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Impact of Subclinical Hypothyroidism on Pregnancy and Newborn

Subklinik Hipotiroidinin Gebelik ve Yenidoğan Üzerine Etkisi

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ABSTRACT

Objective: *The normal free T4 level together with a high TSH level is called subclinical hypothyroidism. In this study, we investigated cases of subclinical hypothyroidism diagnosed in the first trimester for possible adverse effects. The study aims to show the pregnancy outcomes and neonatal effects.*

Material and Methods: *The study we planned was conducted retrospectively as a record study based on diagnoses. Three hospitals; one city and two state hospitals, were included in our study. Pregnant women treated at these centers between 2019 and 2021 were included the screening of newborns was similarly performed by our pediatric colleagues, based on the diagnosis in the form of scanning the files.*

Results: *It became statistically significant when prematurity (p: 0.005), fetal weight, and week of birth were evaluated. The T4 values of the pregnant women who taken part in the study were normal, and their TSH values were ≥ 2.5-4 mIU/L. The evaluation showed that preterm birth was statistically higher and fetal weight and week of birth were significantly lower.*

Conclusions: *In the study of pregnant women diagnosed with subclinical hypothyroidism, it was found that the preterm delivery rate was higher than in the control group, and the delivery week was also lower than in the control group.*

ÖZET

Amaç: Y*üksek TSH düzeyi ile birlikte normal serbest T4 düzeyine subklinik hipotiroidizm denir. Bu çalışmada olası yan etkiler açısından ilk trimesterde teşhis edilen subklinik hipotiroidi vakalarını araştırdık. Çalışma, gebelik sonuçlarını ve yenidoğan etkilerini göstermeyi amaçlamaktadır.*

Gereç ve Yöntem: *Planladığımız çalışma tanılara dayalı olarak retrospektif olarak kayıt çalışması şeklinde yürütülmüştür. Üç hastane; bir şehir ve iki devlet hastanesi çalışmamıza dahil edildi. 2019-2021 yılları arasında bu merkezlerde tedavi gören gebeler dahil edilmiş, yenidoğan taramaları benzer şekilde pediatrik meslektaşlarımız tarafından dosyaların taranması şeklinde tanıya dayalı olarak yapılmıştır.*

Bulgular: *Prematürite (p: 0,005), fetal ağırlık ve doğum haftası değerlendirildiğinde istatistiksel olarak anlamlı hale geldi. Çalışmaya katılan gebelerin T4 değerleri normal, TSH değerleri ≥ 2.5-4 mIU/L idi. Değerlendirme, erken doğumun istatistiksel olarak daha yüksek olduğunu ve fetal ağırlığın ve doğum haftasının önemli ölçüde daha düşük olduğunu gösterdi.*

Sonuç: *Subklinik hipotiroidi tanısı alan gebelerde yapılan çalışmada erken doğum oranının kontrol grubuna göre daha yüksek olduğu ve doğum haftasının da kontrol grubuna göre daha düşük olduğu bulundu.*

Keywords:
Pregnancy
Subclinical hypothyroidism
Newborn

Anahtar Kelimeler:
Gebelik
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Yenidoğan

INTRODUCTION

Thyroid disorders are one of the most common problems in pregnancy, with the incidence increasing up to four percent during pregnancy (1). During pregnancy, thyroid functions may decrease and lead to hypothyroidism or may increase and lead to hyperthyroidism (2). Apart from this, it can also occur in the form of subclinical hypothyroidism, which is our research topic. The condition in which TSH is above 10 mIU/L and free T4 is lower than expected is called hypothyroidism (3). In contrast to this situation, high TSH values in subclinical hypothyroidism are accompanied by typical free T4 values (4). Iodine deficiency affects the size of the thyroid gland. In regions where iodine deficiency is not seen, the size of the gland is smaller than in the areas with iodine deficiency (2-4). The iodine passed from the mother to the baby plays a significant role. It is known to be mainly responsible for fetal growth and fetal neural development in the early stages of pregnancy (5). The main reason this is so important is that the developing fetus does not have the maturity to produce its free T4 (3, 4). The only source of free T4 is the mother. It is essential in the initial stages of pregnancy for proper neural development and the well-being of the child (6). This importance continues unabated in the later stages of pregnancy and plays a vital role in the smooth completion of neuronal migration (7). The thyroid

