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The impact of hypothyroidism and levothyroxine treatment on preeclampsia risk: unraveling the connection for improved maternal and neonatal outcomes

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ABSTRACT

Aims: Preeclampsia, a pregnancy-related complication, may develop in women with hypothyroidism. Possible risk factors may include comorbidities, predisposition to diabetes, obesity, advanced maternal age, and prior infertility treatments. The study aims to investigate the relationship between hypothyroidism and the risk of preeclampsia in pregnant women receiving levothyroxine by examining its application period.

Methods: This is a retrospective cohort included pregnant women who gave birth between December 2022-April 2023. Women with 110 preeclampsia and those without preeclampsia (152 controls) were identified and compared in terms of hypothyroidism status, type of hypothyroidism, and levothyroxine treatment.

Results: The results showed a significant association between the severity of the preeclampsia and its onset that early onset cases were more likely to be severe, while late onset cases were predominantly mild ($p<0.001$). The results showed no association between the onset of the preeclampsia and the starting treatment period ($p=0.372$). In the binary logistic regression, only one variable, "Apgar 5th minute" was significant in the logistic regression analysis ($p=0.032$). The coefficient indicates that as the "Apgar 5th minute" score increases, "during pregnancy" decrease by a factor of 0.603 (ODDs ratio; ranged from 0.380 to 0.957).

Conclusion: There was a difference in the distribution of mild and severe preeclampsia between

the euthyroid and hypothyroidism. Early threating hypothyroid with Levothyroxine might affect the Apgar score.

Keywords: Hypothyroidism, levothyroxine, preeclampsia, Apgar

INTRODUCTION

Thyroid disorders, particularly hypothyroidism, are common endocrine disturbances in women of reproductive age and pregnant women.[1] Overt hypothyroidism, subclinical hypothyroidism, isolated maternal hypothyroxinemia, and the presence of antithyroid antibodies in euthyroid patients are various manifestations of thyroid dysfunction.[2,3] Subclinical hypothyroidism is observed in 3-5% of pregnant women, whereas hypothyroidism occurs in 0.3-1% of the population.[4,5]

Hypothyroidism during pregnancy is associated with an increased risk of early and late obstetric complications, such as anemia, spontaneous abortion, congestive heart failure, preeclampsia, postpartum hemorrhage, placental abnormalities, and gestational hypertension in the mother.[6-8] Adverse neonatal outcomes, including low birth weight, premature birth, stillbirth, and neonatal respiratory distress, may also occur.9 The effects of subclinical hypothyroidism on pregnancy are not as well-defined as those of overt hypothyroidism Nonetheless, treatment of subclinical hypothyroidism during pregnancy is recommended to minimize obstetric complications.[10]

Preeclampsia, a pregnancy-related complication, may develop in women with hypothyroidism.[10,11] Severe preeclampsia are often associated with significant organ damage, as well as increased neonatal morbidity and mortality.[12] Despite previous studies indicating a higher risk of preeclampsia in pregnant women with thyroid disorders (mainly hypothyroidism), little is known about the specific risk factors that contribute to this increased risk.[13] Possible risk factors may include comorbidities, predisposition to diabetes, obesity, advanced maternal age, and prior infertility treatments.[14,15]

In this study, we aim to investigate the relationship between hypothyroidism and the risk of preeclampsia

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in pregnant women receiving levothyroxine. We will examine the presence and application period of levothyroxine treatment in women with preeclampsia and those without control group in a retrospective cohort.

METHODS

Ethical Statement

The study was carried out with the permission of Ankara Etlik City Hospital No:1 Clinical Researches Ethics Committee (Date: 13.06.2023, Decision No: AEŞH-EK1-2023-246). The study was conducted in accordance with the principles of the Declaration of Helsinki and Clinical Practice guidelines. All eligible participants were provided with an information sheet explaining the study's objectives, procedures, potential risks, and benefits. Oral informed consent was obtained from each participant before enrolling them in the study.

