PERINATAL COMPLICATIONS AND THEIR ASSOCIATION WITH MATERNAL HYPOTHYROIDISM

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ABSTRACT Introduction: Hypothyroidism in pregnant patients is more often associated with pregnancy complications. It increases the risk of obesity, diabetes, and hypertensive disorders and impacts the perinatal outcome. In addition, there is a greater risk of congenital hypothyroidism or so-called cretinism, manifested by growth restriction, mental retardation and other neurophysiological defects. Iodine supplementation and proper administration of thyroxine preparations in the first and second trimesters significantly reduce neurological abnormalities. **Purpose:** Evaluation of pregnancies in patients with hypothyroidism and its impact on perinatal complications. **Material and methods:** The patients with hypothyroidism were analyzed from the total deliveries at the University Clinic for Gynecology and Obstetrics in Skopje. Patients are divided into two study groups: study and control groups. The study group includes patients with hypothyroidism. The control group includes patients without hypothyroidism. **Results:** The likelihood of obesity was assessed, and during the third trimester, the likelihood of developing diabetes, gestational hypertension, and preeclampsia as a single risk was compared between the two groups. Patients with hypothyroidism are 3.49 times more likely to have obesity and 5.57 times higher risk of developing diabetes in pregnancy than those without hypothyroidism. The relative risk of developing gestational hypertension is 3.1 and OR 3.22 in patients with hypothyroidism, which is 3.22 times more likely to develop gestational hypertension in this group. Preeclampsia develops in 2 patients (3.33%) with a relative risk of 2.07 and OR 2.11, or 2.11 times higher risk of developing preeclampsia in the hypothyroidism group. **Conclusion:** Early detection of thyroid disorders in a pregnant patient as well as in newborns postpartum allows for proper treatment of both mother and child. At the same time, uncontrolled hypothyroidism leads to adverse pregnancy outcomes and has fetal consequences.

KEYWORDS hypothyroidism, pregnancy, complications, newborn

Introduction

Thyroid diseases in pregnancy are endocrine dysfunctions that are second only to diabetes mellitus and have a significant impact on pregnancy outcomes, the fetus and the newborn [1]. The thyroid gland was first described as an organ by Thomas Warton in the 17th century. Thyroid development is controlled by coordinated activities of the developmental transcription factor TTF-1 (thyroid transcription factor), also known as NKX2A, TTF-2 (known as FKHL15), and PAX-8. Mutual interaction determines thyroid cell development and induces thyroid-specific genes such as thyroglobulin (Tg), thyroid peroxidase (TPO), sodium iodide transporter (aberration-NIS), and thyroid-stimulating hormone (RH) receptor. Mutations in these developmental transcription factors or their target genes cause thyroid agenesis or dysgenesis and lead to the development of congenital hypothyroidism. [2] Etiopathogenesis is due to immune regulatory genes such as the HLA-DR gene, the cytotoxic T lymphocyte-associated protein 4 (CTLA-4) gene, the CD40 gene, and the protein tyrosine phosphatase 22 (PTPN22), and the CD25 gene,

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which have shown an association with autoimmunity. In particular, CTLA-4 has confirmed a major thyroid antibody locus and is the basis of the high thyroid autoantibody values for Graves' disease, Hashimoto's thyroiditis, and postpartum thyroiditis. In these conditions, intrathyroidal fetal microchimeric cells are detected much more frequently than non-autoimmune thyroid diseases.

In pregnancy, plasma iodine levels decrease as a result of fetal iodine utilization as well as increased maternal renal clearance. The recommended daily dose of iodine is 250 micrograms per day, a dose recommended by the WHO. In addition, maternal hypothyroidism also has consequences for the fetus based on the knowledge that maternal thyroid hormones cross the placenta.

