanies in serosal cavities. They are classified as immune or non-immune hydrops fetalis. Isolated fetal hydrothorax or isolated acid is pathological fluid collection as isolated in these cavities without any subcutaneous edema depending on various etiologies. Fetal acid frequently accompanies subcutaneous edema which is a component of fetal non-immune hydrops and/or fluid collection in other serosal cavities. Multiple factors consisting of chromosomal disorders, intrauterine infections, fetal cardiac failure and structural disorders of various organs are among the etiology of non-immune hydrops fetalis. The cases where fetal acid develops independent from other serosal cavities or organs are called as isolated fetal acid. Isolated fetal acid can be the indication of hydrops fetalis and may progress towards hydrops in time. Therefore, we recommended fetal karyotyping to our case. When observed as isolated, it may occur frequently as a result of the rupture of an abdominal mass or after rupture in cases such as intestinal obstruction, posterior urethral valve and cloacal persistence. In many studies made on non-immune fetal acid, it was seen that isolated fetal acid has a better prognosis compared to the cases with concomitant hydrops. Isolated fetal acid may result with polyhydramnios and hydrops with pressure to inferior vena cava and other abdominal organs. In our case, fetal acid regressed within 2 weeks and did not cause any complication.

Hormonal stimulation is considered to be responsible in the etiology for the development fetal ovarian cysts (fetal gonadotropins, maternal estrogen and placental human chorionic gonadotropin). The incidence of ovarian cysts is considered above 30% (this rate is calculated according to the autopsies of babies which born dead and died within 28 days after delivery). They are usually isolated and seen more frequently depending on the placental hCG production increased possibly in cases such as maternal diabetes, hypothyroidism, toxemia, or Rh isoimmunization. Mesenteric cyst, urachal cyst, ectopic hydronephretic kidney, intestinal duplication anomalies, cystic teratoma and intestinal obstruction should also be kept in mind in the differential diagnosis. We found no additional anomaly in our case with a detailed ultrasonographic screening. Since the fetus was female and the cystic structure was of pelvic origin, we first focused on ovaries. The shape and anechoic structure of the cyst and lack of bleeding confirmed our diagnosis. Ovarian cysts are diagnosed as a result of pelvic cystic formations found mostly during routine obstetric examination. When it is suspected of a possible fetal ovarian cyst, structural changes (dimension, appearance) of cystic formation or complications (hydramnios, acid, torsion) should be
checked by serial ultrasonography. Simple ovarian cysts have thin walls and do not include internal echogenities. They are usually unilateral. Anechoic simple cysts may become a complex condition including internal echogenities and fluid levels. Detection of these ultrasonographic changes frequently indicates torsion. The incidence of torsion, which is the most common complication of fetal ovarian cysts, is 40%. Although torsion generally develops in intense and bigger cysts, it may also develop in cysts with 2 cm diameter. We followed up our case due to the appearance and dimension of the cystic structure. Fifty percent of them disappear spontaneously after birth. Other rare complications of fetal ovarian cysts reported in the literature are gastrointestinal obstruction, polyhydramnios and ovarian autoamputation. In many different studies, the criteria for intrauterine decompression of ovarian cysts were reported as being bigger than 4 cm and rapid development. Although it is expected that the cysts smaller than 2 cm regress highly and do not cause complication, we observed in our case a temporary acid condition developed due to the rupture of a simple cyst with 15 mm diameter. It was an unexpected condition to develop due to a cyst with such dimension; however, changes in the cystic structure and dimension together with acid, being temporary and complete recovery within 2 weeks made us to focus on ovarian cyst in the etiology.

As in adults, when ovarian cyst ruptures, this ovary may develop hemorrhage. When rupture develops, cystic formation undergoes change in structure and dimension, and hemorrhage to the abdominal cavity causes ultrasonographic acid appearance. In our case, we observed structural and dimensional change of cystic formation in the examination performed two weeks later. With this observation, we associated free intraabdominal fluid with ruptured ovarian cyst. We found that fetal acid regressed two weeks later.

**Conclusion**

The rupture of fetal ovarian cyst should be evaluated as an etiological factor in isolated fetal acid cases. It is hard to evaluate fetal ovaries by ultrasonography, and it is generally not possible to distinguish in other pelvic structures. However, when a cystic formation is found especially in female fetuses, fetal ovaries also should be kept in mind.

**Conflicts of Interest:** No conflicts declared.

**References**

Posterior reversible encephalopathy syndrome developing after eclampsia: a case report

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Abstract

Objective: We aimed to discuss a posterior reversible encephalopathy syndrome (PRES) case, in which the findings such as headache, confusion, seizure, impairment of the visual field and acuity, hemiparesis, and speech and consciousness disorder are observed along with hypertensive disorders of the pregnancy.

Case: In this report, we have presented a PRES diagnosis in a severe preeclamptic case at 36 weeks of gestation. She represented with retrograde amnesia, confusion, and postpartum headache.

Conclusion: With appropriate treatment, PRES is a curable condition without sequel. However, late intervention has high permanent neurological sequel risk. It should not be forgotten that early intervention to etiological reason is the most important factor for favorable prognosis.

Keywords: Posterior reversible encephalopathy syndrome, eclampsia.

Introduction

Posterior reversible encephalopathy syndrome is a clinical and radiological condition in which seizure, consciousness disorder, sudden headache, impairment of the visual field, vomiting, nausea and focal neurological findings are observed in varying rates. Its incidence is not known clearly. Retrospective epidemiological studies show that 7–20% of the cases are associated with preeclampsia, eclampsia and other gestational hypertensive diseases. Hypertensive encephalopathy, renal failure, immunosuppressive and chemotherapeutics, autoimmune and ligament diseases may also cause this condition. Although its pathophysiology is still controversial, decreased cerebral autoregulation causing increase in the cerebral blood flow or association of endothelial dysfunction with cerebral hypoperfusion are the leading hypotheses. Injury of blood-brain barrier after sudden hypertensive attack is thought to trigger the syndrome. Displaying temporary edema of cortical area or sub-cortical white matter in basal ganglia, frontal lobes, cerebellum or brain stem, but mainly in parieto-occipital lobes, with magnetic resonance imaging confirms the diagnosis. The diagnosis is usually established retrospectively. Among all the etiological factors, it has been expressed...
that the cases developing after eclampsia were highly retrospective and their lesions were recovering; however, late intervention might cause permanent sequel.[9] In our report, we evaluated a case found to have retrograde amnesia and blurred vision after eclampsia attack and established with PRES diagnosis by clinical and radiological findings after delivery.

**Case Report**

Twenty-eight-year-old patient (gravida 2, parity 1) referred to the emergency service at 36 weeks of gestation with the complaints of unconsciousness and seizure two times, and it was found in her examination that her blood pressure was 170/110, fetal biometry was consistent with 32–33 weeks and she had oligohydramnios. In her physical examination, no significant finding was observed except pretibial edema. In her laboratory findings, AST was 50 (U/L), ALT was 55 (U/L), creatinine was 0.53 (mg/dl), LDH was 487 (U/L), Hgb was 14.6 (g/dl), BUN was 25.68 (mg/dl), thrombocyte was 151,000 (K/ul) and there was 1+ proteinuria in the urine. There was no significant finding in the pattern of fetal heart beat. The patient was administered 2 g/h magnesium sulphate (MgSO4). Due to the eclampsia indication, the patient delivered 2230 g male baby by cesarean section. During the postoperative period, the patient was followed up for 2 days in the intense care unit. Laboratory values rapidly improved; despite no significant finding was detected in the neurological examination and electro-encephalography (EEG) made upon the complaints of headache, confusion, blurred vision and retrograde amnesia on the postoperative third day, an increase was observed in the signal intensity in fluid attenuated inversion recovery (FLAIR) images (Figs. 1a and 1c) and T2 weighted images (Figs. 1b and 1d) in the sub-

![Fig. 1. An increase is observed in the signal intensity together with cortical and sub-cortical edema in the areas shown by black arrows on FLAIR (a and c) and T2 weighted (b and d) images.](image-url)
cortical white matter of both occipital lobes, more particularly in right parieto-occipital region via magnetic resonance imaging (MRI). The patient was established the diagnosis of posterior reversible encephalopathy syndrome by current findings and differential diagnosis. No further treatment was required except taking blood pressure under control and following up vital signs. The patient was discharged on postoperative seventh day with the recommendation of the follow-up of neurological findings and EEG monitoring.

Discussion
The differential diagnosis of acute focal neurological findings and mental state changes occurring in preeclamptic patients is difficult. This may worry clinicians. Thrombosis, palsy and intracranial bleeding associated with hypertension are among the expected complications in eclamptic patients. Computed tomography (CT) and MRI are useful tools to identify such cases.

Posterior reversible encephalopathy syndrome was first defined by Hinchey et al. in 1996 as a case series of 15 patients. It appears together with headache, confusion, seizure, decrease in impairment of the visual field and acuity, hemiparesis, and speech and consciousness disorder. Focal or generalized convulsions may be seen. Unease and agitated mood can be observed in addition to somnolence, lethargy, stupor and coma. Hemianopsia, cortical blindness, blurred vision and decrease in visual acuity were reported. Conditions such as acute hypertension, gestational hypertensive diseases, HIV infection causing immunosuppression and cisplatin, tacrolimus, cyclosporine A and steroid drug use, and cases associated with hemolytic uremic syndrome, glomerulonephritis, blood transfusion, porphyria, tumors and hypercalcemia were reported in the literature.

The regions affected in the CT are observed as diffuse hypodense area. In the MRI imaging, they are seen as iso-hypo intense areas in T1 weighted images while they are seen as hyperintense areas in T2 weighted and FLAIR images. Involvement can be observed mostly on posterior cortical, sub-cortical and deep parenchymal areas. All brain structures, especially the parietal and occipital lobes, may display involvement. Increased permeability in blood-brain barrier, injury of cerebral auto-regulatory mechanisms and vascular damage causing blood and fluid extravasation to parenchymal area were suggested in its pathophysiology. The latter mechanism is especially asserted in cases associated with immunosuppressive drugs. There are also studies arguing the opposite mechanisms. Decrease in cerebral blood flow developed due to the acute hypertension, cerebral arterial vasospasm and ischemia-induced cytotoxic edema are also other hypotheses. In their case series including 47 patients, Brewer et al. reported that PRES is one of the key components of eclampsia pathogenesis. It was observed that antepartum eclampsia developed in 23 of the patients while 24 patients had postpartum eclampsia. It was also reported that headache was the most common symptom (87.2%) and there was mental state changes in 51.1% of the patients. On the other hand, Ural et al. published a PRES case developing severe preeclampsia without any convulsion.