Study Design

This was a retrospective cohort conducted at the population that included pregnant women who gave birth between December 2022-April 2023. Women with 110 preeclampsia and those without preeclampsia (152 controls) were identified and compared in terms of hypothyroidism status, type of hypothyroidism, and levothyroxine treatment.

Enrolled Participants

The control group consists of 152 euthyroid preeclampsia patients who were monitored at our clinic due to preeclampsia and subsequently gave birth at similar gestational weeks. The case group, on the other hand, is comprised of preeclampsia patients who were treated with levothyroxine due to subclinical and overt hypothyroidism, and who were also monitored and gave birth at our clinic due to preeclampsia. Based on a comprehensive literature review, we established specific inclusion and exclusion criteria for this study to ensure a well-defined study population and minimize potential confounding factors. Pregnant women who gave birth at the Hospital between January 2016-December 2020 were included if they had singleton pregnancies and complete medical records, including data on key variables. Additionally, they needed to have a confirmed diagnosis of preeclampsia or no preeclampsia (controls) according to the American College of Obstetricians and Gynecologists criteria. Exclusion criteria were designed to eliminate potential biases and confounders. We excluded women with multiple pregnancies, a history of thyroidectomy or radioiodine, other known thyroid disorders, or pregnancies complicated by fetal anomalies or chromosomal abnormalities. Women with incomplete medical records or missing data on key variables, as well as those with a history of chronic hypertension or renal disease, were also excluded from the study.

Definitions of Preterm Delivery

Births between >34 and <37 weeks were classified as late preterm birth, which constitute approximately 90% of such cases. Births before 34 weeks were termed early preterm birth, comprising about 10% of cases. These early preterm births pose an increased risk due to the presence of significant maternal and/or perinatal morbidity or the relatively early gestational age at birth. The most commonly observed subtypes are early-onset (<34 weeks of gestation) and late-onset (≥34 weeks of gestation) preeclampsia.

Diagnostic Criteria of Thyroid & Data Collection

Hypothyroidism was defined as a TSH level >4.2 mU/l and a free T4 level <11 μmol/l, while subclinical hypothyroidism was defined as a TSH level >2.5 mU/l in the first trimester and a TSH level >M mU/l in the second and third trimesters with normal free T4 levels. Data were collected from the electronic medical records of the hospital. The following information was extracted for each participant: maternal age, body mass index (BMI) before pregnancy, parity, gestational age at delivery, hypothyroidism status, type of hypothyroidism (overt or subclinical), levothyroxine treatment status, and levothyroxine dosage. Additional data on comorbidities, such as diabetes, hypertension, and medical conditions were collected.

Laboratory Method

Blood samples were collected from each participant during routine prenatal visits in the first, second, and third trimesters. Samples were collected in serum separator tubes and centrifuged at 3000 rpm for 10 minutes. The serum was then aliquoted and stored at -80°C until analysis. Serum levels of thyroid-stimulating hormone (TSH), free thyroxine (fT4), and total thyroxine (TT4) were measured using an automated chemiluminescent immunoassay system according to the manufacturer's instructions. The reference ranges for TSH, fT4, and TT4 were established based on the guidelines provided by the American Thyroid Association. Internal and external quality control measures were implemented throughout the laboratory analysis process. These included the use of assay-specific quality control materials and participation in an external quality assessment scheme.

Statistical Analysis

The collected data were analyzed using IBM-SPSSv24. Descriptive statistics, including means, medians, and percentages, were calculated for the population. The relationship between hypothyroidism status, type of hypothyroidism, levothyroxine treatment, and

preeclampsia risk was assessed using logistic regression models. To determine the association between severity and onset, and to determine the association between the onset of the condition and the starting treatment period, we performed Chi-Square tests. we analyzed efficiency of early and late treatment of hypothyroid by levothyroxine by binary logistic regression. Adjustments were made for potential confounding factors such as maternal age, Abgar score, onset/late delivery, BMI, parity, and comorbidities. The statistical significance was set at $p<0.05$.