In areas of iodine deficiency, pregnancy causes hypothyroxinaemia and thyroid hyperactivity with goitre. If pregnant women do not receive iodine supplementation, their iodine balance becomes negative, with negative repercussions for the mother, foetus and newborn. To prevent congenital hypothyroidism, iodine deficiency should be corrected no later than the third month of pregnancy. [3] In areas where iodine surplus is achieved, the percentage of adverse pregnancy outcomes is lower in patients with hypothyroidism.

It has been found that there is a transient increase in FT4 in the first trimester as an interaction with the circulatory bHCG. It acts as a TSH agonist, with elevated values contributing to the development of gestational transient hyperthyroidism in 0.3% of pregnancies. Both the condition of hyperemesis in pregnancy and mole hydatidosis are associated with hyperthyroidism. [4] In the second and third trimesters, FT4 follows a downward trend. Significant effects on circulating values are achieved by interacting thyroid-stimulating hormone (TSH), estrogen, and the thyroid-binding protein TBG. In areas where iodine deficiency is present, hypothyroidism with a tendency to increase T3 secretion occurs accompanied by an increase in mean TSH and serum thyroglobulin. Thyroid hormone transporter proteins such as TBG increase due to increased hepatic synthesis and reduced degradation due to oligosaccharide modification. [5].

Hypothyroidism is caused by iodine deficiency or chronic thyroiditis, or chronic autoimmune thyroiditis – Hashimoto's thyroiditis, which are the most common causes of hypothyroidism in pregnant women and postpartum women [6]. However, a few cases are caused by hypothalamic dysfunction. Clinical hypothyroidism is present in 0.3 to 0.5%, while subclinical hypothyroidism is present in 2% to 3% of pregnant women.

50 to 60% of pregnant patients have the presence of autoimmune thyroid disease (TPO antibodies, thyroid globulin antibodies). The trimester reference values need to be adjusted for TSH values. [7] Postpartum thyroiditis develops in the first five months in 50% of patients with preconception thyroid antibodies, so their evaluation is important.

Signs and symptoms of hypothyroidism include fatigue, muscle cramps, constipation, cold intolerance, hair loss and more. As the disease progresses, voice changes, weight gain, intellectual retardation, insomnia, myxedema, and coma may occur. In addition, subclinical hypothyroidism is identified with elevated TSH levels in asymptomatic pregnant women.

Hypothyroidism in pregnant patients is more often associated with pregnancy complications. It increases the risk of obesity, diabetes, and hypertensive disorders and impacts perinatal outcomes. In addition, there is a greater risk of congenital hypothyroidism or so-called cretinism, manifested by growth delay, mental retardation and other neurophysiological defects. Iodine supplementation and proper administration of thyroxine preparations in the first and second trimesters significantly reduce neurological abnormalities.

The fetal thyroid cannot produce thyroid hormones on its own until 10-12 weeks of gestation, while the synthesis and secretion of thyroid hormones are under the control of fetal TSH production after 20 weeks of gestation. Because of this, in the first trimester, the fetus is directly dependent on maternal thyroxine, which crosses the placenta in a small amount. 30% of the T4 in the umbilical cord is from the maternal blood at delivery. Newborn screening is necessary. Treatment of the newborn in the first few weeks of life can form normal intelligence and growth. [8].

Hypothyroidism in pregnant women is treated with levothyroxine in an adequate dose prescribed by an endocrinologist. The dose should be adjusted every four weeks until the TSH level stabilizes. The goal is to maintain an optimal TSH level (2 -2.5 mIU/L).

Purpose

Evaluation of pregnancies in patients with hypothyroidism and its impact on pregnancy complications and perinatal outcome.

