

Can the pathological conditions of the thyroid gland during pregnancy affect the course and outcome of pregnancy and the parameters of the newborn?

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ABSTRACT

Background: To determine the influence of hypothyroidism and hyperthyroidism on the course, outcome of pregnancy, and parameters of the newborn.

Methods: A cross-sectional epidemiological study was conducted. The study included 319 pregnant women of whom 257 had hypothyroidism and 62 had hyperthyroidism. The main parameter was the pathological conditions of the mother's thyroid gland. Data were collected from the protocol, medical history, and discharge letters. The results of the statistical analysis are expressed in absolute and relative frequencies. The significance of the differences was tested using the χ^2 test.

Main findings: In 2020 and 2021, 3,627 children were born. A total of 318 mothers were included in the research, of whom 257 (80.82%) had hypothyroidism and 61 (19.18%) had hyperthyroidism. Ninety-one newborns (35.4%) of mothers suffering from hypothyroidism and 20 newborns (32.79%) of mothers suffering from hyperthyroidism were transferred to the NICU. No statistically significant difference was found in relation to the influence of hypothyroidism and hypothyroidism on newborn parameters. However, a statistically significant difference was observed in the incidence of pathological conditions during pregnancy. In subjects with hypothyroidism, there was significantly more gestational diabetes (15%) and preeclampsia (3.5%).

Principal conclusion: Thyroid dysfunction in pregnant women did not significantly affect the course and outcome of pregnancy or the parameters of the newborn, including gestational age or anthropometric measurements.

Keywords: TSH Deficiency, Primary Hyperthyroidism, Neonate, Perinatal Care, Complications, Pregnancy

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INTRODUCTION

The thyroid status of the mother is crucial for the development of the fetus, particularly from the 12th to 16th week of pregnancy. Disruptions in the metabolic milieu, caused by thyroid dysfunction can lead to negative outcomes for both the fetus and the mother (1). The negative outcomes for the fetus include impaired neurological and intellectual development, a low birth weight, preterm delivery, neonatal jaundice, a higher risk of developing perinatal infection, an increased risk of miscarriage, an increased risk of preeclampsia and eclampsia, and placental abruption (2).

During gestation and the first two years of postnatal life, thyroid hormones play a crucial role in optimal brain development (3). They are critical for the development of the central nervous system, and an insufficient status of the mother's thyroid gland in the early stages of pregnancy can lead to serious disorders in the neurodevelopment of the fetus, with subsequent consequences on postnatal neurocognitive function (4). Women with thyroid disease are over nine times more likely to have a child with newborn encephalopathy than those without. Certain common symptoms that a newborn with encephalopathy could experience immediately after birth are respiratory problems, a subnormal level of consciousness, depressed reflexes, and seizures. In more severe cases of hypoxic-ischemic encephalopathy (HIE), the symptoms may encompass poor reflexes, including little or no grasping and sucking reflexes, lethargy, muscle weakness, and apnea (brief pauses in breathing) (5). Several studies investigate the relationship between maternal thyroid dysfunction during pregnancy and newborn asphyxia. However, none of the search results directly answer the question of whether maternal thyroid dysfunction during pregnancy causes newborn asphyxia (6).

The available evidence suggests that maternal thyroid dysfunction during pregnancy can have negative effects on fetal growth and

development, leading to low birth weight and preterm delivery. The exact pathophysiology behind this association is not fully understood, but it is thought to be related to the role of thyroid hormones in regulating fetal growth and development (7, 8). A study found that the presence of anti-thyroid peroxidase (anti-TPO) antibodies in euthyroid pregnant women was associated with an increased rate of pregnancy complications, including low birth weight. High maternal free thyroxine (FT4) levels during the first half of pregnancy were related to lower birth weight and an increased risk of SGA (small for gestational age) newborns, suggesting that maternal thyroid function may affect fetal growth, even within the normal range (9, 10). The potential long-term effects of low birth weight and preterm delivery on a child's health can be significant, such as developmental disabilities including cerebral palsy and cognitive impairments, chronic conditions in adulthood, such as obesity and diabetes, neurocognitive impairments including mental retardation, and seizure disorders (11). Preterm and low birth weight babies may experience poor health outcomes, including malnutrition and delayed growth (12), and these children have a higher risk of developing mental health issues, such as depression, anxiety, attention deficit-hyperactivity disorder, and sleep disorders (13).