RESULTS

Demographics

As given in Table, our results showed no significant differences in age, with euthyroid women having a mean age of 30.6±6.6 years and hypothyroid women having a mean age of 31.9±6.3 years (p=0.108). Similarly, the BMI did not show any significant difference, with euthyroid women having a mean BMI of 32.8±6.3 kg/m² and hypothyroid women having a mean BMI of 33.2±5.5 kg/m² (p=0.523). Gravida, parity, abortions, living children, birth week, weight, and Apgar scores at the 1st and 5th minutes did not show any significant differences between euthyroid and hypothyroid pregnant women. For instance, the mean gravida for both groups were 3, with a range of 1-7 for euthyroid women and 1-6 for hypothyroid women (p=0.416). Parity also did not differ significantly, with a median of 1 (range: 0-5) in euthyroid women and 1 (range: 0-4) in hypothyroid women (p=0.127).

Table. All data comparison of the Euthyroid and Hypothyroidia groups

Variables	Control (n:152)	Hypothyroid (n:110)	P value
Age (years)	30.6±6.6	31.9±6.3	0.108
BMI (kg/m²)	32.8±6.3	33.2±5.5	0.523
FT3 (pg/ml)	4.98±0.74	4.52±0.83	0.001
FT4 (ng/dl)	14.28±2.56	13.34±2.87	0.006
TSH (µIU/ml)	1.57±0.65	4.17±1.91	0.001
Gravida	3 (1-7)	3 (1-6)	0.416
Parity	1 (0-5)	1 (0-4)	0.127
Abortions	1 (0-4)	0 (0-4)	0.550
Living	1 (0-5)	1 (0-4)	0.138
Birth week	35±4	35±3	0.749
Weight (g)	2405±957	2544±901	0.235
Apgar (1st minute)	8.1±1.4	8.2±1.4	0.752
Apgar (5th minute)	9.3±1.2	9.4±1.1	0.402

Abbreviations. BMI: Body Mass Index, FT3: Free Triiodothyronine, FT4: Free Thyroxine, and TSH: Thyroid Stimulating Hormone. The table presents the comparison of the Euthyroid and Hypothyroid Group with their respective means and standard deviations (Mean±SD) or Median (Min-Max). The p-values are provided for each variable to assess the statistical significance of the differences between the two groups.

Crosstab Analysis

As given in Figure 1, the control had 93 individuals (61.2%) with mild preeclampsia and 59 individuals (38.8%) with severe preeclampsia. On the other hand, the hypothyroidism had 76 individuals (69.1%) with mild preeclampsia and 34 individuals (30.9%) with severe preeclampsia that the asymptotic significance (2-sided) was 0.187. Based on this test, we cannot conclude that there is a significant difference in the distribution of mild and severe preeclampsia between the control and hypothyroidism groups. The results showed a significant association between the severity of the preeclampsia and its onset that Early onset cases were more likely to be severe, while late onset cases were predominantly mild ($p<0.001$). The results showed no significant association between the onset of the preeclampsia and the starting treatment period (p=0.372). The distribution of early and late onset cases appears to be independent of when the treatment was initiated (Figure 2 and 3).