Material and Methods

The patients with hypothyroidism were analyzed from the total deliveries at the University Clinic for Gynecology and Obstetrics in Skopje (UCOG), from 01.2020 to 11.2020 (retrospective, cohort study of 11 months), where the age was analyzed, and anamnestic data on the mode of conception, comorbidities, complications that occurred during the third trimester and then the mode of delivery, a gestational week at delivery as well as the condition of the newborn and the postpartum mother. The patients were under therapy prescribed by an endocrinologist with their appropriate follow-up protocol. Inclusion criteria are patients with a single pregnancy who have previously been diagnosed with a hypothyroid condition. Exclusive criteria are patients with additional diseases (which require therapy that would reflect on the already prescribed therapy for hypothyroidism). This applies to patients with antipsychotic therapy, patients with rheumatic diseases under corticosteroids and other adjunctive therapy, patients with immunodeficiency diseases, etc. Patients with hyperthyroidism (5 patients) were also excluded from the study. Patients are divided into two study groups: study and control groups. The study group includes patients with hypothyroidism. The control group includes patients without hypothyroidism. Statistical data processing was performed using the relative risk calculation. The OR (odd ratio- exposure is positively related to the disease, and higher exposure leads to the more frequent occurrence of the condition) probability ratio. The individual risk and the cumulative risk of the present complications in hypothyroid patients were evaluated, and a comparison was made with the group of patients without hypothyroidism. Regarding the other parameters, the mean values, the standard deviation and the p test between the groups are taken.

Results

Out of a total of 3291 patients who were admitted and delivered at UCOG, 58 (1.76%) patients were diagnosed with hypothyroidism and belong to the study group, while 60 patients without hypothyroidism are in the control group.

The mean values for the age of the patients were analyzed. In the study group, the patients were between 19 and 39 years old, with a mean value of 30.93 (SD-4.99, 1.73 95% CI [29.20, 32.66]), while in the control group, the age ranged from 16 to 40 years, with a mean value of 28.95 (SD-5.70, 1.98 95% CI [26.97, 30.93]), which does not result in a statistically significant result between groups p> 0.05.

Regarding the anamnestic data on the mode of conception, out of the patients with hypothyroidism, 3 patients or 5.17%, became pregnant with assisted reproduction methods (3 with IVF et ET). On the other hand, the patients became pregnant spontaneously in the control group. Regarding the data on previous abortions, 8 patients (13.79%) had a previously unsuccessful pregnancy in the first trimester in the examined group. On the other hand, 2 (3.33%) patients had an abortion in the control group of patients.

The likelihood of obesity was assessed, and during the third trimester, the likelihood of developing diabetes, gestational hypertension, and preeclampsia as a single risk was compared between the two groups.

In the group of patients with hypothyroidism 9 (15.52%) had obesity. In control 3 (5%) patients had obesity. Therefore, the relative risk is 3.1, and the OR is 3.49, which means that patients with hypothyroidism are 3.49 times more likely to have obesity.

5 patients developed gestational diabetes (8.62%). Therefore, the relative risk of developing diabetes is 5.17, and the OR is 5.57, which means that patients with hypothyroidism have a 5.57 times higher risk of developing diabetes in pregnancy than those without hypothyroidism (1 patient). Regarding hypertensive disorders, 3 patients (5.17%) develop gestational hypertension. The relative risk of developing gestational hypertension is 3.1 and OR 3.22 in patients with hypothyroidism, which is 3.22 times more likely to develop gestational hypertension in this group. On the other hand, preeclampsia develops 2 patients (3.33%) with a relative risk of 2.07 and OR 2.11 or 2.11 times higher risk of developing preeclampsia in the hypothyroidism group.

The cumulative or absolute risk between the three conditions in patients with hypothyroidism is 3.28. The OR is 4.38, four times (4.38) more likely to develop pregnancy complications in patients with initial hypothyroidism.

The mean values of the gestational week of delivery were analyzed. The mean value was 38 gestational weeks in the examined group, ranging from 33 to 41.3 g. (SD-1.96, 0.68 95% CI [37.3, 38.4]). The mean of the control group was 38.1 (32.3 to 42 weeks gestation) (SD-2.09, 0.72 95% CI [37.3, 38.6]) p> 0.05, which does not record a statistically significant result of this parameter compared between groups.