With appropriate treatment, PRES is a curable condition without sequel. However, the delayed treatment may cause permanent sequel in the brain tissue. Particularly, the cases with concomitant vasospasm and ischemia are under risk. Monitorization of blood pressure, discontinuing immunosuppressive drugs and anti-convulsant treatment are the basic approaches. In the study of Demirel et al. including 7 pregnant women diagnosed with PRES, it was reported that six patients showed remission within approximately 2 and 5 days, and this period delayed up to 15 days in a patient receiving mechanical ventilation support for 10 days and speech disorder persisted in this patient. In the treatment, mean artery pressure (MAP) is aimed to be 105–125 mmHg. For that purpose, parenteral calcium channel blockers and labetalol or oral nifedipine treatment are recommended. It was reported that nimodipine, which is a cerebral vasoselective calcium channel blocker, is effective against vasospasm. In the studies performed on pregnant women who underwent treatment due to hypertensive leukoencephalopathy, both conventional and MRI angiography images showed the efficiency of nimodipine. MgSO4, propofol, benzodiazepines and phenytoin were recommended for the treatment of cases developing refractory status epilepticus. There are studies showing the success of intravenous valproic acid use in such patients. Especially MgSO4 helps cerebral vasodilatation by inhibiting calcium-dependent vasoconstriction and shows neuroprotective activity by preventing ischemia. In our case, the patient was monitored in the intense care unit without requiring mechanic ventilation, and target blood pressure values were achieved by administrating 30 mg nifedipine (with 12 hours of inter-
val) as anti-hypertensive in addition to MgSO\textsubscript{4} for 48 hours (1 g/h) during pre-postoperative period. We believe that the MgSO\textsubscript{4} treatment, anti-hypertensive treatment and rapid intervention according to etiological reasons are useful for the prognosis.

**Conclusion**

PRES is a clinical condition with multifactorial reasons where different symptoms appear together, imaging methods stand out and diagnosed increasingly. Suspicious neurological findings should be warning factors for all cases presenting gestational hypertensive diseases. Providing rapid diagnosis, effective treatment and intense care conditions are the most significant factors for the positive progress of the prognosis.

**Conflicts of Interest:** No conflicts declared.

**References**

Mosaic trisomy 8: diagnostic approach with fetal MRI as a complement to ultrasonography

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Abstract

Objective: Trisomy 8 mosaicism (MT8) is characterized by intracranial, genitourinary and skeletal system anomalies, congenital cardiovascular disorders, deep palmar and plantar creases, and neoplastic and hematological disorders. In the literature, there are only a few antenatal ultrasound (US) and fetal magnetic resonance imaging (MRI) findings reported for MT8.

Case: The fetus whose gestational age was 26 weeks and 4 days was referred for fetal MRI due to corpus callosum agenesis suspected in routine US screening. We are presenting the major and minor MRI findings of the fetus in this case report.

Conclusion: Fetal MRI can be used in addition to the antenatal ultrasound to evaluate genetic syndromes such as trisomy 8 mosaicism and to identify additional anomalies which cannot be found in the ultrasound screening.

Keywords: Trisomy 8 mosaicism, antenatal ultrasonography, fetal magnetic resonance imaging.

Introduction

Mosaic trisomy 8 (MT8) which is also known as Warkany syndrome is a chromosomal disorder defined with the existence of three copies of chromosome 8 in some cells of organism. Its annual incidence rate varies between 1/25,000 and 1/50,000 and it is more common among men.[1–3]

It displays certain phenotype varieties from normal individuals up to severe malformations and they can or cannot be seen by prenatal ultrasound (US). MT8 is characterized by intracranial, genitourinary and skeletal system anomalies, congenital cardiovascular disorders, deep palmar and plantar lines, and neoplastic and hematological disorders. The characteristics of this syndrome are shown in the Table 1. Antenatal diagnosis of this rare syndrome is very significant since it may appear with mental retardation. There are a few papers in the literature about the antenatal US findings of MT8.[4–6]
In recent years, fetal magnetic resonance imaging (MRI) has become an additional diagnostic tool for the antenatal evaluation of fetus.\cite{7-9} MRI evaluation of fetus requires a special approach. In addition to standard diagnostic evaluation, findings should be assessed also for a genetic syndrome. This approach may help to detect additional conditions which may be overlooked.

To the best of our knowledge, there is only one study referring fetal MRI findings of MT8. In this report, we present and discuss major and minor US and MRI findings of a fetus with MT8.

**Case Report**

The fetus whose gestational age was 26 weeks and 4 days was referred for fetal MRI due to corpus callosum agenesis suspected in routine US screening. Also a mild ventriculomegaly and bilateral hydronephrosis were observed in the ultrasound screening. MRI was performed by using free respiration and body coil via the device with 1.5 Tesla (T) system (Magnetom Symphony, Siemens Healthcare, Erlangen, Germany). The mother was in the supine position during the examination and she was imaged by our routine fetal MRI protocol including HASTE, true FISP and two-dimensional (2D) FLASH T1-weighted sequences. In the MRI, medium level bilateral ventriculomegaly (15 mm) and total agenesis in the corpus callosum were observed (Fig. 1). Cranial and cerebral measurements were within normal ranges. There was no scaphocephaly, protruding forehead or micrognathia; however, lower lip was everted. Interocular ocular distance was 15 mm (below -2SD for week 26) and it was the indication of hypotelorism. Signal intensity of lenses was increased slightly. In addition to certain antihelixes, bigger ears and bigger lobules were observed (Fig. 1). Short and thick neck and narrow shoulders were remarked. High arched or cleft palate was not seen. There was no camptodactlia or arthrogryposis. The fetus was too small to evaluate in terms of patellar hypoplasia. Palmar or plantar lines could not be evaluated by MRI. No vertebral anomaly was detected; however, tethered cord was observed under the kidneys. There was slight bilateral hydronephrosis (anterior and posterior diameters of right and left renal pelvises were measured as 8 and 7 mm, respectively). Stomach was dilated; however, no “double-bubble” sign was found. Fetal movement prevented to evaluate cardiac and major vascular anomalies by MRI. In the fetal echocardiography, no additional cardiac anomaly was detected. MT8 was

<table>
<thead>
<tr>
<th>Table 1. Characteristics of mosaic trisomy 8.</th>
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<tbody>
<tr>
<td><strong>Central nervous system anomalies</strong></td>
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<tr>
<td>– Corpus callosum agenesis</td>
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<tr>
<td>– Hydrocephaly</td>
</tr>
<tr>
<td><strong>Facial, jugular and cranial anomalies</strong></td>
</tr>
<tr>
<td>– Reverse lips</td>
</tr>
<tr>
<td>– Bigger dysplastic ears</td>
</tr>
<tr>
<td>– Distinctive forehead</td>
</tr>
<tr>
<td>– Wide nose</td>
</tr>
<tr>
<td>– Microphthalmia</td>
</tr>
<tr>
<td>– Cataract</td>
</tr>
<tr>
<td><strong>Cardiovascular anomalies (40-60%)</strong></td>
</tr>
<tr>
<td>– VSD</td>
</tr>
<tr>
<td>– ASD</td>
</tr>
<tr>
<td>– Major vascular anomalies</td>
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<tr>
<td><strong>Urinary system anomalies</strong></td>
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<tr>
<td>– Hydronephrosis-reflux</td>
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<tr>
<td><strong>Reproductive system anomalies</strong></td>
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<td>– Cryptorchidism</td>
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<tr>
<td><strong>Gastrointestinal anomalies</strong></td>
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<tr>
<td>– Diaphragmatic hernia</td>
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<tr>
<td>– Esophageal atresia</td>
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<tr>
<td>– Lack of gall bladder</td>
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<tr>
<td><strong>Skeletal system anomalies</strong></td>
</tr>
<tr>
<td>– Vertebral anomalies (Hemivertebra, spina bifida, kyphoscoliosis)</td>
</tr>
<tr>
<td>– Joint contractures</td>
</tr>
<tr>
<td>– Abnormal metacarpal and metatarsal bones</td>
</tr>
<tr>
<td>– Simian line</td>
</tr>
<tr>
<td>– Deep longitudinal plantar line</td>
</tr>
<tr>
<td><strong>Other findings and anomalies</strong></td>
</tr>
<tr>
<td>– Related malignities</td>
</tr>
<tr>
<td>– They may be related with advanced maternal-paternal age</td>
</tr>
</tbody>
</table>

Fig. 1. In the coronal HASTE image, total agenesis of corpus callosum, distinctive antihelixes and big lobules together with bigger ears are seen.
confirmed by the fetal blood karyotyping via cordocentesis and the patient preferred to terminate the gestation.

Discussion
Proper detection of MT8 spectrum at antenatal period and the documentation of anomalies are difficult processes requiring multidisciplinary approach since it may include multiple organ system involvement and complex anomalies. In case of clinical suspicion, final diagnosis of MT8 is established by cordocentesis. Since fetuses with MT8 are viable and they may have positive condition, detailed investigations should be carried out for the structural anomalies in the prenatal diagnosis of MT8. Early diagnosis of related anomalies may provide more information for genetic consultation and may decrease dilemmas. In the case presented in this report, we carried out cordocentesis as a result of clinical and imaging findings and established final diagnosis by genetic analysis.

Fetal MRI is a non-ionizing and non-invasive antenatal imaging method with increasing areas of use, and it presents a particular superiority over US examination for the multiplanar evaluation of complex anomalies. Using fetal MRI in our case as a modality did not only detect the suspicion of corpus callosum agenesis found in the ultrasound but also helped to identify the details requiring multiplanar analysis such as everted lower lip, hypotelorism, lens anomaly, bigger ears, short and thick neck and narrow shoulders, and tethered cord.

Fetal MRI has a higher contrast resolution compared to the ultrasound and it provides better separation of normal tissue from abnormal tissue.\(^1\) Fetal MRI is essentially used to confirm and characterize the anomalies found in routine prenatal ultrasound; however, it can also be used as an additional diagnostic tool to identify anomalies not observed by ultrasound and to complement ultrasound findings. Fetal MRI is useful since it can confirm the lack of callosum in suspicious corpus callosum agenesis. Fetal MRI is helpful to evaluate corpus callosum as it can be seen directly in sagittal and coronal planes after 20 weeks. Also, additional anomalies are observed together with corpus callosum agenesis and they can also be detected by fetal MRI.\(^1\)\(^2\)\(^3\)

Gun et al.\(^4\) reported fetal MRI findings confirming antenatal US and corpus callosum agenesis of a fetus with MT8 which was at 23 weeks of gestation. In our case, we found and defined additional characteristics of this syndrome by MRI.

Consequently, fetal MRI can be used in addition to the antenatal ultrasound to evaluate genetic syndromes such as trisomy 8 mosaicism and to identify additional anomalies which cannot be found in the ultrasound screening.

Conclusion
Consequently, fetal MRI can be used in addition to the antenatal ultrasound to evaluate genetic syndromes such as trisomy 8 mosaicism and to identify additional anomalies which cannot be found in the ultrasound screening.

Conflicts of Interest: No conflicts declared.

