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Comparison of fetal cardiac structure in hypothyroid pregnant women receiving thyroid hormone replacement therapy and healthy controls

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Abstract

Objective: Thyroid hormone is required for normal fetal brain development, neuronal proliferation, migration and structural organization. We aimed to investigate fetal cardiac structure in fetuses of hypothyroid pregnant women receiving thyroid hormone replacement therapy and to compare it with normal pregnancies, including fetal outcome and delivery results.

Methods: Singleton pregnant women whose ages were between 18–45 years and weeks of gestation were between 26–34 were included in the study. Their routine laboratory test reports, ultrasonographic measurements (fetal echo) and postnatal follow-up data were recorded. Patients were grouped according to the presence of diagnosis of hypothyroidism. The patients with hypothyroidism during pregnancy were included in Group 1 while healthy pregnancies with similar features were considered as controls and included in Group 2. All women with hypothyroidism were taking thyroid hormone replacement. All ultrasonographic and laboratory data measurements were collected from the system files and were compared between groups.

Results: A total of 89 patients (41 hypothyroidism and 48 controls) were recruited to the study. Serum TSH levels of patients with hypothyroidism (Group 1) was significantly higher than the controls. In fetal cardiac examination, left ventricular (LV) and right ventricular (RV) wall thicknesses, and interventricular septum thicknesses at the end of systole and diastole were not statistically significant in both groups. Apgar scores, fetal gender and mean fetal birth weight were all similar between the groups.

Conclusion: There is no myocardial structural difference in fetuses of pregnant women who were diagnosed with hypothyroidism and received thyroid hormone replacement therapy compared to healthy controls. Thyroid replacement therapy in hypothyroid mothers might affect and treat fetal cardiac abnormalities.

Keywords: Hypothyroidism, fetal cardiac structure, fetal Doppler, end diastolic myocardial thickness, interventricular septum.

Introduction

Thyroid dysfunction is widespread in pregnancy with a morbidity of 2–3%.[1] Hypothyroidism, including overt and subclinic types, is the big part of thyroid dysfunction. Overt hypothyroidism in pregnancy, similar to non-pregnant patients, is defined as elevated thyrotropin (TSH) levels and reduced free thyroxine (fT4) levels in serum.[2] These altered serum laboratory results accompanied by clinical symptoms including fatigue, cold intolerance, constipation and weight gain lead to diagnose hypothyroidism during pregnancy.[2] Anovulation and first trimester spontaneous abortions are associated with hypothyroidism.[3,4] Some studies have reported that

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preterm delivery, low birth weight, preeclampsia and gestational hypertension, placental abruption, and postpartum hemorrhage have increased in hypothyroidism identified during pregnancy compared to euthyroid women.[4–7] Due to conflicting results in relation to adverse perinatal outcomes of positive serum anti-thyroid peroxidase (TPO) antibodies, the evaluation of antibody results and levothyroxine treatment are also important during pregnancy.[4,8]

Most studies focus on cognitive development rather than other systems such as fetal heart function and structure during pregnancy.[8,9] Insufficient transplacental maternal thyroid hormone transmission for the fetus in the first and second trimesters causes impaired fetal brain development.[9] Therefore, thyroid hormone is required for normal fetal brain development, neuronal proliferation, migration and structural organization.[10] For this reason, thyroid hormone has an important role in embryogenesis and fetal maturation.[10] Although many studies have been investigated the adult hypothyroidism and its effects on cardiac function,[11,12] little research has been conducted on fetal cardiac functions and in utero fetal cardiac structure in pregnancies with hypothyroidism.

In this study, we aimed to investigate the fetal cardiac structure in the fetuses of hypothyroid pregnant women receiving thyroid hormone replacement therapy and to compare them with normal pregnancies.

Methods

Study design and participants

A retrospective cohort study was performed to evaluate characteristics of fetal cardiac structure and function in pregnancies with hypothyroidism receiving thyroid hormone replacement therapy in a tertiary hospital between January 2020 and December 2021. Ethical approval was obtained from the local institutional ethics committee (numbered E-48670771-514.99). The written informed consent was taken from all participants before examinations.