32 (55.17%) patients gave birth by caesarean section versus 26 (44.83%) spontaneously delivered in the study group. In comparison, 29 (48.33%) by caesarean section versus 31 (51.66%) gave birth spontaneously in the control group, which does not result in a statistical significance of p > 0.05. Fetal distress as a reason for immediate termination of pregnancy by caesarean section in the study group occurred in 6 patients (10.34%). In one, there was abruption of the placenta (1.72%). 4 patients (6.66%) had fetal distress intrapartum and emergency caesarean section in the control group. The relative risk is 1.55 and OR 1.62, meaning 1.62 is more common fetal distress in patients with hypothyroidism.

The fetus's condition is shown by mean values of birth weight, length, and Apgar score in the first and fifth minutes. In the study group, the minimum weight was 1790 (one case of IUGR) grams, and the maximum was 4070 grams, the mean body weight was 3116 grams (SD = 506.89, 175.63, 95% CI [2940, 3291]). In the control group, the mean body weight was 3141 grams (between 2190 and 3870 grams (SD = 481.52, 166.84, 95% CI [2974, 3307]) (p> 0.05 which is not a statistically significant result. Regarding the length of the neonates 49.2 cm mean in the examined group, from 40 to 52 cm (SD = 2.26, 0.78, 95% CI [48.5, 50.05]). In the control group, the mean value for the length of the neonates was 49.45 cm (44-53 cm) p> 0.05, which is not a statistically significant result.

The Apgar score in the first minute in neonates in mothers with hypothyroidism was between 5 and 9, and in the fifth minute between 7 and 10, while in the control group, the Apgar score in the first minute was between 6 and 9, and in the fifth minute between 8 and 10. The analysis of fetal TSH showed a result of two neonates with the neonatal hypothyroid condition and in the same prescribed therapy with levothyroxine by a paediatrician. Postpartum thyroiditis developed in 3.45% (2 patients) in the first three months of the postpartum period.

Discussion

The presence of thyroid dysfunction such as hypothyroidism affects the unfavourable outcome of pregnancy, the development of peripartum complications and consequences for the fetus. [9] More frequent abortions, obesity, gestational hypertension, preeclampsia, and gestational diabetes. Cesarean deliveries are more frequent, and intrapartum finding of fetal distress is more frequent. The above results from this study on the absolute risk of developing complications explain that patients with hypothyroidism have four times the risk of developing complications. Genetic predisposition and environmental and endogenous factors contribute to the development of autoimmune thyroid disease. Special attention is paid to the role of HLA genes. A meta-analysis demonstrated evidence for the association of HLA-DR3 HLA-DR4 with Hashimoto's thyroiditis. [10]. Pregnancy as an immune balance of cellular and humoral immunity suppresses the activity of autoantibodies with the help of T regulatory cells. [11]

TSH values> 3.5mIU / L are associated with infertility or early pregnancy loss in the first trimester (missed abortion). The association between maternal hypothyroidism, especially in early pregnancy, and adverse perinatal outcomes. Untreated hypothyroidism with TSH values> 6mIU / L is associated with intrauterine fetal death. Levothyroxine correction improves perinatal outcomes. [12] In this study, 13.79% of patients with hypothyroidism had a miscarriage in the first trimester of pregnancy. Negro et al. [7] reported more frequent fetal death in patients with TSH values between 2.5 and 5 mIU / L in the first trimester. At the same time, there was a twofold increase in recurrent first-trimester pregnancy loss in patients with antibodies present and IVF pregnancy. For example, the upper limit for TSH in non-pregnant patients is 4.5 to 5 mIU / L. Therefore, it should be reduced below 3.5 mIU / L. Pre-conceptual recommended values are 2.5 mIU / L due to the proven risk of miscarriage at values above 3.5 mIU / L. [13].