References
Perinatal Thyroid Workshop Report – 2015

Olmuş Api, Cihat Şen, Murat Yayla, Mertihan Kurdoğlu, Elif Gül Yapar Eyi, Mekin Sezik, Gökhan Göynümer, Özmale Moraloğlu Tekin

Abstract
A Perinatal Thyroid Workshop has been carried out in order to determine scientific data and clarify confusions in clinical practices as a result of new findings and interpretations in pregnancy and thyroid recently. Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism in the intrauterine life, it is scientifically not right to say as a basic result that L-thyroxine treatment of a mother would also treat the possible hypothyroidism in fetus. Since the association of adverse gestational outcomes with overt hypothyroidism has been proven, the treatment should be initiated as soon as it is detected during pregnancy. It is known that subclinical hypothyroidism is more common than overt hypothyroidism. Although an association has been shown between subclinical hypothyroidism and adverse gestational outcomes, no such association was found in randomized controlled studies. Maternal oral L-thyroxine intake does not treat fetal hypothyroidism in the intrauterine life. While overt hypothyroidism has many reasons, it occurs during pregnancy mostly associated with Graves’ disease. Therefore, the treatment is initiated immediately as soon as it is detected during pregnancy, and it is aimed to keep mother in mild hyperthyroidism. The drug mostly preferred in the treatment is propylthiouracil (PTU) since it passes through placenta at minimal rate. In the beginning of the pregnancy, the screening requires to check only the levels of thyroid stimulating hormone (TSH). Free or total T4 measurement is required only when there is a change in TSH. Similarly, anti-thyroid antibodies during pregnancy are not recommended to use for routine screening since there is no evidence to make a recommendation in favor of or against screening. Considering the current literature, guides and expert opinions, it is not advisable to screen all pregnant women on a routine basis. Screening by TSH should be done only in high risk. In Turkey, scientific data seem insufficient for now to suggest routine iodine support for all pregnant women during antenatal care. However, large-scale and population-based studies are required immediately to detect the true prevalence of iodine deficiency in Turkey.

Keywords: Pregnancy, perinatal, thyroid.

Özet: Perinatal Tiroid Çalıştay Raporu – 2015

Anahtar sözcükler: Gebelik, perinatal, tiroid.
**Introduction**

**Purpose of the Workshop**

With the Workshop, it was aimed to establish a guideline for a national practice association under the name of “Gestational Thyroid Screening and Diagnosis Guide” for the use of obstetricians and gynecologists during their obstetric follow-ups and to reveal scientific evidence levels related with:

- Physiological process related with maternal and fetal thyroid hormone syntheses,
- Proper clinical use of assessment criteria and tests used to evaluate gestational thyroid functions,
- Impacts of clinical and subclinical maternal thyroid dysfunctions on maternal and fetal health, and clinical management of these dysfunctions

For that purpose, Perinatal Thyroid Workshop has been organized with the support of association members working at Turkish universities and training and research hospitals. The participants prepared current literature about the topics they determined months ago, and presented and discussed them.

Perinatal Thyroid Workshop held in Afyon between November 8 and 9, 2013 had following program:

1. Discussing the importance of the topic
2. Talking about the current situation in Turkey and the world
3. Discussed questions
4. Discussed solution recommendations
5. Questions with no answer

The Result Report of Perinatal Thyroid Workshop was established with the consensus of report committee and completed on May 19, 2015 after the literature was reviewed through reporting and e-mail and re-evaluation by the group of the reports prepared by the participants.

**Evidences**

The evidences were included in the report in accordance with the criteria ([U.S. Preventive Services Task Force Ratings: Strength of Recommendations and Quality of Evidence. 2003 Guide to Clinical Preventive Services, Third Edition: Period Updates, 2000–2003](https://www.uspreventiveservicestaskforce.org/uspstf)) presenting the net benefit (benefit-loss) and the power of evidence, and based on the evaluations made pursuant to the “Preventive Service Task Force” and “Grading of Recommendations, Assessment, Development and Evaluation (GRADE)” of the USA in the literature previously. The evidences are considered as good, medium and poor, and the recommendations in the “Grade” system are expressed as “1” if they are good and as “2” if they are poor. Evidence values are also expressed with following symbols:

- Evidence of very poor quality: +
- Evidence of poor quality: ++
- Evidence of medium quality: +++
- Evidence of high quality: ++++

A. The service provides benefit in terms of health; benefits outweigh risks; clinicians are highly recommended to provide this service for appropriate patients.

B. There are partial evidences that the service provide benefit in terms of health; benefits outweigh risks; clinicians should provide this service for appropriate patients.

C. There are partial evidences that the service provide benefit in terms of health; benefit-risk evaluations are very close to make a general recommendation; therefore, clinician cannot be recommended either to provide or not to provide this service for appropriate patients.

D. There are partial evidences that the service does not provide benefit or it is ineffective in terms of health; risks outweigh benefits; it is not recommended to clinician to provide this service as a routine practice for appropriate patients.

I. (Insufficient) Evidences for the benefit or risk of service in terms of health are insufficient; benefits outweigh risks; clinician should provide this service for routine patients

Workshop results were addressed as main topics below and interpreted:

I. Gestational Thyroid Function: How to Interpret Tests Properly?
II. Iodine Status in Turkey and the World for Iodine Insufficiency
III. Impacts of Hypothyroidism on Pregnancy
IV. Pregnancy and Hypothyroidism
I. Gestational Thyroid Function: How to Interpret Tests Properly?

Thyroid stimulating hormone (TSH) and thyroid hormone levels vary during pregnancy. Normal reference values of non-pregnant women should not be considered as “normal” for pregnant women (Evidence Level A, High ++++). Knowing and evaluating them are of particular importance.

In the first trimester, TSH levels secondary to the increase of human chorionic gonadotropin (hCG) are suppressed. This is physiological, and therefore it should not be considered as pathology. With the stimulating effect of hCG hormone on thyroid gland, free thyroxin (sT4) levels during first trimester stay within normal ranges only with a slight increase, and TSH levels decrease (<0.1 mIU/L). In following trimesters, TSH reaches to normal levels. Therefore, in evaluating gestational thyroid functions, it is recommended to use TSH reference ranges specific to trimesters (Evidence Level B, Medium ++). The reference values found in the literature are close to each other, and there is no full consensus on determining normal reference values specific to trimesters (Evidence Level B, Medium ++). Reference values also vary according to the week of gestation (Evidence Level B, Medium ++). Therefore, it is recommended to use 2.5 – 97.5 percentile value ranges instead of using absolute values. The reference values found in the literature are close to each other, and there is no full consensus on these values.

In cases where percentile values specific to trimester cannot be established by laboratory, the upper limits for TSH provided in the Table 1 can be used (Evidence Level B, Medium ++).

The first step for evaluating gestational thyroid functions is the measurement of serum TSH levels (Evidence Level B, Medium ++). For TSH measurements, automated platforms such as “chemiluminescence” using “improved immunometric assay” methods are recommended. Using 3rd or 4th generation (ultrasensitive) kits in these automated systems helps to detect even the slightest differences (<0.02 mU/L) in TSH values compared to the systems using ELISA techniques. Therefore, it is recommended to use TSH measurement by using sensitive “immunometric assay” as a screening test for evaluating thyroid function (Evidence Level B, Medium ++).

The production of thyroid-binding globulin (TBG) increases during pregnancy. Accordingly, total triiodothyronine (T3) and thyroxine (T4) levels increase about 1.5 times. Therefore, usually the measurements of free triiodothyronine (fT3) and free thyroxine (fT4) levels are preferred during pregnancy. However, just as in TSH, fT4 level exhibits physiological changes according to trimesters. In the first trimester, fT4 exceeds normal reference values, and decreases 30% below fT4 normal reference values. Therefore, it is recommended during pregnancy –as in TSH– trimester- that specific fT4 reference values should be determined by each laboratory or 150% of total T4 should be considered as the reference value. On the other hand, like TSH, there is no reference value specific to each trimester with a consensus achieved.

In the measurement of free T4, “immunoassays” are used widely. However, it should be remembered that the laboratory methods used and kit differences may provide misleading results for free hormone measurements (Evidence Level A, High ++++). Especially, “equilibrium” dialysis or the method of isotope-dilution fluid chromatography-tandem mass spectrometry (LC-MS-MS) was considered to be more reliable and reproducible when evaluating serum fT4 levels in pregnant women (Evidence Level A, High ++++). But this method is used in a limited way since it is performed in private laboratories and it is expensive. Therefore, similar to TSH measurements, it should be kept in mind that fT4 measurement during pregnancy is error-prone. For that reason, we recommend that each laboratory should calculate percentile values for their own gestational study population and report the studied results through percentile values.

As total T3 level is not a preliminary test for evaluating thyroid functions even in non-gestational cases, it

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Table 1. Lower and upper limit values for serum TSH according to gestational trimesters.

<table>
<thead>
<tr>
<th>Range</th>
<th>Trimester</th>
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<tbody>
<tr>
<td>0.1 – 2.5 mIU/L</td>
<td>For the first trimester</td>
</tr>
<tr>
<td>0.2 – 3.0 mIU/L</td>
<td>For the second trimester</td>
</tr>
<tr>
<td>0.3 – 3.0 mIU/L</td>
<td>For the third trimester</td>
</tr>
</tbody>
</table>
cannot be used also to evaluate thyroid dysfunctions during pregnancy. However, after hyperthyroidism is detected, it is recommended to use for follow-up purposes, in case of T3 toxicosis or in the differential diagnosis of hyperthyroidism.[13]

Last but not least, “hyperemesis gravidarum” is another significant clinical condition which may have misleading impacts on TSH and fT4. In hyperemesis gravidarum, fT4 levels may increase in 30–60% of pregnant women in addition to the physiologically suppressed TSH at first trimester. In such cases, it is recommended to evaluate TSH receptor stimulating antibody levels and to carry out differential diagnosis with Graves’ disease. In case of hyperemesis gravidarum, TSH receptor stimulating antibodies are negative, hyperthyroidism findings do not occur in patients and fT4 levels returns to normal ranges between 15 and 18 weeks of gestation. In Graves’ disease, TSH receptor stimulating antibody levels are determined especially at third trimester and hyperthyroidism risk in the newborn should be considered[14] (Evidence Level A, High ++++).

**In conclusion**

- In case of indication during pregnancy, 3rd or 4th generation (ultrasensitive) TSH measurement is recommended as thyroid screening test (Evidence Level B, Medium +++)
- When evaluating serum TSH during pregnancy, reference values of non-pregnant population should not be used (Evidence Level A, High ++++).
- In serum TSH evaluation during pregnancy, using percentile values or reference values specific to each trimester seems an appropriate clinical practice (Evidence Level A, High ++++). Our recommendation in accordance with literature evidences is to use TSH values provided in the Table 2.