Pregnant women aged 18–45 years who applied to our hospital for pregnancy follow-ups in the first trimester and whose treatments are started because of a new diagnosis of hypothyroidism were included in the study. The patients with completed fetal echo parameters at 26–34 weeks of gestation and fetal outcome follow-ups were also noted. Hypothyroid pregnant women who received thyroid hormone replacement therapy formed Group 1, and healthy pregnancies with similar characteristics formed Group 2.

Each pregnant woman underwent laboratory examination of thyroid function in the first trimester. The laboratory diagnostic criteria for hypothyroidism were based on the diagnosis and treatment guide of thyroid diseases (2020 Turkish Society of Endocrinology and Metabolism). The diagnosis of hypothyroidism was biochemically defined as a fT4 hormone below the lower limit of the reference range, and TSH hormone level above the upper limit of the reference range. The normal serum TSH, fT4 and fT3 hormone levels are 0.27–4.4 mU/L, 9.3–17 ng/L, and 2.0–4.4 ng/L, respectively.

All women with hypothyroidism were taking thyroid hormone replacement (all treated with levothyroxine). The routine treatment of hypothyroidism were controlled by endocrinology.

The patients with maternal cardiac disease, evidence of congenital fetal anomaly of any organ including fetal heart, multiple pregnancies, anemia, chromosomal abnormalities, fetal demise, all types of diabetes (DM), preeclampsia, maternal hypertension, connective tissue disease, intrauterine growth restriction and smoker pregnant women were excluded.

The demographic characteristics, gravidity (G), parity (P), and abortion (A) history of patients including body mass index (kg/m^2) were recorded. Apgar scores, fetal birth weight (g), gestational age at delivery (week), fetal gender, types of delivery, and laboratory thyroid levels were also written.

Fetal echocardiographic measurements

All patients underwent an ultrasonographic examination using a Mindray Resona 7 ultrasound (Mindray Bio-Medical Electronics Co., Ltd., Shenzhen, China) diagnostic apparatus with a 1.2–6 MHz convex abdominal probe. Beside the routine ultrasonographic measurements including fetal biometry, fetal Doppler measurements (umbilical artery (UA), middle cerebral artery (MCA) pulsatility index (PI), resistance index (RI)) of fetal ECHO parameters were performed. The 2D and M-mode fetal ECHO was performed by one fetal medicine specialist (HAS). The ultrasound parameters were performed between 26 and 34 weeks of gestation.

A standard lateral four-chamber view was obtained after adequate magnification in 2D ECHO followed by

the application of M Mode. The thicknesses of left ventricular (LV) and right ventricular (RV) walls were measured at the end of systole and diastole (**Fig. 1**). The interventricular septum (IVS) was also measured with the cursor perpendicular to the interventricular septum during breath holding by the mother and with minimal fetal breathing and movement artifacts. An average of 4 measurements was taken online as well as from a cine loop (end-diastolic phase) stored for offline measurements.[13] All these data measurements were collected from the system files and were compared between groups.

Statical analysis

All analyses was performed using SPSS 18.0 statistical software package (SPSS Inc., Chicago, IL, USA). Normally distributed continuous variables in the group data were indicated with mean±standard deviation. Non-normally distributed variables were presented as median and lowest-highest (min-max) values while categorical variables were indicated with numbers and percentages. In univariate comparisons between groups, according to the distribution of continuous variables, t-test and analysis of variance in independent groups from parametric tests, Mann-Whitney U-test and Kruskall-Wallis test from non-parametric tests were used. The chi-square test was used to compare categorical variables. A p-value <0.01 was considered significant.

Results

The age of patients, demographical characteristics including gravidity, parity, number of abortion, BMI, mean weeks of gestation, laboratory results including TSH, fT3, fT4, anti-TPO and first trimester test results were recorded. After screening the data system, a total of 89 patients (41 hypothyroidism receiving thyroid hormone replacement therapy and 48 controls) were recruited to the study shown in **Table 1**. Apart from TSH and T3, all parameters were similar between the groups. Serum TSH value of patients with hypothyroidism (Group 1) was significantly higher than controls.

The fetal Doppler and ECHO parameters, fetal Apgar scores, fetal gender and weight including delivery types were compared in **Table 2**. There were no statistically significant difference in mean scores of Doppler and ECHO parameters between the groups. Apgar scores, fetal gender and mean fetal birth weight were all similar between the groups.