According to several studies, maternal thyroid dysfunction during pregnancy can cause neonatal jaundice. Factors that can affect the infant's thyroid function include maternal iodine deficiency, exposure to iodine, thyroid diseases (such as Hashimoto's thyroiditis and Graves' disease), and drugs used by the mother, and it has been proven that thyroid dysfunction can affect the liver's ability to process bilirubin, potentially contributing to the development of jaundice (6, 14).

Maternal thyroid dysfunction during pregnancy can affect the newborn's risk of infection indirectly by impacting their overall health and immune system. As we have already mentioned, untreated pathological

thyroid conditions during pregnancy are associated with premature birth and low birth weight, and both factors increase the risk of perinatal infection (15).

All these complications can have long-term effects on the health and development of the child. The goal of our research was to identify pregnant women with thyroid disorders and to assess the unfavorable outcome of pregnancy, that is, to investigate the connection between the pathological conditions of the thyroid gland in the mother and the early outcome of newborns. Therefore, it is important to detect and manage thyroid dysfunction during pregnancy to minimize the risks and ensure a healthy pregnancy outcome.

PARTICIPANTS AND METHODS

Participants

The research was conducted at the Clinic for Gynecology and Obstetrics, as well as at the Clinical Department for Intensive Care and Neonatology at the University Clinical Hospital (UCH) Mostar in the period from January 1, 2020 to December 31, 2021. The study included 319 pregnant women who gave birth at the Clinic for Gynecology and Obstetrics and their newborns, as well as those newborns who were transferred to the Clinical Department for Intensive Care and Neonatology.

Methods

Data from the protocol and the medical history and discharge letters of pregnant women and newborns were used. The main parameter was the pathological conditions of the mother's thyroid gland, primary hypothyroidism, and hyperthyroidism, and all other parameters were considered according to this parameter. In addition, the parameters considered in relation to the mother were: age, parity, type of delivery, method of fertilization, pathological conditions during pregnancy, complications during pregnancy, medication during pregnancy, and whether the mother was treated for thyroid disorders. The parameters

that were considered in the newborns were: anthropometric measurements (birth weight, birth length), sex, gestational age, Apgar index, antibiotic therapy, laboratory parameters (C-reactive protein (CRP), bilirubin, complete blood count (CBC)), and eventual transfer to the Clinical Department for Intensive Care and Neonatology. The birth weight of the newborn was determined with a digital scale manufactured by Momert, model MM6475, immediately after birth, and the progress of the newborn was monitored by daily weighing using the same scale. Birth length was measured with a centimeter tape manufactured by Wintape, model BWT-016. The gestational age was calculated based on the due date and date of delivery of the pregnant woman and was recorded on the transfer list for the child by the Clinic for Gynecology and Obstetrics, found in the medical documentation of each child. The Apgar index is the sum of the values of five criteria that are scored from 0 to 2, and the total value of the index can be from 0 to 10. This was determined in the 1st and 5th minutes. For the biochemical tests in the laboratory, 2 mL of venous blood was taken in a test tube without anticoagulant. The blood sample was taken in a tube with anticoagulant (EDTA), also 2 mL. The concentration of glucose, bilirubin, and CRP was determined from a sample of the liquid part of the blood (serum or plasma) by biochemical testing using different methods (agglutination, ELISA test, rapid immunodiffusion).

During our research, we monitored certain pathological conditions of the newborn. Neonatal jaundice occurs due to the physiologically increased production of bilirubin in newborns, as well as the reduced possibility of excretion due to reduced liver function in the first weeks of life. The increased formation of bilirubin is a consequence of the shorter lifespan of erythrocytes. Pathological jaundice is indicated by the appearance of jaundice within 24 hours of birth when the concentration of bilirubin in the serum exceeds 85 $\mu\text{mol/L}$ per day, and when the