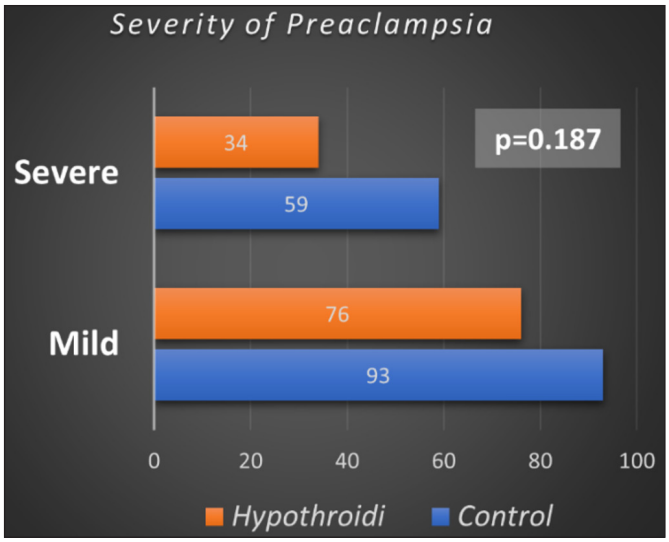

Figure 1. Severity of preeclampsia for hypothyroid or control groups

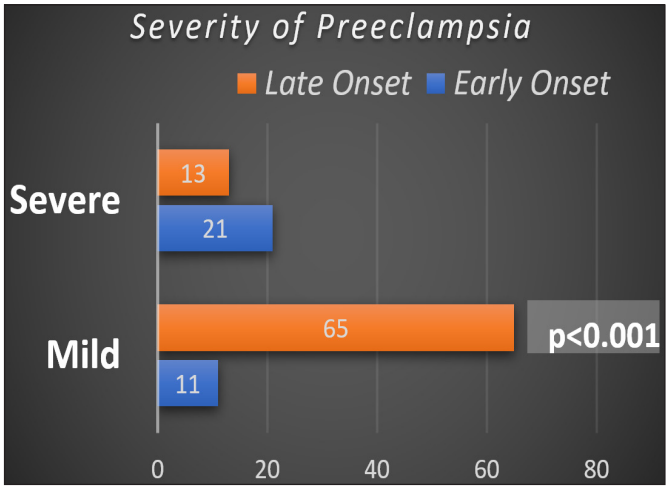

Figure 2. Severity of preeclampsia for early or late onset

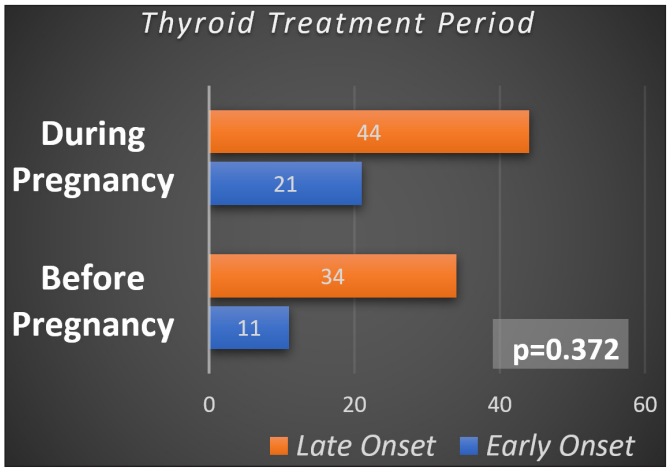

Figure 3. Thyroid Treatment Period of preeclampsia for early or late onset

Logistic Analysis

In the study, we analyzed efficiency of early and late treatment of hypothyroid by levothyroxine by binary logistic regression. The overall model was statistically significant, with an accuracy of 59.1%. Only one variable, "Apgar 5th minute" was significant in the logistic regression analysis (p=0.032). The coefficient indicates that as the "Apgar 5th minute" score increases, the odds of the pregnancy outcome being classified as "during pregnancy" decrease by a factor of 0.603 (ODDs ratio; ranged from 0.380 to 0.957). Several other variables were tested for their association with pregnancy outcomes, but none were significant. These variables included abortus (p=0.584), kilo (p=0.403), Apgar 1st minute (p=0.691), delivery type (p=0.81), gender of baby (p=0.311), delivery time (p=0.366), and severity of preeclampsia (p=0.208).

DISCUSSION

In this study, we investigated the relationship between initialing the hypothyroid treatment period in pregnant women with and without preeclampsia. The distribution of early and late onset cases appears to be independent of when the treatment was initiated. Our findings contribute to the growing body of evidence on the role of thyroid function in the development of obstetric complications, particularly in the context of levothyroxine therapy.

