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The findings about relationship between autoimmune thyroid disease and first-trimester aneuploidy results

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ABSTRACT

Aim: The aim of this study was to investigate the relationship between thyroid autoantibody and first-trimester aneuploidy results. Thyroid autoimmunity (TAI) is the most common autoimmune disorder. Patients with TAI are usually euthyroid. Thyroid peroxidase (TPO-Ab) in patients with or without thyroid dysfunction is associated with infertility, recurrent embryo implantation failure, and early pregnancy loss. The impact of TPO-Ab on first-trimester aneuploidy test results needs to be studied.

Material and Method: This retrospective case-control study was conducted between December 2019 and May 2022. Patients with thyroid autoantibody positivity (n=112) were included in the study as the case group. The control group was selected from age and body mass index (BMI)-matched patients (n=130). Nuchal translucency (NT), crown rump length (CRL), pregnancy-associated plasma protein A (PAPP-A) and free beta subunit of human chorionic gonadotropin (β-hCG)) values were compared between the two groups.

Results: This study included two hundred forty two age-matched (29.86±4.51) and BMI-matched (23.96±2.34) women. There was no statistically significant difference between groups in terms of free thyroxine (FT4), PAPP-A and free β-hCG (p>0.05). NT as a marker for major chromosomal defects and CRL were comparable in case and control groups (p>0.05).

Conclusion: There is no statistically significant relationship between thyroid autoimmune diseases and the first-trimester aneuploidy results.

Keywords: Aneuploidy, thyroid, autoimmune thyroid disease

INTRODUCTION

Screening for aneuploidy abnormalities has become an important part of prenatal cares and is performed all over the world for pregnant women, especially in the first trimester, and many women want to ensure that their child is healthy before birth (1). The risk of aneuploidy abnormalities increases with increasing maternal age (2). Therefore, screening methods were recommended in the past for women over 35 years old, but these methods are recommended in recent years for all pregnant women (3).

Chromosomal abnormalities can include additional or absent whole chromosomes, and duplications, deletions, and translocations of various sizes. About one out of 150 pregnancies is affected by chromosomal abnormalities which are responsible for 50% of early pregnancy losses (4). Aneuploidy is defined as the existence of one or more additional chromosomes or the lack of one or more chromosomes. The fetal aneuploidy's outcomes differ from incompatibility with life to physical and intellectual disability (5). The prevalence of most common chromosomal aneuploidy is as follows: Down syndrome (with a prevalence of approximately 1 in 700 live births), Edward syndrome (with a prevalence of about 1 in 3,000 live births), Patau syndrome (approximately 1 in 6,000), and Klinefelter syndrome (with a prevalence of 1 in 500 males) (6). The childhood disability considerably affects health system, family, and society (7).

The aim of prenatal screening is to detect the most common types of aneuploidy consistent with survival beyond the early embryologic development into viability (8). Risk can be calculated through evaluation of biomarkers in maternal blood and ultrasound findings with a double test/ combined test in the first trimester and a quadruple/triple test in the second trimester. The combined first-trimester screening between 11+0 to 13+6 weeks of gestation was used as the most effective and standard screening method (9). Crown-rump length (CRL) and Nuchal translucency (NT) assess with the

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ultrasonography for the combined test (9). In addition, the pregnancy-associated plasma protein A (PAPP-A) levels and free beta subunit of human chorionic gonadotropin (β-hCG) check from the maternal blood .(10)

Normal pregnancy and fetal development require thyroid hormone. Placental and fetal development in the first half of pregnancy is dependent on the maternal thyroid hormone supply. Thyroid peroxidase (TPO) as the primary enzyme of the thyroid, is stimulated by thyroid-stimulating hormone (TSH) and it is involved in the production of thyroid hormones. Thyroid Peroxidase Antibodies (TPO-Ab) disrupt the TPO enzymes' normal function causing thyroid inflammation (11).