concentration of bilirubin in the serum exceeds 255 $\mu\text{mol/L}$ in a term newborn (16, 17). Neonatal infection is a systemic inflammatory response that occurs due to infection. CRP is an acute-phase reactant that has been studied as a biomarker to diagnose neonatal sepsis (18). Thrombocytopenia is defined as a platelet count less than $150 \times 10^9/\text{L}$ and, in this study, it was present in 4.9% of newborns whose mothers had been diagnosed with hypothyroidism and 4.9% of newborns whose mothers had hyperthyroidism (19). Prematurity refers to a condition whereby a baby is born before completing 37 weeks of gestation (GA). The definition of the National Institutes of Health for moderate preterm infants is 32+0/7 to 33+6/7 weeks GA and for late preterm infants is between 34 and 37 completed weeks GA (34+0/7 to 36+6/7 weeks' GA) (20). Newborn asphyxia refers to a condition whereby a newborn baby does not receive enough oxygen before, during, or after birth. The diagnosis of newborn asphyxia is often based on clinical indicators such as fetal distress, depression at birth, and metabolic acidosis (21). Newborn encephalopathy is a clinically defined condition of abnormal neurological behaviors in the newborn period. It is a crucial link between intrapartum events and permanent neurological problems in the child (22).

Statistical analysis

The results of the statistical analysis are expressed in absolute and relative frequencies. The significance of the differences was tested with the χ^2 test (in the absence of expected frequencies with Fisher's exact test). The results of statistical tests were interpreted at the significance level of 0.05. P values that could not be expressed to three decimal places are presented as $P < 0.001$. A statistical analysis of the collected data was conducted using IBM SPSS Statistics (version 25.0, SPSS Inc, Chicago, Illinois, USA) and Microsoft Excel 2019 (Microsoft Corporation, Redmond, WA, USA).

RESULTS

In 2020 and 2021, a total of 3,627 children were born at the Clinic for Gynecology and Obstetrics at the UCH Mostar. Of the 3,627 children born during that period, 319 mothers, who gave birth between January 1, 2020 and December 31, 2021, had hypothyroidism or hyperthyroidism. Of the 319 pregnant women, 257 (80.82 %) had primary hypothyroidism and 62 (19.18%) had hyperthyroidism. Ninety-one newborns (35.4%) of mothers suffering from hypothyroidism and 20 newborns (32.79%) of mothers suffering from hyperthyroidism were transferred to the Clinical Department for Intensive Care and Neonatology.

Statistically significant differences were found in the number of births and in the treatment of thyroid disorders during pregnancy. Mothers with hypothyroidism had a lower birth rate than those with hyperthyroidism. Most pregnant women were treated with medication. Two hundred and forty-seven (96.1%) pregnant women with hypothyroidism and 55 (88.7%) women with hyperthyroidism were treated with medication. Only one case of surgical treatment of a pregnant woman with hyperthyroidism was recorded. According to research, most pregnancies are not accompanied by complications. In a smaller number of cases, bleeding occurs as a complication, more often in mothers with hypothyroidism. No significant statistical difference was found in other monitored parameters (age of the pregnant woman, type of delivery, method of conception, and abortion), which is shown in Table 1.

We have demonstrated a statistically significant difference in the frequency of pathological conditions during pregnancy in relation to the type of thyroid disorder. There was significantly more gestational diabetes and preeclampsia in subjects with hypothyroidism. Hypertension, infections, and thrombophilia were the most common associated pathologies in pregnant women with hyperthyroidism. Other diseases such as

oligohydramnios, polyhydramnios, BHSB infection, and proteinuria were more common

in pregnant women with hyperthyroidism, which is shown in Figure 1.

Table 1. Differences in the parameters related to maternity as regards thyroid disorders

	Disorders of the thyroid gland				χ^2	p
	Hypothyroidism		Hyperthyroidism			
	n	%	n	%		
Mother's age					1.745	0.644*
<20	1	0.4	1	1.6		
20-29	105	40.9	26	41.9		
30-39	142	55.3	33	53.2		
40+	9	3.5	2	3.2		
Type of birth					1.529	0.466
Vaginal	126	49.0	25	40.3		
Induced labor	59	23.0	17	27.4		
Cesarean section	72	28.0	20	32.3		
Maternal parity					9.022	0.046*
1	109	42.4	19	30.6		
2	80	31.1	31	50.0		
3	50	19.5	7	11.3		
4	17	6.6	5	8.1		
5	1	0.4	0	0.0		
Type of conception					0	1*
Natural	249	96.9	60	96.8		
IVF	8	3.1	2	3.2		
Number of abortions					1.788	0.593*
0	207	80.9	52	83.9		
1	41	16.0	9	14.5		
2	6	2.3	0	0.0		
3	2	0.8	1	1.6		
Complications during pregnancy					2.608	0.379*
No complications	240	93.4	57	91.9		
Bleeding	12	4.7	2	3.2		
Cervical cerclage	2	0.8	1	1.6		
Premature uterine contractions	3	1.2	2	3.2		
Method of treatment of thyroid disorders during pregnancy					6.783	0.022*
Not treated	10	3.9	6	9.7		
Drug treatment	247	96.1	55	88.7		
Operation	0	0.0	1	1.6		