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gland, which must cope with the physiological changes of the mother during pregnancy, also gains importance by working for the fetus that is not yet born (8). From the second month of pregnancy, the level of thyroxine-binding globin reaches about twice the average level due to the high amount of estrogen. It should be remembered that an elevated level of HCG during pregnancy has an effect like that of thyroid hormone. In the first trimester of pregnancy, there is a transient increase in free T4 levels and a decrease in TSH levels (9). While free T4 levels decrease in the next period, TSH increases toward normal levels with this decrease (10). These variable values change as pregnancy progresses. The American Thyroid Association (ATA), which aims to set up a standard for these variable values, has agreed on the values that can be used as reference values for each trimester (11). According to the results of this consensus, values of 0.1-2.5 mIU/L in the first trimester can be used as normal limits; 0.2-3.0 mIU/L in the second trimester; and 0.3-3.5 mIU/L in the third trimester (12). Although many studies on this topic have had controversial results, the National Academy of Clinical Biochemistry (NACB) recommends the range between the 2.5 and 97.5 percentile within normal limits (13). ATA updated its recommendations in the literature and suggested the use of a value of 4.0 mIU/L as an upper limit in cases where there is no TSH value that we can rely on before pregnancy (12). There are many studies linking thyroid problems in the mother to pregnancy complications. Normally, existing hypothyroidism should be treated and there is consensus on this (12). In contrast, however, there is no consensus on our subject, subclinical hypothyroidism. Our motivation to conduct this study stems from the fact that we think we can contribute to the literature. Our study aimed to evaluate the presence of an association with possible complications by comparing pregnant women with subclinical hypothyroidism, whom we examined in the first trimester, with a control group.

MATERIAL AND METHODS

The study we planned was conducted retrospectively as a file study based on diagnoses. Three hospitals, one urban and two state hospitals were included in our study. Pregnant women treated at these centers between 2019 and 2021 were included. Newborn screening was similarly performed by our pediatric colleagues, based on diagnosis retrospectively. If the patient remembered the last menstruation, the gestational age was decided from this date; if this information was not available, it was decided by ultrasound at the twentieth week (14). In the medical history of all patients, information such as the number of births, the number of pregnancies, and the number of live births was added to the sources we used for statistics. Written informed consent was obtained from all patients. Information such as chronic diseases, family history, substance abuse, smoking, and alcohol consumption was recorded in the data we used. Based on these medical histories, mothers with thyroid disease before pregnancy were not included in our study. To obtain more efficient results, blood tests were performed in the fasting state (15). In these examinations, TSH and free T4 levels were checked. Our control group consisted of pregnant women with normal TSH and T4 levels. Another group consisted of pregnant women with normal free T4 and TSH values of ≥ 2.5-4 mIU/L; pregnant women with TSH values ≥ 4-10 mIU/L formed another group (16). 669 pregnant women took part in our study. The birth modes of these pregnant women, weights, and demographic characteristics of the babies were recorded. In addition, weight characteristics such as LGA, SGA, and neonatal complications were also recorded by our pediatric colleagues. In the maternal part of the data, our colleagues from obstetrics recorded many variables from adequate amniotic fluid to premature rupture of membranes. The principles of the Declaration of Helsinki were followed in this study. This study was approved by the University of Afyon, Medical Faculty Clinical/Human Research Ethics Committee with the date 10.12.2021 and decision number 119. Input errors were checked and corrected before analysis. The Mann-Whitney u test and chi-square tests were used for comparisons. The 26th version of the spss software was used for analysis. Calculations with p values less than 0.05 were considered statistically significant.

RESULTS

Our pregnant women were divided into 3 groups based on their free T4 and TSH values. The first group was the control group consisting of healthy pregnant women, the second and third groups were formed according to their TSH values (Table 1). While our patients in the second group had TSH ≥ 2.5-4 mIU/L, the patients in our third

Table 1: Obstretric results

	Control Group (n/%)	Group 2 (n/%)	Group 3 (n/%)	p(G2)*	p(G3)*
PRETERM	63/ 9.48%	23/18.16 %	3/12.14%	0.005	0.868
NICU	21/3.98%	2/3.99%	1/1.02%	0.962	0.366
PROM	40/7.2%	7/7.32%	1/7.11%	0.946	0.921
PPROM	5/1.96%	1/0.63%	1/0.92%	0.321	0.473
LBW	36/5.8%	9/7.87%	1/1.47%	0.342	0.165
SGA	24/4.96%	6/5.47%	2/4.22%	0.421	0.403
LGA	67/9.78%	11/8.27%	8/13.71%	0.096	0.503

chi-square tests, NICU: Neonatal Intensive Care Unit, PROM: Premature Rupture of Membranes, PPROM: Preterm Premature Rupture of Membranes, LBW: Low Birth Weight, SGA: Small for Gestational Age, LGA: Large for gestational age*
Control group: Free T4 normal,TSH normal,
Group 2: Free T4 normal,TSH ≥ 2.5-4 mIU/L,
Group 3:Free T4 normal, TSH ≥ 4-10 mIU/L

and final group were selected from patients with TSH ≥ 4-10 mIU/L. When the first and second groups were compared, there was no difference between the frequency of cesarean sections and the demographic data. When the first group, which is also the control group, and the third group were compared, no difference was found in the same variables. However, when we included birth weights in the comparison between group 2 and the control group, it was found that the mean values for fetal weight were statistically significantly lower in our group. Significant results were seen when comparing the control group and the second patient group in terms of the frequency of preterm births (p = 0.005).