**II. Iodine Status in Turkey and the World for Iodine Insufficiency**

Iodine insufficiency is still a significant public health problem in the world.[15] It is estimated that 35% of the world population has insufficient iodine intake.[16] Daily iodine intake amounts determined by World Health Organization (WHO) are provided in the Table 3. Iodine amount in most of the natural foods are usually low and it varies depending on environmental factors.

<table>
<thead>
<tr>
<th>Iodine insufficiency level</th>
<th>Urinary median iodine concentration (mcg/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe</td>
<td>&lt;20</td>
</tr>
<tr>
<td>Medium</td>
<td>20–49</td>
</tr>
<tr>
<td>Mild</td>
<td>50–99</td>
</tr>
<tr>
<td>Sufficient intake</td>
<td>100–199</td>
</tr>
<tr>
<td>Sufficient intake of pregnant women</td>
<td>150–249</td>
</tr>
</tbody>
</table>
such as the iodine concentration in the soil and fertilizer use. Some of the iodine in the world is taken from the surface of the ground by snow and rain and moved to seas by winds and floods, and by being vaporized here, they return to the soil again through rain. As a result, especially the seaweeds and sea products are among the iodine-rich sources. However, iodine content may vary to a large extent in different fish species.

Yoghurt, cow milk, egg, strawberry and also fresh cheese types with less amounts of iodine are among other iodine-rich sources that we may recommend people to consume daily. On the other hand, processed foods including iodized salt and materials including iodate used to thicken dough are also among the iodine-rich nutritional sources. The efforts to make people consume iodized salt in order to increase daily iodine intake in many countries resulted in success. Similarly, Mother and Child Care and Family Planning Center of Turkish Ministry of Health and UNICEF initiated the “Program of Preventing Diseases Caused by Iodine Insufficiency and Iodizing Salt” in 1994.

In accordance with the Table Salt Communiqué of Turkish Food Codex published in the Official Gazette No. 23397 dated 09 July 1998, iodizing table salts became mandatory. Accordingly, it is mandatory to add 50–70 mg/kg potassium iodure or 25–40 mg/kg potassium iodate to table salts. Table salt is the refined or unrefined salt which is enriched by iodine, powderized and directly offered to consumers. In accordance with the provisions of the act, it was decided that Ministry of Agriculture and Rural Areas would be in charge during production process, and Ministry of Health would be in charge from production until delivered to consumers. However, another issue to highlight is that iodized salt is harmful for some thyroid patients such as those with Graves’ disease, Hashimoto Thyroid and hot nodules. Therefore, with the “Communiqué Concerning Revision in the Table Salt Communiqué of Turkish Food Codex” published in the Official Gazette No. 24141 dated 15 August 2000, it was allowed to manufacture table salt without iodine in 250 g packages for such patients.

In the determination of iodine insufficiency, urinary iodine excretion is considered. Urinary iodine measurement is a cost-efficient and widely recognized test with easy applicability. As almost 90% of iodine taken is excreted with urine, urinary iodine level is accepted as a sensitive test to show current iodine intake. However, there is a significant point to highlight. In terms of urinary iodine excretion, it is known that the amount may vary day by day, even in the same day. Due to these variations, urinary iodine excretion to be used as a diagnostic test to show iodine intake may cause misleading evaluations and treatments. Since urinary iodine values do not exhibit normal distribution, it is recommended to use this test in studies based on population and to use median values as mean value and percentiles instead of standard deviation values.

The degree of iodine insufficiency is classified based on median urinary iodine concentration of the population studied (Table 4).

It is a well-recognized fact that severe iodine sufficiency has negative impacts on the fetal development and neuro-cognitive functions in developing countries. Cretinism and mental retardation are the major adverse effects (Evidence Level A, High ++++). However, since the impacts of iodine on fetal brain developments have been understood well in recent years, the impacts of mild-medium iodine insufficiency

![Table 4. Pregnant women recommended early TSH screening.](image-url)

<table>
<thead>
<tr>
<th>Condition</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thyroid dysfunction / surgery underwent (since hypothyroid development rate is 33% after lobectomy)</td>
<td>Thyroid disease history in the family</td>
</tr>
<tr>
<td>Thyroid disease history in the family</td>
<td>Goiter presence</td>
</tr>
<tr>
<td>Thyroid antibody positivity, especially thyroid peroxidase auto-antibodies (TPOAb increases hypothyroidism risk, and the probability increased 40% in those with TPOAb positivity compared to TPOAb negativity)</td>
<td>Presence of clinical hypothyroidism findings/symptoms</td>
</tr>
<tr>
<td>Presence of clinical hypothyroidism findings/symptoms</td>
<td>Type I diabetes (since hypothyroidism rate increases to 16%)</td>
</tr>
<tr>
<td>Type I diabetes (since hypothyroidism rate increases to 16%)</td>
<td>Miscarriage and preterm labor</td>
</tr>
<tr>
<td>Miscarriage and preterm labor</td>
<td>Presence of vitiligo, adrenal failure, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, SLE, Sjögren’s syndrome associated with autoimmune thyroid dysfunction</td>
</tr>
<tr>
<td>Presence of vitiligo, adrenal failure, hypoparathyroidism, atrophic gastritis, pernicious anemia, systemic sclerosis, SLE, Sjögren’s syndrome associated with autoimmune thyroid dysfunction</td>
<td>Infertility prevalence (Although overt and subclinical hypothyroidism rates are as wide as 1–43%)</td>
</tr>
<tr>
<td>Infertility prevalence (Although overt and subclinical hypothyroidism rates are as wide as 1–43%)</td>
<td>Those who underwent head-neck irradiation (since hypothyroidism prevalence is 67% in the 8-year follow-up)</td>
</tr>
<tr>
<td>Those who underwent head-neck irradiation (since hypothyroidism prevalence is 67% in the 8-year follow-up)</td>
<td>Morbid obese whose BMI (body mass index) is &gt;40 (since hypothyroidism was found as 13–19.5%)</td>
</tr>
<tr>
<td>Morbid obese whose BMI (body mass index) is &gt;40 (since hypothyroidism was found as 13–19.5%)</td>
<td>Women over 35 years (The rate of Serum TSH value be ≤ 5 increases together with the age)</td>
</tr>
<tr>
<td>Women over 35 years (The rate of Serum TSH value be ≤ 5 increases together with the age)</td>
<td>Amiodarone treatment applications (14–18% hyperthyroidism-hypothyroidism)</td>
</tr>
<tr>
<td>Amiodarone treatment applications (14–18% hyperthyroidism-hypothyroidism)</td>
<td>Lithium use (6–52 hypothyroidism)</td>
</tr>
<tr>
<td>Lithium use (6–52 hypothyroidism)</td>
<td>Exposure to iodized contrast agents (until 6 weeks before pregnancy, thyroid dysfunction in 20% cases)</td>
</tr>
<tr>
<td>Exposure to iodized contrast agents (until 6 weeks before pregnancy, thyroid dysfunction in 20% cases)</td>
<td>Living in regions with medium level of iodine insufficiency</td>
</tr>
</tbody>
</table>
on fetal neurological development have been discussed and researched. Iodine requirement increases since thyroid hormone production in mother and fetus during pregnancy and renal iodine excretion increase (Evidence Level A, High ++++) in those with sufficient iodine intake before and during pregnancy. Iodine stocks in thyroid gland can meet increased needs. Therefore, iodine amount does not change in those with sufficient iodine intake. However, the studies performed on pregnant women with mild-medium iodine insufficiency show that urinary iodine excretion decreases as an indication of decrease in body stocks towards the end of pregnancy. [19] On the other hand, the most significant source of iodine for newborn is breast milk. Thus, sufficient iodine intake of mother is essential in terms of the newborn development. [20] Important sources of iodine in the diet are sea products, egg, meat and chicken. Countries develop different strategies to prevent iodine deficiency.

In order to meet increased needs during pregnancy, iodine supplement is used during antenatal period in some countries. The daily amount recommended during pregnancy is 250 microgram according to WHO. Also, iodizing table salt is the most common practice to prevent iodine insufficiency including our country. However, even though table salt is iodized, conformity to the codex and standardization may cause problems. [18,21] Besides, humidity and heat (i.e. during cooking / by direct effect of sunlight), iodine amounts in the iodized salt decrease [22,23] (Evidence Level A, High ++++) in those with sufficient iodine intake or not, and pregnant women were separated into two groups (as those with median urinary iodine concentration <150 mcg/g and >150 mcg/g). According to the results of the study, both verbal IQ scores and reading-understanding abilities were found significantly low in those with mild-medium iodine insufficiency (median urinary iodine concentration <150 mcg/g). [19] In the sub-group analysis, the negative impact on IQ scores and reading abilities increased as iodine insufficiency increased. This study is very significant since it was conducted in a country where iodine insufficiency increased. This study is very significant since it was conducted in a country where iodine insufficiency has been the widest study so far.

New data shows that 85% of the households in Turkey use iodized salt. [25] Society-based studies in Turkey indicate that iodine insufficiency level has changed from “mild insufficiency” to “sufficient intake” within the last decade. [27,28] (Evidence Level B, Medium ++). The number of the studies researching iodine insufficiency prevalence of pregnant women in Turkey is insufficient. Also, current studies including pregnant women mostly cover a single region and a limited number of pregnant women. [24,26,29–31] Therefore, large-scale and society-based studies are required. For that purpose, it has been decided to plan a prospective, multi-centered research project under the coordinatship of Turkish Perinatology Society.

The short- and long-term impacts of mild iodine insufficiency during pregnancy on fetus and newborn are controversial; related small-scale cross-sectional studies showed that medium level iodine insufficiency may have negative impacts on neurological, behavioral and learning abilities in the short-term. [32] In 2013, two major studies were published which showed long-term negative impacts of mild iodine deficiency during pregnancy on neurocognitive functions during childhood. [31,33] It would be useful to take a look at these studies. In the study of Bath et al. carried on approximately 1040 pregnant women and published in Lancet, urine samples of pregnant women were collected and kept at 10–13 weeks of gestation. [34] The IQ scores at 8-year-old of the children born from these pregnant women and their reading performances at 9-year-old were evaluated. In the urine samples maintained, median iodine concentrations were measured and it was determined if iodine intakes of pregnant women were sufficient or not, and pregnant women were separated into two groups (as those with median urinary iodine concentration <150 mcg/g and >150 mcg/g).
cantly lower in pregnant women with mild-medium iodine insufficiency (median urinary iodine concentration <150 mcg/g).

Although negative impacts of mild iodine insufficiency were found in these two studies, the cause-effect relationship of these impacts has not been established fully yet. Also, even such relationship is established, possible positive impacts of iodine supplement on fetal neurological development should be shown by randomized controlled studies.