*Fisher's exact test

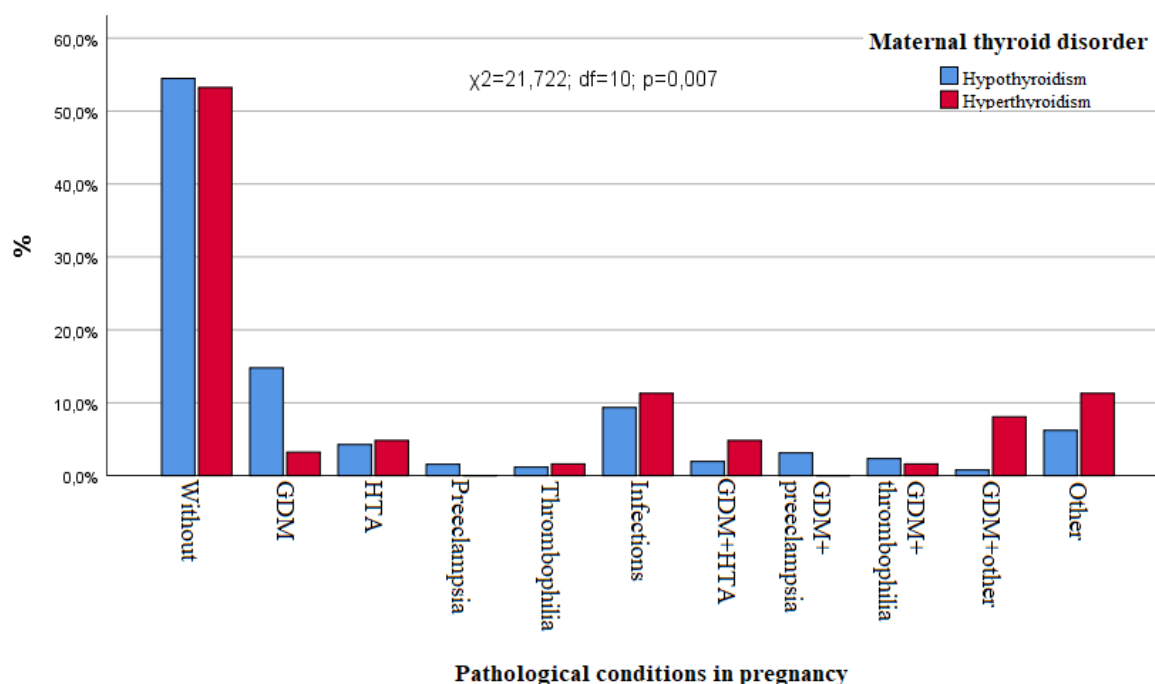


Figure 1. Differences in the occurrence of pathological conditions in pregnancy in relation to thyroid disorders

The results in Table 1 illustrate that there is a significant difference in the parameters of the mothers with respect to parity and spontaneous abortion as regards paternal age. The findings indicate that with older fathers, the parity was 2+, and spontaneous abortions were more frequent among women with older partners. Older fathers often had older partners, which is significant. The results in Table 2 do not show any significant difference between the newborns in relation to paternal age.

There were no statistically significant differences in the parameters related to the newborns concerning maternal thyroid disorders. Most newborns of mothers suffering from hypothyroidism were born between the 37th and 40th week of pregnancy, while 7.4% of newborns of the same mothers were born before the 37th week, which means that they were premature. On the other hand, 4.9% of the newborns of mothers suffering from hyperthyroidism were premature (Table 2).

There is no significant statistical difference in the number of newborns transferred from the Department of Gynecology and Obstetrics to the Clinical Department for Intensive Care and Neonatology in relation to hypothyroidism and hyperthyroidism in the mother, as well as in the parameters related to the method, outcome of treatment, and length of hospitalization of the newborns.