Discussion

Little is known about fetal cardiac functions and in utero fetal cardiac structure in pregnancies with hypothyroidism. This study reports that there is no myocardial structural difference in fetuses of pregnant women diagnosed with hypothyroidism and receiving thyroid hormone replacement therapy compared to healthy controls.

In adult studies, it was found that hypothyroidism can affect cardiac contractility including impaired cardiac muscle relaxation especially in diastole.[12,14] Diastolic hypertension, and together with coronary artery diseases, hypothyroidism can change myocardial diastolic function.[12] In another double blind randomized placebo-control study, the authors found no difference between systolic and diastolic heart function with a treatment of levothyroxine after a median follow-up of 18.4 months in the patients with subclinical hypothyroidism older than 65 year old.[11] In neonatal studies, it was found

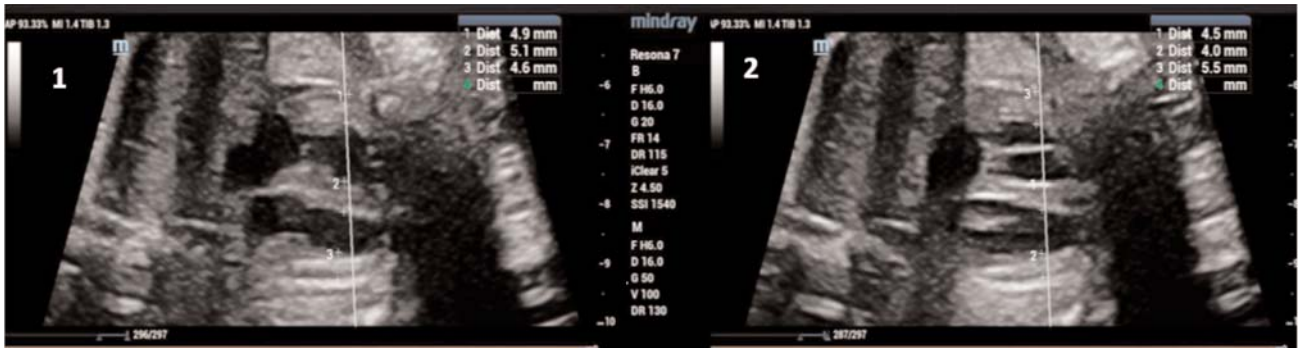

Fig. 1. The thickness of left ventricular (LV) and right ventricular (RV) walls.

Table 1. Demographic characteristics and laboratory parameters between groups.

	Group 1 (n=41) (Hypothyroidism)	Group 2 (n=48) (Controls)	p-value*
Age (year)	29.4±5.9	30.4±5.1	0.4
Gravidity (min–max)	2 (1–5)	2 (1–9)	0.6
Parity (min–max)	1 (0–3)	1 (0–5)	0.1
Live birth (min–ax)	1 (0–3)	1 (0–5)	0.2
Abortion (min–max)	0 (0–3)	0 (0–3)	0.07
BMI	30.9±4.0	31.6±4.3	0.3
Gestational age (week)	30.9±1.8	30.9±1.9	0.9
PAPP-A	0.9±0.3	0.9±0.3	0.4
free βhCG	0.9±0.5	0.7±0.3	0.02
TSH	2.8±1.1	1.4±0.6	<0.01
T3	2.7±0.3	2.9±0.3	0.01
T4	9.4±2.1	10±2.5	0.2
Anti-TPO (min–max)	9 (7–18)	8 (2–12)	0.005

*p<0.01 was considered significant. **Anti-TPO:** anti-thyroid peroxidase; **BMI:** body mass index; **βhCG:** human chorionic gonadotropin; **PAPP-A:** pregnancy-associated plasma protein-A; **T3:** triiodothyronine; **T4:** free thyroxine; **TSH:** thyrotropin.

that congenital hypothyroidism can reduce the left ventricular systolic function and increase the risk of arrhythmia in newborn.[15] It is known that thyroid hormones play a significant role in regulating cardiac, vascular, and metabolic physiology.[12,14] In utero life is like a simulation of real life. Similar to adult and neonatal physiology, hypothyroidism can affect fetal cardiac function; however, the research about this field is lacking.