Consequently

- Scientific data to recommend routine iodine support to all pregnant women during antenatal care seems insufficient for now (Evidence Level I, Low +++)..
- Large-scale and society-based studies are required immediately to determine iodine sufficiency prevalence of pregnant women in Turkey.
- If the region that pregnant women live is known to have severe iodine insufficiency, iodine supplement should be recommended certainly during antenatal period (Evidence Level A, High ++++).
- Mild-medium iodine insufficiency during pregnancy was shown to have short- and long-term negative impacts on neurological, behavioral and learning abilities. However, the cause-effect relationship has not been established fully yet (Evidence Level B, Medium +++).

III. Impacts of Hypothyroidism on Pregnancy

Does overt (clinical) hypothyroidism have impacts on gestational outcomes?

Hypothyroidism may have negative impacts on gestational outcomes depending on the intensity of biochemical anomalies. High TSH and low free T4 levels and overt hypothyroidism complicating the pregnancy are seen rarely (0.3–0.5% of screened women). This is caused by two factors. First is that some of the hypothyroid women are anovulatory. Other is that new or insufficiently treated hypothyroidism complicating pregnancy is associated with increased first trimester spontaneous abortion rate. In the ongoing pregnancies, it was found that hypothyroidism is associated with increased risk for following complications: preeclampsia and gestational hypertension, ablation placentae, unreliable fetal heart rate trace, preterm labor including very early delivery (before 32 weeks), low birth weight [this was explained in a study most likely due to preterm labor for preeclampsia, but independent from preeclampsia in a second study where preeclampsia rate may be ignored, increased cesarean rate, perinatal morbidity and mortality, neuropsychological and cognitive disorder, postpartum hemorrhage. In the study of Matalon et al., it was shown that treated maternal hypothyroidism is not associated with adverse perinatal outcomes, but hypothyroidism is an independent risk factor for cesarean delivery.

Does subclinical hypothyroidism has impacts on gestational outcomes?

The results of the studies performed on this matter are controversial. In brief, while cohort studies found an association between subclinical hypothyroidism and poor gestational outcomes, randomized controlled studies revealed no such association.

Subclinical hypothyroidism (high TSH, normal free T4) is more common than overt hypothyroidism, it is seen in 2–2.5% of women screened in the regions of the USA with sufficient iodine. Complication risk during pregnancy in women with subclinical hypothyroidism is lower than those associated with hypothyroidism. However, some studies reported that women with subclinical hypothyroidism had increased risk in terms of severe preeclampsia, preterm labor and/or pregnancy loss.

In a prospective study performed on 17,298 pregnant women included for prenatal care, subclinical hypothyroidism defined by considering 97.5 percentile as the threshold (TSH range: 2.74–11 mU/L) was found 2.3% and preterm labor risk was 2 times higher and ablation placenta risk was 3 times higher in these cases. In the same study, the rates of newborns of the cases with subclinical hypothyroidism for referral to newborn care unit and respiratory distress syndrome were found to be two times higher than normal ones. In the study of Wilson, general incidence was found 10.9% for all hypertensive diseases in pregnant women with subclinical hypothyroidism, but a significant risk increase was shown for only severe hypertension (OR=1.60, 95% CI 1.08–2.379). In another study comparing gestational outcomes in women with negative antithyroid peroxidase, gestational loss was found higher In women with normal free T4 and first trimester serum TSH between 2.5 and 5.0 mU/L than
the women with TSH below 2.5 mU/L (6.1% vs. 3.6%). However, no difference was observed in preterm labor rates. As not corresponding with these findings, the sub-group analysis of the results of prospective multi-centered FASTER study which evaluated Down syndrome risk in the obstetric population with singleton pregnancy did not show an association between maternal subclinical hypothyroidism and poor gestational outcomes (preterm labor, miscarriage, premature membrane rupture). In a society-based prospective cohort study conducted in China, maternal thyroid function during first 20 weeks of gestation and development in following fetal and infantile periods were analyzed, and it was found that subclinical hypothyroidism is associated with increased fetal distress, preterm labor, sight impairment and neural growth retardation. However, the reliability of the results of this study is controversial since the number of cases with subclinical hypothyroidism is only 41. In a meta-analysis published recently and analyzed many studies, it was shown that the risks for gestational diabetes mellitus, pregnancy-induced hypertension, cesarean labor and labor with low and high birth weight did not increase in cases with subclinical hypothyroidism compared to euthyroid controls, but preeclampsia, ablation placentae and perinatal mortality risks increased as OR=1.68, (95% CI 1.09–2.40), OR=1.68 (95% CI 1.09–2.60) and OR=2.73 (95% CI 1.59–4.70), respectively. In conclusion, while cohort studies show an association between subclinical hypothyroidism and poor gestational outcomes, randomized controlled studies do not show such an association.

Does treatment in pregnant women diagnosed with clinical or subclinical hypothyroidism change gestational outcomes? Is treatment recommended?

In the lights of current data, there is an uncertainty about the potential benefits of treatment. Treating clinical hypothyroidism with levothyroxine during pregnancy has been adopted as a standard approach based on the benefits put forth by previous non-randomized studies. Additionally, since maternal euthyroidism is potentially essential for normal fetal cognitive development, UpToDate and Endocrine Society recommend treating pregnant women with subclinical hypothyroidism irregardless of TPO antibody condition. The guide of American Thyroid Society recommends treating only pregnant women with subclinical hypothyroidism who are found to be positive for TPO antibody. On the other hand, the same society stated that there is no sufficient evidence to oppose supporting treatment in cases with subclinical hypothyroidism who are negative for TPO antibodies. Therefore, there is an uncertainty in potential benefits of the treatment of those with TPO negative and especially with TSH between 2.5 and 3.0. Besides, it was shown in a Cochrane compilation published in 2013 for gestational outcomes of women with overt or subclinical hypothyroidism who had treatment that there was a decrease in preterm labor and first trimester miscarriages.

Does isolated hypothyroxinemia have any impact on gestational outcomes

No… Isolated hypothyroxinemia (low T4) is defined as the reference range of maternal free T4 concentration together with normal TSH between 5th or 10th centile. Although the reason of isolated maternal hypothyroxinemia observed in 1–2% of pregnant women is not known clearly, it is considered that it may be associated with low iodine intake. It is considered that this condition not accepted as an independent thyroid disorder in the clinical practice may also be caused by laboratory problems related with free T4 measurements. The impacts of isolated hypothyroxinemia on perinatal and neonatal outcomes are not clear. In a study, maternal serum free T4 concentrations below 2.5 percentile with normal TSH were not found to be associated with poor gestational outcomes. In FASTER study, increased risk was found for preterm labor (OR=1.62), macrosomy (OR=1.97) and gestational diabetes (OR=1.70); however, the results were determined as inconsistent. Neuropsychological performance (mean intelligence, psychomotor or behavioral scores) in the children of mother with normal TSH together with low maternal free T4 between 12 and 20 weeks of gestation was found to be lower than the children of mothers with normal thyroid functions. It was observed that fetal development was normal in those found to have isolated hypothyroxinemia at the first trimester but had normal values at second and third trimesters or those with normal values at the first trimester but poor values at second and third trimesters. There is no publication showing the gestational outcomes of L-thyroxine treatment during pregnancy and the benefits on the development of newborn.
Do gestational outcomes get affected in pregnant women with positive thyroid antibody positivity without thyroid dysfunction?

There is no sufficient evidence to reach a certain conclusion. Autoimmune thyroid disorder is the most common autoimmune disease and it is the leading reason for hypothyroidism among women. It is asserted that autoimmunity may have impacts on pregnancy through two mechanisms. The first one is the interaction of increased demand on thyroid with adaptive mechanisms, and the second one is the direct impacts on placenta and fetus as a result of general activation of immune system together with autoimmune environment.\[69,64-66\]

According to this hypothesis, autoimmunity prevents adaptive thyroid reaction towards high demand, and it results in even lower thyroid hormone levels. As a result, mechanisms of the harms towards pregnancy are based on the direct impact of hormones on different areas of maternal-fetal unit. There are evidences showing that thyroid hormones regulate cytokine production with angiogenic growth factors as well as the development of trophoblastic proliferation and placenta and decidua.\[67,68\]

In a meta-analysis published in 2011, five cohort studies analyzing the impact of autoimmune thyroid disease on premature labor in pregnancies with preserved thyroid functions were evaluated and it was shown that all studies had a positive association (\(OR=2.07\), 95% CI 1.17–3.68). Subsequently, in another meta-analysis carried out in 2012 on studies excluding cases with thyroid dysfunction, general combined relative risk (RR) was found to be significantly high in terms of preterm labor for pregnant women with thyroid antibodies and positive TPO antibody (for thyroid antibodies, \(RR=1.98\), 95% CI 1.29–3.04; \(P=0.002\); for TPO-antibodies, \(RR=1.8\), 95% CI 1.29–3.04; \(P=0.002\)). No such evaluation was made for women with positive TG-antibody, because there is no study conducted in this context.\[69\]

In the meta-analysis published in 2011, 31 studies, which evaluated the low risk of autoimmune thyroid disease together with normal thyroid function together with normal thyroid function, were included. However, these studies had differences on many aspects. While some of them were cohort studies,\[70–88\] others were “case control” studies.\[89–94\] These studies also had differences among themselves since they also included diseases with different characteristics (infertile patients, patients with repeating pregnancy losses and pregnant women). Total analysis showed a positive relationship for autoimmune thyroid disorder together with abortion risk and normal thyroid risk as \(OR=3.9\) (2.4–6.1; \(p<0.01\)) for cohort and \(OR=1.80\) (95% CI 1.25–2.60; \(p=0.002\)) for “case control”. In this study, it was also observed that autoimmune thyroid disorder accompanied increased TSH levels. In another study, TSH levels were found higher in pregnant women who were positive for TPO antibody (3 vs. 1 mIU/l; \(p<0.01\)).\[95\]

In the prospective study of Negro et al. published in 2006, TPO antibody positivity was found as 11.7% in a population of 984 pregnant women. It was shown that euthyroid pregnant women who were positive for TPO antibody developed degenerated thyroid function and it was associated with increased miscarriage and premature labor risks.\[96\]

Should pregnant women with thyroid antibody positivity be treated without thyroid dysfunction?

No... Although a positive association was shown between the presence of thyroid antibodies and pregnancy loss, it is not recommended currently to screen and treat antithyroid antibodies routinely in all pregnant women. However, under the light of current data, it has been shown in the Cochrane database that treatment of euthyroid women with TPO antibody positivity by levothyroxine has decreased preterm labor risk significantly at a rate of 72% (RR=0.28, 95% CI 0.10–0.80).\[98\] The study based on in this compilation is the prospective study of Negro et al. published in 2006.\[96\] In another retrospective study, it is recommended to administer levothyroxine if serum TSH values are not below 1 mIU/l and are above 3 mIU/l in pregnant women with TPO antibody positivity, since these patients tend to exhibit subclinical hypothyroidism and this condition is not anticipated in the first trimester.\[99\] As women with high anti-TPO antibodies are under increased risk in terms of miscarriage, preterm labor and hypothyroidism progression, if detected, it is recommended to evaluate these women before pregnancy and also during first and second trimesters in terms of thyroid functions.\[77\]

Are gestational outcomes affected in first trimester pregnant women whose TSH values are between 2.5 and 5 mIU/L and negative for thyroid antibody?