Then, in this research, differences were observed in the parameters related to the laboratory parameters of the newborns as regards the disorders of the mother's thyroid gland. A total of 12.5% of the newborns of mothers with hypothyroidism and 18.0% of the newborns of mothers with hyperthyroidism had elevated CRP values. Furthermore, 10.5% and 9.8% of the newborns of hypothyroid and hyperthyroid mothers had elevated bilirubin levels for their age (16). Thrombocytopenia was present in 4.9% of the newborns of mothers with hypothyroidism and 4.9% of the newborns of mothers with hyperthyroidism.

Table 2. Differences in newborn-related parameters in relation to maternal thyroid disorders

	Disorders of the thyroid gland				χ^2	p
	Hypothyroidism		Hyperthyroidism			
	n	%	n	%		
Sex					0.038	0.735
Male	141	54.9	32	52.5		
Female	116	45.1	29	47.5		
Birth weight (g)					4.055	0.063*
1500-2499	10	3.9	1	1.6		
2500-4199	240	93.4	55	90.2		
4200+	7	2.7	5	8.2		
Birth length (cm)					1.632	0.419*
-48	5	1.9	1	1.6		
48-56	180	70.0	38	62.3		
56+	72	28.0	22	36.1		
Gestational age					1.386	0.713*
-25.9	2	0.8	1	1.6		
26-33.9	3	1.2	0	0.0		
34-36.9	14	5.4	2	3.3		
37-42	238	92.6	58	95.1		
Apgar score (1st minute)					0.257	1*
0-3	4	1.6	1	1.6		
4-7	9	3.5	2	3.3		
8-10	244	94.9	58	95.1		
Apgar score (5th minute)					0.827	1*
0-3	1	0.4	0	0.0		
4-7	4	1.6	0	0.0		
8-10	252	98.1	61	100.0		
Antibiotic therapy					0.002	0.963
Yes	75	29.2	17	27.9		
No	182	70.8	44	72.1		

*Fisher's exact test

There are no significant statistical differences in the occurrence of pathological conditions in the newborns of mothers suffering from hypothyroidism or hyperthyroidism, given the fact that newborn jaundice, perinatal infection, prematurity, and asphyxia are the most common discharge diagnoses among these newborns (Figure 2).

DISCUSSION

The presence of thyroid hormones is very important for the normal course and outcome of pregnancy, as well as for optimal growth

and the development of the fetus. The reported prevalence of thyroid disease in pregnancy varies widely in different studies. These discrepancies are due to differences in criteria for euthyroidism, iodine status, and gestational age at screening. As a result, there is currently no accepted prevalence rate for various thyroid diseases in pregnancy, and this varies from study to study (23). During the research we conducted at the UCH Mostar between 2020 and 2021, 9% of pregnant women had a thyroid disorder, of which 7% had hypothyroidism while 2% had hyperthyroidism.