Table 2. Evaluation of the fetal Doppler and echo parameters, fetal Apgar scores, fetal gender and weight including delivery types..

	Group 1 (n=41) (Hypothyroidism)	Group 2 (n=48) (Controls)	p-value
UAPI	1.0±0.1	1.0±0.1	0.7
MCAPI	1.8±0.2	1.8±0.2	0.6
RV EST (mm)	4.7±0.6	4.7±0.7	0.8
IV EST (mm)	5.3±0.7	5.3±0.8	0.8
LV EST (mm)	4.9±0.6	4.9±0.8	0.9
RV EDT (mm)	4.0±0.7	4.1±0.7	0.8
IVS EDT (mm)	4.4±0.7	4.5±0.8	0.5
LV EDT (mm)	4.3±0.7	4.3±0.8	0.9
1-minute Apgar score (min–max)	5 (3–6)	5 (3–6)	0.9
5-minute Apgar score (min–max)	8 (7–9)	9 (7–9)	0.5
Fetal birth weight (g)	3113±461	2985±493	0.2
Type of delivery			
Vaginal	26	23	0.1
Cesarean section	15	25	
Fetal gender			
Girl	21	26	0.7
Boy	20	22	

EDT: end-diastolic thickness; **EST:** end-systolic thickness; **IVS:** interventricular septum; **LV:** left ventricle; **MCAPI:** middle cerebral artery pulsatility index; **RV:** right ventricle; **UAPI:** umbilical artery pulsatility index.

The fetal echocardiography is a safe, cheap and perfect method to evaluate fetal heart structure and function for prenatal diagnosis.[16] Being part of routine screening, and common use of fetal echocardiography are advantages of the tool. It is frequently performed between 18 and 22 weeks of gestation; however, Tague et al. reported the helpful use of fetal echocardiography and common findings in late gestation especially in third trimester (24 to 38 weeks).[17] Any fetuses with structurally abnormal heart diagnoses were excluded, therefore, we preferred the weeks of gestation between 26 and 34 in our study.

In our study, the patients with hypothyroidism (Group 1) had significantly higher serum TSH levels than the controls. However, since they received thyroid hormone therapy, it is not illuminating the effect of hypothyroidism on fetal myocardial structure.

On the other hand, Ingul et al. found fetal myocardial dysfunction with reduced left and right ventricle global strain rate in fetuses of obese pregnant women (BMI>30 kg/m^2).[18] They also showed thicker fetal interventricular septum in late pregnancy of obese mothers. The obesity induced inflammation may be the cause of structural changes in the fetal heart. The mean BMI was similar in our study (31 kg/m^2, 30.9 kg/m^2, study and control groups respectively). Therefore, we did not find any difference between groups.

Serum TSH levels of patients with hypothyroidism (Group 1) were significantly higher than the levels of the controls as expected. However, all serum levels were in normalized range and there were no significant findings regarding fetal echo parameters. We think that early starting of replacement therapy might prevent fetal heart.

In another point of view, the miracle physiology of maternal fetal balance improves fetal resistance to changes. In the first trimester, TSH receptor is directly stimulated by maternal hCG, leading to increase thyroid hormone production and results in a subsequent reduction in serum TSH concentration.[19] Little is known about thyroid dysfunction and its effects on fetal organs. Most studies are about brain development. There should be more researches about thyroid dysfunction and fetal organs like heart, fetal lungs or extremities.

This study has many strengths. All measurements were performed by one fetal medicine specialist, and the control group of patients has matching gestational age. Our study had some limitations. We did not investigate the fetal cardiac structure in untreated hypothyroid pregnancies in the present study. In addition to that, the number of patients is small.

Conclusion

In conclusion, there is no significant myocardial structural difference among fetuses of pregnant women diagnosed with hypothyroidism and receiving thyroid hormone replacement therapy compared to healthy controls. We do not yet know whether thyroid replacement therapy affects fetal cardiac abnormality in hypothyroid pregnant women or not. Further studies can be done in trimester-dependent and untreated hypothyroid pregnant women.

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Compliance with Ethical Standards: The authors stated that the standards regarding research and publication ethics, the Personal Data Protection Law and the copyright regulations applicable to intellectual and artistic works are complied with and there is no conflict of interest.

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