Diabetes is often associated with other concurrent endocrine disorders. For example, thyroid autoantibodies are more frequent in patients with diabetes than in the normal population. Also, subclinical hypothyroidism is more common in women with diabetes. The results throughout the literature correspond to the above results from this study. In addition, postpartum thy-

roiditis is more common (10 to 25%) in patients with diabetes.

Two patients in this group with hypothyroidism from the study developed postpartum thyroiditis (3.45%). According to Jovanovic and Peterson [14], patients with type 2 diabetes mellitus in pregnancy more often experience an alteration of thyroid function, as well as postpartum (15%) but also a double and triple increase in TSH values according to Gray et al. [15] According to Beach et al., HbA1c levels were significantly higher in the second and third trimesters in patients with autoimmune thyroid antibodies. [16]

This study found that patients with hypothyroidism had a fivefold higher risk (OR 5.57) of developing gestational diabetes. Hypothyroidism clinically presents with several pathogenic vascular effects, including endothelial dysfunction, which is the hallmark of patients with preeclampsia. [17,18]. A Finnish study demonstrated that maternal hypothyroidism is associated with a higher risk of gestational hypertension (OR-1.20), severe preeclampsia (OR-1.38), preterm delivery (OR-1.25), and major congenital anomalies (OR-1.14), and prolonged stay in neonatology unit (OR-23)) [19]. Casey et al. described a correlation between maternal hypothyroidism and obstetric complications in 17,000 patients. There is a two to three times higher risk of developing preterm delivery, placental abruption and preeclampsia [20].

In a study based on data from 6031 pregnant patients, it was confirmed that after diagnosing hypothyroidism preconception and appropriate treatment in patients, there is a risk of developing preeclampsia, but not a significant risk, while in patients with developed hypothyroidism in the third trimester, there is a higher risk for development of preeclampsia [21].

In this group of subjects with hypothyroidism, there was also a double risk of developing preeclampsia while a triple risk of developing gestational hypertension during pregnancy. Although the results of this study in terms of comparison of body weight, height and Apgar scores do not result in statistical significance, it is due to a smaller group of patients examined. There has been one case of intrauterine growth retardation and one with placental abruption. Regarding childbirth, intrapartum fetal distress and caesarean sections are more frequent in patients with hypothyroidism. Two neonates have had hypothyroidism.

From the presented results within the project and the published monograph "Iodine and thyroid status of the population in Macedonia 2018", more specifically from the analysis of the results of the examination of iodine and thyroid status in pregnant women with and without iodine supplementation, conducted interdisciplinary between the University and obstetrics in Skopje and the Institute of Pathophysiology and Nuclear Medicine, indicated a state of safe iodine sufficiency in pregnant women in this study. It could be concluded that the achieved and maintained iodine surplus in our country provides a sufficient substrate for the normal functioning of the thyroid gland in pregnant women, even in those who do not take additional iodine supplementation. On the other hand, iodine supplementation of 150μg / day does not induce thyroid autoimmunity, which would pose a health risk to the mother. [3]

Thyroid dysfunction is important to be recognized and treated during pregnancy to avoid complications. In addition, the mother with hypothyroidism may affect the fetus in the antenatal period or later in life due to the role of maternal antithyroid antibodies. According to the results of this study, two neonates were in the laboratory diagnosed with hypothyroidism. Subclinical conditions in the mother are most common with the presence of thyroid autoantibodies. Therefore, there is a need for all newborns to be examined routinely.

Conclusion

The presence of hypothyroidism in pregnancy is a risk factor for developing complications in pregnancy and a risk factor for possible adverse peripartal outcomes. The impact of hypothyroidism is directly reflected in a number of clinical entities that deserve vigilant monitoring, evaluation, and appropriate treatment. Early detection of thyroid disorders in a pregnant patient and neonatal postpartum allows proper treatment of both mother and child. At the same time, uncontrolled hypothyroidism leads to adverse pregnancy outcomes and has fetal consequences.

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Conflict of interest

There are no conflicts of interest to declare by any of the authors of this study.

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