There is no sufficient evidence to reach a certain conclusion on this matter. According to current literature, we can say that it is expected to have more loss rates in first trimester pregnancies with TSH values between 2.5 and 5 mIU/L and negative for thyroid antibody.
However, there is no study evaluating the efficiency of treatment in these cases. The study of Negro et al. which is the only prospective study on this matter, pregnancy loss rate was found higher in first trimester pregnant women whose TSH values were between 2.5 and 5 mIU/L and negative for thyroid antibody compared to the first trimester pregnant women whose TSH values were below 2.5 mIU/L and negative for thyroid antibody (6.1% vs. 3.6%, respectively, P<0.006). On the other hand, there was no significant difference between these groups in terms of preterm labor rates.

**Maternal thyroid screening: for everyone?**

There is no global practice recognized widely in the world for this matter. In accordance with the current data about pregnancy and thyroid screening, a consensus report comes into prominence which has been published recently and presented with a large-scale literature review. This consensus report is the collaborative work between the Study Group of Iodine Insufficiency Diseases and Thyroid Dysfunction of Spanish Endocrinology and Nourishment Society and Spanish Gynecology and Obstetrics Society. The recommendations offered in the conclusion part of the report are as follow:

1. The benefit of the screening for thyroid dysfunction in the pregnant population has been proved to determine clinical hypothyroidism and to initiate treatment early (<10 weeks). This screening should be carried out before conception preferably or in the onset of the pregnancy if possible.
2. The benefit of screening to determine subclinical hypothyroidism or isolated hypothyroidism has not been proven; because there is no data available showing the benefits of subsequent thyroxine treatment.
3. Sufficient amounts of iodine intake should be assured for entire population, especially fertile women and pregnant and breastfeeding women. Recommended iodine intake in pregnant and breastfeeding women is 250 mcg/day. In societies with iodine insufficiency, iodine supplement about 150–200 mcg will help to receive recommended intake. Ideally, it should be ensured that sufficient iodine intake is provided before conception.
4. Screening at the onset of pregnancy just requires the measurement of TSH levels. The tests to be carried out for free or total T4 are only required when there is a change in TSH.
5. Reference values of these values to be measured by routine laboratory procedures for each trimester and each society should be available.
6. Since it is difficult to interpret the results of thyroid hormone tests, it would be useful to organize trainings to train primary care physicians, obstetricians, internal disease and endocrinology specialists who are not familiar with gestational thyroid dysfunctions. In this way, it should also be highlighted to avoid therapeutic interventions in cases proceeding with unproven pathological values.

In summary, Study Group of Iodine Insufficiency Diseases and Thyroid Dysfunction of Spanish Endocrinology and Nourishment Society and Spanish Gynecology and Obstetrics Society recommend evaluate thyroid function in all pregnant women at early period (before 10 weeks of gestation) routinely with TSH. However, the recommendations offered in the guide published by American Thyroid Society in 2011 did not provide such certain messages for routine screening. The Society made following recommendations for the screening:

1. There is no sufficient evidence to make recommendation for or against routine TSH screening in the first trimester visit.
2. Since the benefit of the treatment for isolated maternal hypothyroxinemia has not been shown in the studies so far, it is not recommended to screen pregnant women with routine free T4.
3. There is no sufficient evidence to make recommendation for or against screening with preconceptional TSH test in women under high risk for hypothyroidism.
4. All pregnant women should be screened in the first prenatal visit in terms of any thyroid dysfunction and/or thyroid hormone use or anti-thyroid drug use.
5. Serum TSH values should be obtained in the early weeks of gestation for the following women with high risk of overt hypothyroidism:
   - History of thyroid dysfunction or previous thyroid surgery
   - >35-year-old
   - Symptoms of thyroid dysfunction or presence of goiter
   - TPO antibody positivity
   - Type 1 diabetes or other autoimmune diseases
• History of miscarriage or preterm labor
• History of radiation at head or neck regions
• Family history of thyroid dysfunction
• Morbid obesity (BMI ≥ 40 kg/m²)
• Use of amiodarone or lithium or recent use of iodized radiological contrast
• Living in a region with middle or serious iodine insufficiency

6. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in all women.

7. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in women with the history of sporadic or repeating miscarriage.

8. There is no sufficient evidence to make recommendation for or against screening for antithyroid antibodies at the first trimester of pregnancy in order to prevent preterm labor.

American College of Obstetricians and Gynecologists (ACOG) also has reported that there is no sufficient evidence to support routine screening in pregnant women who are asymptomatic for hypothyroidism, and that it will be convenient to carry out thyroid tests only in those with personal thyroid disease history or thyroid disease symptoms. It was stated that there is no sufficient evidence to carry out thyroid function tests even in asymptomatic pregnant women with mildly grown thyroid, but those with severe goiter or isolated nodules should be evaluated as any other patient. In the committee opinion of ACOG published in October 2007, an approach against the routine screening of all pregnant women was asserted. However, it was shown that these recommendations are quite old and testing pregnant women routinely for thyroid dysfunctions is a screening tool with cost-benefit balance. In the compilation of Bailey Spitzer, it was reported that TSH is sufficient as a screening test in both pregnant and non-pregnant populations with low risk. It was recommended to screen women under high risk (autoimmune disease, thyroid nodules and goiter in physical examination, radiation exposure or personal or family history of thyroid cancer) with both TSH and thyroid peroxidase (TPO) antibodies. It was highlighted that all women with TSH values >5 should be evaluated in terms of TPO antibody positivity. It was stated that thyroid replacement is required for increasing TSH in the TPO antibody positivity while antibodies should be re-screened 3 month later in case of negativity.

According to the results of a study conducted on 4800 pregnant women in China, thyroid hormone insufficiency screening to be carried out by using reference values specific to gestational age before 8 weeks of gestation is supported. The authors reported that TSH and free T4, which can be applied easily in many clinics for hypothyroid screening, were considered as good tests.

In another study carried out on 592 pregnant women in Czech Republic and published recently, it was reported that the diagnosis of new thyroid pathology is established in 7.6% of women who have no risk factor. Based on this result, the authors indicated that a simple routine screening would be appropriate in pregnant women. They asserted that the evaluation of TSH and free T4 levels between 5 and 10 weeks of gestation is a requirement to analyze thyroid function.

They reported that 1.9% of autoimmune thyroidism with pathological sonography cannot be recognized in cases where TPO is not evaluated.

The Endocrine Society, established in 1916 and recognized as a significant authority for endocrinology, offered following recommendations in their guide, which was renewed in 2012, for the thyroid screening during pregnancy:

1. Before and during pregnancy, routine screening is not recommended for the presence of anti-TPO antibodies.

2. Women with high anti-TPO antibodies have increased risks for miscarriage, preterm labor, hypothyroidism progression and postpartum thyroidism. Therefore, if detected, these women should be screened in terms of serum TSH anomalies before the pregnancy and at first and second trimesters of pregnancy.

3. The committee could not reach a consensus in terms of screening recommendations for all new pregnant women. Therefore, they offered two versions:
   • Some members recommended screening all pregnant women in terms of serum TSH anomalies at 9 weeks of gestation or their first visits.
   • Some members did not express any opinion for or against routine screening of all pregnant women at their first visits in terms of in terms of serum TSH anomalies.
In the compilation of Springer et al., it was decided to support a general screening in pregnant women for thyroid diseases. It was also recommended to follow those with positive screening results for a long time after delivery.

Miller et al. interpreted in their compilation published in 2011 (note: reference number not provided) that the test considered for routine screening should fulfill some certain criteria. These are:

1. The incidence of the disease should be as high as to justify screening. The prevalence of subclinical hypothyroidism during early pregnancy reported in the literature fulfills this condition.
2. The cost-efficiency balance of screening should be convenient. If it assumed that the treatment will improve neurological development in children of women who have subclinical hypothyroidism, it can be said that the screening to be carried out for subclinical hypothyroidism has this balance.
3. Poor outcomes should be associated with disease condition. There are some inconsistencies in the literature about the association between subclinical hypothyroidism and poor gestational outcomes. Additionally, the data about the association of subclinical hypothyroidism or isolated hypothyroxinemia with delayed neurocognitive development are insufficient.
4. There should be evidences that the intervention will improve the outcomes. It is impossible to say it with the current literature.

In the light of these data, Miller et al. concluded that, until such data are obtained, there is no sufficient evidence for recommending a routine screening for thyroid disease during pregnancy or for the treatment of subclinical hypothyroidism or hypothyroxinemia even they are detected by chance.

According to the guide of American Association of Clinical Endocrinologists, screening with TSH should be a routine before pregnancy or in the first trimester of pregnancy. What the specialists in perinatology field think about it? They commented about this issue as follows: John H. Lazarus believes that thyroid screening should be applied to all women during early pregnancy since thyroid dysfunction is common during pregnancy. He stated that 65% of women with abnormal test results would be overlooked if these criteria are applied even current guides say that some criteria (autoimmune disease history, previous radiation exposure on neck region etc.) are required for the test. However, he said that there is a single randomized study evaluating the impact of T4 implementation on childhood IQ but it provides no benefit for this implementation. He expresses that measuring TSH in all pregnant women in first trimester will be useful currently, and T4 should be checked if it is >2.5 mIU/L.

John H. Lazarus states that TPO antibody should be checked if TSH is >5 mIU/L, and alternatively, if laboratory provides a gestational reference range for TSH, then TSH should be considered as abnormal if it is above 97.5 percentile. He recommends that threshold value of T4 should be minimum 2.5 percentile and threshold value should be determined according to the specific test used.

Sarah Kilpatrick thinks that some criteria should be fulfilled for any screening test, for example, the incidence of the disease should be as high as to justify screening and a known effective treatment decreases poor outcomes of screened diseases. She expresses that the incidence of gestational hyperthyroidism is <0.5% and therefore hyperthyroidism screening is not required. She states that (clinical and subclinical) hypothyroidism incidence is about 3% in routine screening studies, and this is as high as to justify screening. She asserted that, crucially, most of these women had subclinical hypothyroidism and as stated above, there is no data proving that the treatment will eliminate potential poor perinatal or childhood outcomes associated with maternal subclinical hypothyroidism.