DISCUSSION

If we must define it, subclinical hypothyroidism is a condition in which normal free T4 levels are accompanied by elevated TSH levels (11, 12). Definitions of the association between hypothyroidism and poor pregnancy outcomes exist in the literature, but absolute conclusions about subclinical hypothyroidism have not been drawn (17). We felt it right to divide our pregnant women with subclinical hypothyroidism into two groups based on their TSH levels, as this may lead to clearer and more detailed results. As a result of our evaluation, we found that the rate of preterm birth was higher in pregnant women who belonged to the group with TSH levels between 2.5-4 mIU/L. At the same time, it was found that the fetal birth weight was significantly low, and the week of birth was statistically low. Several studies have commented on the benefit of thyroid testing before pregnancy (18). However, there are studies believe that it should be done and those that say the opposite (17, 18). Some of the studies advocate that it should be before pregnancy, while others claim that it should only be in pregnant women who are considered in a high-risk group (17, 18). However, most studies point to the first trimester as the most recommended time for screening in high-risk pregnancies (19). In our study, we performed thyroid function tests in the first trimester at an average of nine weeks. When utilizing a threshold of above 2.5 mIU/L in our research, the occurrence of subclinical hypothyroidism was recorded at 21%. However, when the TSH level was raised to 4 mIU/L, the incidence dropped to 6%. If we ask ourselves why we have higher rates compared to other studies, we can count that our centers included in the studies are second and third-tier hospitals, where the number of patient applications is high. One of the reasons why it is not easy to clearly define the right TSH ranges could be that the values are influenced by the ethnicity of the patient and the geographic region in which she lives (20). In a study from India, the authors used the 5th to 95th percentile as the normal reference range (21). In a similar study, they extended the normal reference range from 5 to 95%.The normal range for TSH in early pregnancy is 5.0-6.0 mIU/L. However, different studies reach different conclusions. In India, the authors accept a TSH value of 3.0 mIU/L for subclinical hypothyroidism instead of 4.0 mIU/L as in the revised guidelines from ATA 2017 (22). In a similar study, the risks of prom, low birth weight, and pregnancy-related hypertension were higher in patients with subclinical hypothyroidism (23). There was no significant difference in the incidence of pregnancy loss or complications such as gestational diabetes, and placenta previa (24). Neurodevelopmental, cognitive, and intellectual outcomes were worse in children of pregnant women with subclinical hypothyroidism compared with the control group (25). On the other hand, no significant difference was found in subclinical hypothyroidism and preterm birth in different studies (26). In our study, the level of preterm birth rate was found to be statistically significant. (p: 0.05). In the group with TSH values of 4-10 mIU/L, the risk of preterm birth was not statistically significant. In another study, the risk of severe preeclampsia was found to be increased in pregnant women diagnosed with subclinical hypothyroidism (27). However, in our study, there was no statistically significant increase in the incidence of preeclampsia or detachment. Bein M et al. In their study, no significant difference was found in the subclinical hypothyroidism group when babies with SGA were compared with the control group (7). Although the rate of babies with SGA was higher in our study than in the control group, it was not statistically significant.Chen J et al. state that there is no association between subclinical hypothyroidism and adverse neonatal outcomes (23). According to another study, although there is an association between gestational diabetes and hypothyroidism, there is no similar association between subclinical hypothyroidism and hypothyroidism (28). In our study, there was no increase in gestational diabetes when comparing the 2nd and 3rd groups with the control group. Fetal loss is seen only in untreated cases of hypothyroidism (28). Because the TSH values of the followed-up patients with subclinical hypothyroidism did not reach high values as in hypothyroidism, no increase in mortality was seen. In contrast to our results, Maraka S et al reported in their study that mortality was also high in patients with subclinical hypothyroidism (4).

CONCLUSION

As a result of statistical analysis performed on pregnant women diagnosed with subclinical hypothyroidism and TSH levels between 2.5-4 mIU/L, it was found that the rate of preterm birth was high, while the rate of fetal weight and preterm birth was low. Only checking the thyroid functions of pregnant women, whom we have classified as substantial risk, will lead to an increase in the number of overlooked patients and complications. Studies in larger groups may help to find consensus on studies that stand for different opinions.

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