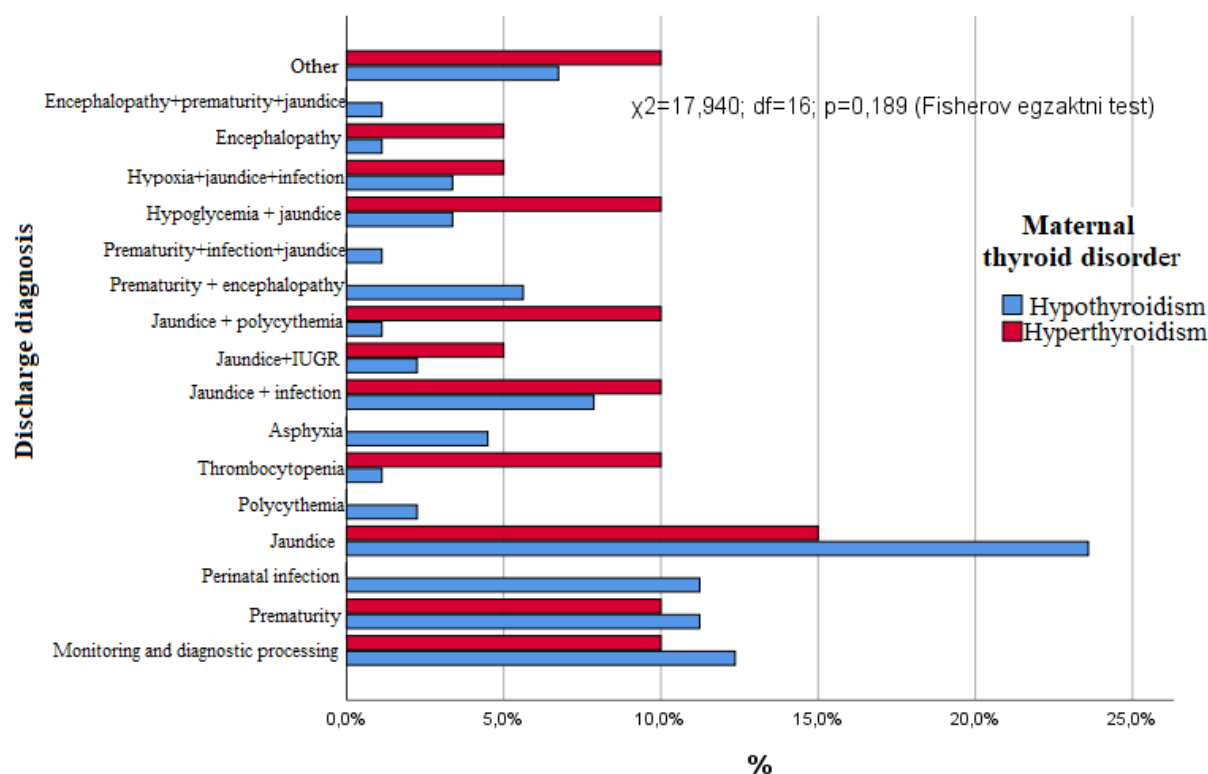


Figure 2. Differences in the incidence of pathological conditions in newborns in relation to thyroid disorders

According to the conducted research, the influence of hypothyroidism and hyperthyroidism on the course and outcome of pregnancy was partially proven, but not in relation to the parameters of newborns as expected.

This research showed that the most frequent occurrence of hypothyroidism and hyperthyroidism was in the age group of 30 to 39 years. The younger and older age groups of pregnant women were also observed, but no significant statistical difference between hypothyroidism and hyperthyroidism itself was shown in this parameter. A study conducted in Iran showed a higher incidence of abortion in pregnant women suffering from some of the thyroid gland disorders and positive antibodies (TPO), around 24.5% (24). On the other hand, in the research we conducted, 19% of pregnant women with hypothyroidism and 10% with hyperthyroidism had one or more abortions, but no significant difference in frequency between the two disorders was shown.

Furthermore, a statistically significant difference in parity was evident. A lower incidence in the number of births was shown in pregnant women with hypothyroidism compared to those with hyperthyroidism, while, according to research conducted in Brazil in 2010, there is no link between parity and thyroid disorders (25). According to the publication of the World Health Organization (WHO), under normal circumstances, the frequency of cesarean births should not exceed 10-15% of all births (4), and the result of this research shows that the frequency of cesarean births in the group of pregnant women with thyroid disorders is two to three times higher than this.

Previous research has shown that pregnant women suffering from hypothyroidism have a higher risk of developing placental abruption, bleeding, and more frequent cesarean sections (26). According to the conducted research, most pregnancies are not accompanied by complications. In a smaller number of cases of mothers with hypothyroidism and mothers

with hyperthyroidism, bleeding occurs as a complication. The guidelines of the American Association for the Diagnosis and Treatment of Thyroid Disease During Pregnancy recommend treating overt hypothyroidism with levothyroxine in most cases. Guidelines for the treatment of hyperthyroidism in pregnancy include only hyperthyroidism, due to Graves' disease (27). Most of the pregnant women in this study were treated with medication. Only one case of surgical treatment of a pregnant woman with hyperthyroidism was recorded.

The most common pathological condition in pregnancy in this study is gestational diabetes. However, there is a statistically significant difference in the incidence of gestational diabetes between thyroid disorders, where the incidence is three to four times higher in pregnant women with hypothyroidism than in pregnant women with hyperthyroidism. Similar results were recorded during research conducted in 2011, whereby the incidence of gestational diabetes in pregnant women with hypothyroidism was 14.3%, and in those with hyperthyroidism, 5.8% (28). The International Diabetes Federation (IDF) states that the worldwide prevalence of gestational diabetes ranges from 1 to 22% (29), which this research also confirms. Infections are the second most common condition among pregnant women with thyroid disorders. Pregnant women with hyperthyroidism exhibited a greater tendency to hypertension, infections, thrombophilia, and other conditions (oligohydramnios, polyhydramnios, BHSB infection, and proteinuria). Contrary to this research, Wilson KL et al. proved that hypertension occurs more often in pregnant women with hypothyroidism than in those with hyperthyroidism. On the other hand, it has been confirmed that pregnant women with hypothyroidism have a higher risk of developing preeclampsia (30), which our research confirmed.