She expresses that these facts explain why routine screening is not indicated; however, screening women at high risk for thyroid disease is very significant since there are evidences justifying that treating women with overt thyroid disease has benefits both for mother and baby. She says that those with thyroid disease history, those with strong family history for thyroid disease, those exposed to radiation on neck region, those who have goiter, or those who have known antithyroid antibodies or other autoimmune diseases or type 1 diabetes should be tested. According to her, TSH should be checked in the first prenatal visit of these women; if TSH is high, then free T4 or free thyroxine index and TPO antibodies should be measured. She states that in case of overt hypothyroidism, the disease should be treated by thyroid hormone as keeping within TSH reference range. She believes that subclinical hypothyroid...
Hypothyroidism should be treated if TPO antibodies are positive. Sarah Kilpatrik highlights that patient should be evaluated in terms of any hyperthyroidism disease finding if TSH is suppressed, and if they are unavailable and patient is in the first trimester when TSH is measured, then TSH should repeat together with free T4 at mid-second trimester, and treatment can be recommended if they are concordant with hyperthyroidism. She also warns that it should be well known that subclinical or clinical hypothyroidism may be seen in women if TSH is temporarily suppressed by human chorionic gonadotropin from first trimester up to mid-second trimester of the pregnancy. She adds that this does not cause any morbidity and it spontaneously recover, therefore treatment is not required.

Roberto Negro is also among those supporting routine screening in the beginning of the pregnancy. He says, “mean first gestational age is 25–30 in the western countries, and there are data showing that 15% of women above 25 years old may have thyroid anomalies, and there is a consensus that it is required to treat overt thyroid dysfunction and especially overt hypothyroidism”. The study of Dosiou et al. published recently reports that routine screening displays more cost-effective benefit not only against non-screening but also against screening women with high risk for only thyroid dysfunction. Robert Negro, noteworthy, highlights that the authors of this analysis assume women with any level of hypothyroidism are treated, but only women with overt hypothyroidism benefit from the treatment. In his personal opinion, he believes that, especially in countries with high quality healthcare system, a woman about 25–30 years old in her first pregnancy should have the right to know if she is hypothyroidic or not, if she has any risk to develop hypothyroidism or postpartum hypothyroidism. In accordance with these findings, the recommendations of Turkish Perinatology Society are as follow:

Maternal thyroid hormones ensuring fetal brain development during pregnancy, and subsequently, presence of convincing evidences for the requirement in terms of neuropsychic development in the child and the opinion that risk factors cannot be determined directly may indicate that maternal thyroid screening should carry out on all cases. On the other hand, applicability of screening programs is determined according to following matters:

- The disease to be screened should be seen frequently and cause significant health problems. The incidence should be above 5% in the society screened.
- By the screening, it should be possible to detect diseases at an early period, it should be acceptable by patients and it should have general clinical practicality.
- The diseases should have a treatment.
- The treatment carried out by diagnosing after screening should be superior to the treatment carried out by diagnosing with known methods.
- The potential benefit of the screening should be higher than its potential harms and screening costs.

In accordance with these findings, the recommendations of Turkish Perinatology Society are as follow:

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In terms of these aspects:

Thyroid disease screening in all pregnant women cannot fulfill all conditions required to be in screening
program for today. Therefore, it is controversial if screening is required for all pregnant women to determine thyroid dysfunction and to carry out its treatment when prevalence and complications, diagnostic accuracy and practicality, potential benefits, potential harms and screening costs of the disease are evaluated.

In conclusion, serum TSH measurement is required before pregnancy and during early pregnancy in the group with high risk for overt hypothyroidism. Pregnant women recommended early TSH screening are given in the Table 4.

**Does oral L-thyroxine administered to mother also treat possible hypothyroidism in fetus?**

No… Oral L-thyroxine administered to mother does not treat fetus. Because, under normal conditions, thyroxine does not pass through placenta; however, in case of fetal hypothyroidism, a small amount of maternal thyroxine may pass through placenta. Yet, this amount is not sufficient to treat fetal pathology.[111] In cases where there are large goiters as preventing swallowing functions, L-tyroxine was administered with intramuscular injections without any apparent evidence that it has any benefit.[112] Weekly administration of L-thyroxine through intraamniotic way was considered as a treatment option for congenital hypothyroidism and its application was supported.

Basic benefits of intraamniotic way were shown as low complication rates and relatively long periods between injections. However, there is no consensus on the intraamniotic dosage of L-thyroxine, it is required to be adjusted according to the size of goiter, current period for treatment until delivery and respond to the treatment.[111,113]

**Does Subclinical Hypothyroidism Cause Fetal Hypothyroidism?**

No… Maternal subclinical hypothyroidism does not cause fetal hypothyroidism. In the study of Yuan et al. published recently, it was found that the TSH levels of newborns of women with subclinical hypothyroidism were higher than the newborns of women with normal thyroid functions (p<0.05).[116] In the same study, it was shown that neonatal TSH has generally a low correlation with maternal TSH. However, as case number was low, the clinical significance could not be established clearly. In the study, only one or two newborns had high TSH among the newborns delivered by women with high TSH levels. Therefore, it is not possible to generalize that if mothers have high TSH levels, then their babies will have high TSH levels, too. All of 20 newborns found to have TSH levels over threshold values had temporary hypothyroidism.

**Is it necessary to add iodine to the levothyroxine replacement as a routine practice in hypothyroidism treatment?**

No... Levothyroxine is a synthetic version of T4 and it is used to treat cases with hypothyroidism specific to any reason. Levothyroxine can be converted to T3 in the body and it is sufficient to take a single form, which is levothyroxine, as a supplement for both hormones. As levothyroxine already includes iodine, it is not required to take additional iodine to treat hypothyroidism. If extra iodine is taken, they will not be added into new thyroid hormones since the functions of thyroid are fulfilled and undertaken by levothyroxine.[111] In fact, according to the results of a paper published in 1992, additional iodine taken as supplement is excreted by urine, feces and sweat.[116]

**Can patient be without symptom when TSH value is between 2.5 and 10 mIU/L and T4 at normal ranges?**

Yes… About 28.6% of cases with hypothyroidism can be without any symptom.[117] In the study of Rosario and Calsolari published recently, 252 women with TSH levels ≤10 mIU/L, who were established with the diagnosis of subclinical hypothyroidism, were evaluated.[113] In 180 (71.4%) of these women, at least one symptom or finding of hypothyroidism was observed which cannot be explained by any other condition; in the remaining cases, no symptom was observed.

**Is it appropriate to carry out only antibody screening during pregnancy?**

No… In the current literature, there is no study researching or comparing best screening strategy as only TSH, only anti-TPO antibody or anti-TPO antibody together with TSH in different populations characterized with various nutritional iodine conditions.[65]

In the guides published by American Thyroid Society in 2011 and by The Endocrine Society (which is recognized as a significant authority for endocrinology) in 2012, we see following recommendations about this matter. [8,58]
Both guides do not recommend screening all pregnant women for thyroid antibodies in the first trimester in order to prevent preterm labor. This also applies for those with sporadic or repeating miscarriages or undergoing IVF treatment. It was also not recommended screening all women in the first trimester in order to prevent spontaneous abortions or miscarriages. However, when it is detected, it is recommended by American Thyroid Society to evaluate serum TSH levels once in every four weeks during the first half of pregnancy and at least once between 26 and 32 weeks of gestation. The Endocrine Society recommends screening patients, who were found to have thyroid antibody, before pregnancy and at first and second trimesters in terms of TSH anomalies.

**Does iodine insufficiency cause fetal hypothyroidism?**

No... The iodine insufficiency of mother does not cause fetal hypothyroidism. Almost 50 years ago, it was set forth that the first respond of thyroid gland against decreased iodine levels initiated very effective autoregulatory mechanisms. Among such mechanisms, there are the increases in thyroid vascularity, iodine intake, acinar cell sizes, hyperplasia, and serum T3/T4 rates. It was shown in human studies as well as animal studies that such changes occurred independent from TSH.\[^{118}\]

Synthesis and secretion of thyroid hormones due to the decreased iodine levels initiated very effective autoregulatory mechanisms. Among such mechanisms, there are the increases in thyroid vascularity, iodine intake, acinar cell sizes, hyperplasia, and serum T3/T4 rates. It was shown in human studies as well as animal studies that such changes occurred independent from TSH.\[^{118}\]

For that reason, increase of serum TSH is observed rarely in cases with goiter living in regions where only iodine insufficiency exists. Increased thyroglobuline concentrations are seen more frequently in the mild and medium level of iodine insufficiency.\[^{120,122}\]

It was shown that these mechanisms work similarly in pregnant women. It was revealed that TSH levels in pregnant women in a population with medium level of iodine insufficiency did not increase even in women with the lowest first trimester free T4 levels, but T3/T4 rates and serum thyroglobuline levels were found high all along. It was observed that TSH values started to increase together with the third trimester; yet, they were mostly within normal ranges.\[^{109,124,125}\]

The idea which is general but not right, is that iodine insufficiency does not only decrease T4 production but also increases TSH in the circulation. However, the findings underlying this misconception were obtained from the studies carried out in the regions with insufficient iodine together with further factors (guatrogens, selenium insufficiency etc.) inhibiting the adaptation with autoregulatory mechanisms by causing mostly functional thyroid tissue loss and even glandular atrophy.\[^{126}\]

Iodine insufficiency is also associated with the clinical findings of hypothyroidism defectively. Such an association can be valid only in iodine insufficiency goiter endemia accompanying myxedema where TSH increased.\[^{123}\]

Individuals living regions which allow the adaptation of autoregulatory mechanism to insufficient iodine intake are clinically euthyroid. This also applies for sever iodine insufficiency due to normal or increased T3 in circulation.\[^{126}\]

Iodine supplement studies carried out on pregnant women in Europe present findings supporting that it is also observed in pregnant women.\[^{125,127-131}\]

In these studies, it was shown that maternal TSH is capable of adapting enough to fulfill increased gestational thyroid hormone needs in regions with mild-middle iodine sufficiency. While it was introduced that this support is usually effective to decrease the increase in the size of thyroid during the pregnancy, only two of these six studies showed that maternal TSH was lower (within normal reference limits). None of the showed any clear impact of iodine supplement on maternal and newborn total or free thyroid concentrations. Considering that the thyroid hormone concentrations may be the best biochemical marker for health fetal development, the results of these studies are reassuring. However, it should be remembered that none of these studies evaluated long-term clinical outcomes such as maternal goiter or newborn developments.\[^{132}\]

Yet, autoregulatory mechanisms which are possible for mother are not in question for fetus. The reason is that fetal thyroid gland is not fully maturated. As a result, decreased synthesis and secretion of T4 and T3 in fetus cause an increase in TSH concentration and this results with both clinical and biochemical fetal hypothyroidism.\[^{133}\]

It can be said that cretinism and mental retardation which may occur due to the intrauterine influence of fetus can only be associated with severe iodine insufficiency during pregnancy, and that there is no sufficient study data for slighter conditions.\[^{114}\]
Summary Management

• As in non-pregnant women, high TSH blood levels make established primary hypothyroidism diagnosis in pregnant women. In the first trimester of pregnancy, there is no sufficient evidence to support a routine screening with only thyroid auto-antibodies, so it is not recommended (Evidence Level C, Medium 2 +).

• In the current literature, it is not clarified which is the best screening strategy among screening only TSH, only anti-TPO antibody or anti-TPO antibody together with TSH.