Hypothyroidism during pregnancy is associated with an increased risk of early and late obstetric complications, such preeclampsia and placental abnormalities. A recent meta-analysis by Li et al.[16] reported an increased risk of preeclampsia in pregnant women with hypothyroidism, while also highlighting that levothyroxine treatment may reduce this risk. Likewise, Zhang et al.[17] demonstrated that levothyroxine therapy in pregnant women with subclinical hypothyroidism was associated with a lower incidence of preeclampsia and other adverse pregnancy outcomes. Further supporting our findings, Gietka-Czernel et al.[18] reported that pregnant women with subclinical hypothyroidism who received levothyroxine treatment had a lower risk of preeclampsia compared to those who did not receive treatment. Moreover, two different studies demonstrated that appropriate levothyroxine dosage adjustment during pregnancy could significantly reduce the risk of obstetric complications, including preeclampsia.[19,20] According to our result, we cannot conclude that there is a significant difference in the distribution of mild and severe preeclampsia between the control and hypothyroidism groups. In the study, we analyzed efficiency of early and late treatment of hypothyroid by levothyroxine by binary logistic regression that the model was significant, with an accuracy of 59.1%. The coefficient indicates that as the "Apgar 5th minute" score increases, the odds of the pregnancy outcome being classified as "during pregnancy" decrease.

In a comparison with prior studies, the research conducted by Su et al.[21] demonstrated that hypothyroxinemia is only associated with a risk of preeclampsia-eclampsia, particularly escalating the risk in women with persistent hypothyroxinemia in the first half of pregnancy. Even though our study did not find a significant association with the severity of preeclampsia, these results support the relationship between thyroid dysfunction and preeclampsia risk. The study by Wang et al.[22] showcased the significance of thyroid function tests before and during pregnancy, indicating their role in the early diagnosis of hypothyroidism and in reducing the risk of preeclampsia. These findings are consistent with our study's results that early-onset cases are more severe, underscoring the importance of early diagnosis. The research by Maraka et al.[23] proposed that levothyroxine treatment could potentially reduce the risk of preeclampsia in pregnant women with subclinical hypothyroidism and isolated hypothyroxinemia, though this benefit may be limited. Even though our study did not find a significant relationship between the initiation of treatment and the onset of preeclampsia, it suggests that levothyroxine treatment could play an essential role in managing the risk of preeclampsia. In another study, Jiao and co-authors [24] evaluated the impact of thyroid dysfunction on the development of preeclampsia and found a significant association between subclinical hypothyroidism and the risk of preeclampsia. Despite the lack of a significant relationship with the severity of preeclampsia in our study, this research supports the connection between thyroid dysfunction and preeclampsia risk.

In the context of these recent findings, our study adds valuable insights into the complex interplay between thyroid function, levothyroxine treatment, and preeclampsia. However, it is important to acknowledge some limitations in our study. The sample size of the study may not be large enough to achieve sufficient power in statistical analyses, which can limit the generalizability of the study results and make it difficult to detect certain relationships. Measurement errors in continuous variables, such as thyroid hormone levels and other clinical measurements, can affect the accuracy of the analyses and the interpretability of the results. The study may not control for all potential confounding factors, for instance, genetic factors, nutrition, and lifestyle factors can have effects on thyroid dysfunction and preeclampsia risk and may not be fully addressed in this study. Prospective, long-term studies can help to better understand the causal relationships between thyroid dysfunction and preeclampsia.

CONCLUSION

Our study highlights the potential influence of thyroid function and levothyroxine treatment on the risk of abnormal invasive placentation in pregnant women with and without preeclampsia. According to our result, we cannot conclude that there is a difference in the distribution of mild and severe preeclampsia between the control and hypothyroidism. However, early threating hypothyroid with Levothyroxine might affect the Abgar score. Future research should involve larger, prospective studies to further explore the impact of levothyroxine treatment on the risk of preeclampsia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Ankara Etlik City Hospital No:1 Clinical Researches Ethics Committee (Date: 13.06.2023, Decision No: AEŞH-EK1-2023-246).

Informed consent: Written consent was obtained from the patient participating in the study.

Referee Evaluation Process: Externally peer reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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Author Contributions: All the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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