The autoimmune-related thyroid problems seems to have more common in female population. TPO-Abs are present in 75% of Graves' disease and 90% of cases of Hashimoto's thyroiditis as the most common anti-thyroid autoantibodies (12,13). Thyroid autoimmunity (TAI) is prevalent among women, especially in women with a history of recurrent miscarriage and subfertility (11). TAI describes the existence of circulating anti-thyroid autoantibodies targeted against the thyroid with or without affecting the thyroid function. Thyroglobulin antibodies (TGAb), thyrotropin receptor antibodies (TRAb), and TPO-Ab are the three most clinically important (11).

It is necessary to investigate the prevalence of coexisting of TAI disease and aneuploidy abnormalities. We studied the presence of autoimmune thyroid disease on first-trimester aneuploidy results. The main aim of study investigate the effects of TPOab as TAI disease and fetal health.

MATERIAL AND METHOD

The study was carried out with the permission of Bezmialem University Clinical Researchs Ethics Committee (Date:06.09.2022, Decision No:2022/262). All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki. Two hundred forty two women participated in this study between December 2019 and May 2022.

Women between the ages of 25 and 39 were included in this study and 130 women for the control group, and 112 women with thyroid autoantibody positivity were included in the case group. The exclusion criteria were as follows: 1) known chronic disease other than Hashimoto, 2) over 39 years of age, 3) history of recurrent miscarriage, 4) known chromosomal disorder, 5) history of fetus with anomaly, and 6) medication for thyroid dysfunction.

The inclusion criteria were as follows: 1) 20-39 years old, 2) with known thyroid dysfunction, 3) with three or less pregnancies, and 4) with a body mass index (BMI) between 18.5 and 30.

Anti-TPO, anti-TG, fT3, fT4, TSH were studied with ECLIA (electrochemiluminescence immunoassay) (Roche Diagnostics GmbH, D-68298 Mannheim). TSH was measured with an analytical sensitivity of 0.005 μIU/mL. The anti-TG measurement range is 10–4000 IU/mL, and the anti-TPO measurement range is 5–600 IU/mL. Anti-TG<115 IU/mL, anti-TPO<35 IU/mL were accepted as negative. ELISA (BioVendor, Heidelberg, Germany) was used to measure serum TSH and T4 concentrations.

Ultrasonography of the clear space behind the neck (NT) biochemical tests, including PAPP-A and free β-hCG were performed between 11-13 weeks and six days of pregnancy by operator.

Statistical Analysis

The Kolmogorov-Smirnov test performed to check the normality, and the nonparametric tests performed given the non-normality of the groups before the statistical analyses. Mean and standard deviations (SD) measured to check each continuous variable, including age, BMI, PAPP-A, free β-hCG, TSH, FT4, CRL, Anti-TPO, Anti-TG and NT. The Mann-Whitney U test performed to study the difference between the two groups. SPSS v22 used for statistical analyses. A value of $p < 0.05$ was accepted as statistically significant.

To calculate the sample size with the G-Power 3.1 program, two independent means(two groups) was measured based on the Mann-Whitney test with the allocation ratio N1/N2 =1, the power of 90%, effect size of 40%, and 0.05 type 1 error for at least 216 patients (14).

RESULTS

This study included two hundred forty two age-matched (29.86±4.51) and BMI-matched (23.96±2.34) women. The majority of study participants do not smoke. In the parity of mother, 193 (79.8%) was primipara mother, 49 (20.2%) was nullipara or multipara mothers. **Table 1** shows descriptive statistics of study parameters.

Table 1. Descriptive statistics of study parameters in women

Study parameters	Median (range)	Mean±SD
Maternal characteristics		
Age	29 (20-39)	29.86±4.51
BMI	24 (18.8-29.8)	23.96±2.34
Laboratory values		
PAPP-A(IU/L)	3.115 (0.17-19.3)	3.52±2.55
free β-hCG (IU/L)	36.79 (10.18-779)	46.64±54.76
TSH	2 (1-2.5)	1.8±0.34
FT4	1.2 (0.9-1.8)	1.18±0.14
Anti-TPO	10 (1.1-144)	29.86±28.85
Anti-TG	2.1 (1-126.1)	19.02±23.18
Fetal data		
CRL	55 (45-76)	56.11±6.47
NT	1.5 (1.1-2.5)	1.55±0.32

SD, standard deviation.