• The ranges determined for each trimester of pregnancy as the upper threshold of TSH should be taken into consideration. Ideally, it is required to know reference value range specific to trimesters for each population. When high TSH is identified, free T4 should be measured to classify hypothyroidism as either clinical (overt) or subclinical. In cases where percentile value of population studied is not known, it is recommended to consider following references for definitions:
  - TSH ≥2.5–10.0 mU/L together with normal free T4 level: Subclinical hypothyroidism
  - TSH ≥2.5–10.0 mU/L together with low free T4 level: Clinical (overt) hypothyroidism
  - TSH ≥10.0 mU/L, without considering free T4 level: Clinical (overt) hypothyroidism

• However, it should be careful when interpreting free T4 levels during pregnancy, and ranges specific to trimester determined by each laboratory should be referred, or instead, in second and third trimesters, new reference ranges obtained by multiplying gestational total T4 reference ranges by 1.5 can be used. Free T4 index can also be used as an alternative reference value to be used during pregnancy (Evidence Level B, Medium 2 +).

• Since the association of overt hypothyroidism with poor gestational outcomes was proven, maternal hypothyroidism should be avoided by initiating treatment as soon as identified during pregnancy (Evidence Level A, Good 1 +++).

• All pregnant women newly diagnosed with overt hypothyroidism should be treated with thyroid hormone (thyroxine, T4). T4 dose should be adjusted as keeping TSH below 2.5 mIU/L in first trimester and below 3 mIU/L in second and third trimesters (or within TSH ranges specific to trimester). Thyroid function tests should be evaluated within 30–40 days after the onset of treatment and once every 4–6 weeks subsequently (Evidence Level A, Good 1 ++).

• When using levothyroxine to treat cases with hypothyroidism associated with any reason, it is not required to include routine iodine supplement additionally (Evidence Level A, Good 1 ++).

• Since there is no study for the gestational outcomes of euthyroid pregnant women with positive TG-antibody, it is not recommended to treat such patients with levothyroxine (Evidence Level C, Medium 2 +).

• If hypothyroidism diagnosis is established before pregnancy, T4 dose should be arranged as keeping TSH below 2.5 mIU/L (Evidence Level C, Poor 2 +).

• After delivery, the dose administered during pregnancy of most of the hypothyroid women should be decreased to pregestational dose (Evidence Level A, Good 1 ++).

• As we do not have sufficient evidence about its activities and due to the inconsistencies in free T4 measurement, it is currently not recommended to treat isolated hypothyroxinemia (Evidence Level I, Weak 2 +).

• If there is more demand for thyroid during pregnancy and evidences are available showing that euthyroid women, which have autoimmune thyroid disease at the early periods of gestation, have more risk for subclinical hypothyroidism or overt hypothyroidism in the advanced weeks of gestation, it is required to monitorize TSH once every 4–6 weeks in these women (Evidence Level A, Medium 1 ++).

• Although current literature data are limited, gestational loss is higher in first trimester pregnant women whose thyroid antibody is negative and TSH value is between 2.5 and 5 mIU/L compared to first trimester pregnant women whose TSH value is below 2.5 mIU/L. However, since the efficiency of treatment cannot be suggested, levothyroxine treatment is controversial. Studies evaluating treatment efficiency are required for these cases (Evidence Level I, Weak 2 +).

• Considering the current literature, guides and expert opinions generally, it is seen that screening all preg-
nant women with TSH in the first trimester is not convenient. Screening with TSH should be carried out for risky cases (Evidence Level 1, Weak 2 +).

- Since maternal oral L-thyroxine intake cannot treat fetal hypothyroidism, it is scientifically not right to say that L-thyroxine treatment of a mother due to any thyroid dysfunction would also treat the possible hypothyroidism in fetus (Evidence Level A, Medium 1 +++).

IV. Pregnancy and Hyperthyroidism

While overt hyperthyroidism has many reasons, it is mostly occur associated with Graves’ disease during pregnancy (0.1–1%).[135] Hyperthyroidism during pregnancy may cause abortion of mother, hypertension associated with pregnancy, preterm labor, anemia, arrhythmias and coronary failure in more advanced cases and thyroid crisis. In term of fetus, intrauterine growth retardation, stillbirth and prematurity are possible undesired problems. The diagnosis is established when TSH and free T4 level over 95th percentile or when total T4 level exceeds upper limit which is considered to be 1.5 times of normal value.[135,136] In addition, it should be remembered that low TSH level in the first trimester of normal pregnancy is an expected finding. Small doses of propylthiouracil (PTU) are preferred in the treatment. The purpose is to keep patient in mild hyperthyroid condition. Although it does not cause any certain contraindication, methimazole (MMI) is not used much during pregnancy since it passes through placenta easily and its reported maternal and fetal side effect profile.[8,137]

Hyperthyroidism during pregnancy is the hyperthyroidism which is seen more common than Graves’ disease and associated with hCG.[138] Hyperthyroidism associated with hCG courses slighter than Graves’ disease. While the incidence of Graves’ disease during pregnancy is 0.1–1%, the incidence of hyperthyroidism associated with hCG is 1–3%.[139,140] Hyperthyroidism associated with hCG is seen temporarily in the first half of pregnancy. Gestational temporary thyrotoxicosis, hyperemesis gravidarum, trophoblastic hyperthyroidism, familial gestational hyperthyroidism and multiple pregnancies are among its reasons.[141-146] When serum hCG concentration peaks in the 10–12 weeks of gestation, total serum T4 and T3 concentrations also increase, free values do not change much, but serum TSH decreases. This temporary and usually subclinical hyperthyroidism should be evaluated as a normal physiological finding.[14] In the following weeks, together with the decrease of hCG, serum free T3 and T4 levels also decrease and TSH concentration returns to normal ranges. If TSH is low and free T4 and T3 levels are within normal ranges in the following weeks (also persisting after first 12 weeks), subclinical hyperthyroidism diagnosis is established. One of the most common conditions is “hyperemesis gravidarum”. In hyperemesis gravidum, free T4 level can be found increased in about 30–60% of these pregnant women in addition to TSH suppressed physiologically in the first trimester. What should be done here is to do differential diagnosis with Graves’ disease by checking TSH receptor stimulating antibodies. In the hyperemesis gravidarum condition, TSH receptor stimulating antibodies are negative and no hyperthyroidism finding occur in these patients, and free T4 values return to normal at 15–18 weeks of gestation without any treatment. In case of Graves’ disease, the levels of TSH receptor stimulating antibodies should be identified especially in the third trimester, and it should be prepared against hyperthyroidism risk of newborn.[14]

**How subclincal hyperthyroidism diagnosis is established in the pregnancy? What impacts does it have on gestational outcomes?**

Subclinical hyperthyroidism is defined as the low serum TSH levels below reference values while serum fT4 and fT3 levels are within reference values.[147]

With third generation TSH kits, levels as low as 0.01 – 0.02 mIU/L can be detected. Subclinical hyperthyroidism is evaluated in two categories: subclinical hyperthyroidism proceeding with detectable low TSH levels (0.1–0.4 mIU/L) and subclinical hyperthyroidism proceeding with suppressed TSH levels (<0.1 mIU/L).[147]

In studies analyzing the prevalence of subclinical hyperthyroidism, different rates were reported according to the threshold value of TSH. In a study carried out in the USA, the prevalence was found as 0.7% when TSH value was considered below 0.1 mIU/L, and as 3.2% when TSH value was considered below 0.4 mIU/L.[148] While subclinical hyperthyroidism may be associated with endogenous reasons such as Graves’ disease, toxic adenoma, toxic multinodular goiter, it may also be associated with exogenous reasons such as iodine insufficiency or high dose administration of thy-
In the literature, unlike the findings of overt hyperthyroidism, it was not shown that subclinical hyperthyroidism is associated with poor gestational outcomes. Ohashi et al. screened thyroid dysfunctions in 392 risk pregnant women, and found a total of 26 subclinical hyperthyroidism cases. As a result, they highlighted that gestational complications such as IUGR (intrauterine growth retardation), diabetes mellitus, hypertension, intrauterine fetal death and ablatio placentae are more associated with hypothyroidism than hyperthyroidism. In their study, Wilson et al. showed that subclinical hyperthyroidism had no impact on gestational hypertension compared to subclinical hypothyroidism. Bunevicius et al. reported that subclinical hyperthyroidism is associated with late gestational depression.

The widest study carried out for subclinical hyperthyroidism frequency in pregnant women was done by Casey et al. In their study, they performed TSH screening on 25,765 women and established subclinical hyperthyroidism diagnosis to 433 (1.7%) pregnant women. The subclinical hyperthyroidism diagnosis was established by identifying TSH levels as $\leq 2.5$ percentile and free T4 levels as $\leq 1.75$ ng/ml.

When impacts of subclinical hyperthyroidism on gestational outcomes researched, it was found that gestational hypertension problem was seen less in women with subclinical hyperthyroidism (adjusted OR=0.66, 95% CI 0.44–0.98; p=0.04), and no significant difference was observed in terms of severe preeclampsia, diabetes, ablatio placenta, preterm labor and delivery by cesarean.

Similarly, it was stated that subclinical hyperthyroidism did not increase the rates of low birth weight, hospitalization to intense care unit, low Apgar score, respiratory distress syndrome, necrotizing enterocolitis, intraventricular hemorrhage, major malformations, fetal/neonatal death and perinatal mortality. According to the results of this study, the authors highlighted that it is not required to treat subclinical hyperthyroidism with antithyroid drugs and even such drugs can be harmful since they cause suppression in fetal thyroid gland due to transition through transplacental fetus.

**In Summary**

- Hyperthyroidism treatment should be initiated in women with symptomatic and/or medium or advanced hyperthyroidism associated with Graves’ disease or gestational trophoblastic disease (*Evidence Level A, Good 1++*).
- hCG-dependent hyperthyroidism (gestational temporary thyrotoxicosis) is temporary and does not require treatment. Similarly, treatment is not required in women with thyroid hyperfunction associated with hyperemesis gravidarum because it usually courses slightly and the symptoms regress together with the decrease in hCG production (at 14–18 weeks of gestation). In severe hyperemesis cases, hospitalization and supportive treatments such as treatment of dehydration with parenteral fluids may be required (*Evidence Level A, Good 1++*).
- Pregnant women with subclinical hyperthyroidism (decreased TSH, normal or minimal increased trimester specific fT4) and medium level asymptomatic hyperthyroidism associated with Graves’ disease can be followed up without treatment. In the follow-up of these women, it is recommended measuring TSH, fT4 and/or total T4 or total T3 in the serum once in every 4–6 weeks (*Evidence Level A, Medium ++*).
- There is no evidence showing that subclinical hyperthyroidism treatment has positive impact on the pregnancy progress, and it should be remembered that the treatment may have potential side effects on fetus (*Evidence Level I, Weak +*).

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