Prematurity is the leading cause of perinatal morbidity and mortality in the United States. Stagnaro-Green A. proves the connection

between hypothyroidism and premature birth in a study conducted in 2009 (8). Although this study did not show a significant statistical difference between hypothyroidism and hyperthyroidism in prematurity, there is a slightly higher incidence of premature babies among mothers with hypothyroidism than in mothers with hyperthyroidism. This research did not show a significant dependence on the pathological conditions of the thyroid gland and the physical characteristics of the newborn (birth length and weight), while most global research connects both hypothyroidism and hyperthyroidism with intrauterine growth retardation (IUGR) and low birth weight (LBW). Moreover, there is no significant difference in the Apgar score at one and five minutes. This result does not coincide with the results of research from 2014, in which there is a significant association between hypothyroidism and hyperthyroidism with a low Apgar score (31).

Furthermore, a third of newborns of mothers with thyroid disorders had an indication for transfer to the Department of Neonatology. There is no significant statistical difference in the number of people transferred in relation to hypothyroidism and hyperthyroidism, or as regards other parameters related to the method and outcome of treatment and length of hospitalization. Worldwide research indicates that newborns are most often hospitalized in the Department of Neonatology under the diagnosis of neonatal infection, asphyxia, neonatal jaundice, and then prematurity (32). During the research conducted at the UCH Mostar, regardless of the thyroid disorder, newborn jaundice, perinatal infection, prematurity, and then asphyxia were the most common.

Moreover, no statistically significant difference was found in the parameters related to laboratory parameters (CRP, bilirubin, leukocytes, platelets) of the newborn in relation to maternal thyroid disorders.

According to research conducted in 2005, thyroid diseases in pregnant women are one of the main risk factors for the development of

neonatal encephalopathy (33). However, in this study, there is no great difference in the incidence of encephalopathy in relation to hypothyroidism and hyperthyroidism.

We consider the small number of samples as limitations of the study. In order to determine the concrete influence of the pathological conditions of the thyroid gland on the selected parameters and their incidence, it would be necessary to conduct research over a longer period and with a larger number of participants. In addition to the pathological conditions of the thyroid gland, other parameters were investigated, i.e., the pathological conditions of the pregnant women, such as gestational diabetes and hypertension. For this reason, it is impossible to fully reveal the influence of only the pathological conditions of the thyroid gland on the parameters of the newborn, since other parameters greatly influence the course and outcome of the pregnancy, as well as the parameters of the newborn.

CONCLUSION

Since pregnant women with hypothyroidism and hyperthyroidism are exposed to numerous complications during pregnancy and childbirth, as well as after the pregnancy itself, detailed monitoring is necessary. Although targeted case finding is generally practiced, it is thought that screening pregnant women may be a better option. In conclusion, a routine examination, early confirmation of the diagnosis, and timely treatment, along with regular follow-ups after delivery are the only options to reduce the frequency of the pathological conditions of the thyroid gland, as well as the numerous consequences for newborns.

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CONFLICT OF INTEREST

The author(s) declare no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

AUTHORS' CONTRIBUTIONS

MJR and AK: contribution to study conception and design, literature review, supervision, writing of the paper, interpretation of data, critical revision of the paper; AP: acquisition of data, contribution to study conception and design, literature review, critical revision of the paper, assistance in writing the paper; LD: acquisition of data, contribution to study conception and design, literature review, assistance in writing the paper.

ETHICAL BACKGROUND

Institutional Review Board statement: The study was conducted according to the guidelines of the Declaration of Helsinki and approved by the Ethics Committee of the University Hospital in Mostar (Reg. No. 1112/22, Mostar, May 23, 2022).

Informed consent statement: Informed consent was obtained from all subjects involved in the study.

Data availability statement: We deny any restrictions on the availability of data, materials, and associated protocols. Derived data supporting the findings of this study are available from the corresponding author on request.

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