Table 2 shows comparison of case and control groups on the study parameters.

Table 2. Comparison of case and control groups

Study parameters	Thyroid autoantibody positive Case (n=112) M±SD	Thyroid autoantibody negative Control (n=130) M±SD	p-value
Laboratory values			
PAPP-A (IU/L)	3.14±1.8	3.85±3.03	0.201
free β-hCG (IU/L)	42.95±26.78	49.82±70.45	0.898
TSH	1.88±0.32	1.74±0.35	<0.001
fT4	1.19±0.1	1.18±0.17	0.208
Anti-TPO	58.26±16.85	5.39±2.54	<0.001
Anti-TG	39.35±19.75	1.5±0.41	<0.001
Fetal data			
CRL	56.12±7.41	56.1±5.55	0.315
NT	1.56±0.33	1.55±0.31	0.850

M, Mean; N, number of subjects; PAPP-A, Pregnancy-associated plasma protein-A; free β-hCG, Free Beta human chorionic gonadotropin; TSH, thyroid-stimulating hormone; FT4, Free thyroxin; CRL, crown-rump length; Anti-TPO, Anti-thyroid peroxidase; Anti-TG anti-thyroglobulin; NT, nuchal translucency scan. All variables tested by a Mann-Whitney U test.

As stated in **Table 2**, a Mann-Whitney test did not find a statistically significant association between case and control in regard to PAPP-A (p>0.05). The control group was relatively higher than the case group (3.85±3.03 vs. 3.14±1.8). There was no statistically significant difference between groups in terms of FT4 and free β-hCG (p>0.05).

There was a statistically significant difference between groups in regard to TSH (p-value<0.001). The case group was statistically higher than control (1.88±0.32 vs. 1.74±0.35).

There was a statistically significant difference between case group and controls in regard to number of Anti-TPO and Anti-TG (p<0.001). The value of Anti-TPO in the case group is ten times more than the control. The value of Anti-TG in the case group is forty times more than the control.

PAPP-A and free β-hCG, along with CRL and NT, are the main parameters of aneuploidy test. There was no statistically significant difference between groups in terms of CRL and NT (p>0.05). CRL and NT values in both groups were nearly similar (56.12±7.41 vs. 56.10±5.55 for CRL) and (1.56±0.33 vs. 1.55±0.31 for NT).

DISCUSSION

In our study, we investigated the impact of thyroid autoantibody positivity on first-trimester aneuploidy results. NT as a marker for major chromosomal defects and CRL were comparable in case and control groups. FT4 was significantly higher in the thyroid autoantibody positive group. PAPP-A and free β-hCG are the major parameters of the aneuploidy test. There was not a statistically significant difference between groups in regard to PAPP-A and free β-hCG.

Based on the conducted studies, the prevalence of TPO-Ab in women is about ten percent. Several studies have been conducted on the effect of TPO-Ab on mother and fetus in recent years. Based on high-quality evidence, TPO-Ab are strongly associated with miscarriage, the development of thyroid disease in pregnancy, and pre-term birth. Weaker evidence suggests that TPO-Ab may also be related to premature rupture of membranes, a higher risk of placental abruption, and maternal anaemia. neurodevelopmental delay, sensorineural hearing loss, and behavioral problems are among the fetal risks associated with TPO-Ab (11).

Identifying the risk factors of aneuploidy abnormalities is very important. The adverse effects of TPO-Ab on the female reproductive system such as infertility, recurrent embryo implantation failure, miscarriages and the fetus's health reported in previous studies were the primary motivation for performing this study.

TPO-Ab was confirmed to be a valuable marker for determining the risk for recurrent miscarriages in many studies (15). Midan et al. (16) reported a significantly higher frequency of antibody-positive among Egyptian women with recurrent miscarriages. Iravani et al. (17) and Lata et al. (18) showed that TAI disease may cause recurrent miscarriages. Somewhat, there are still suspicions about the correlation between recurrent miscarriages and TAI (19,20).

Perminova (21) reported that TAI had adverse effect on endometriosis, idiopathic and endocrine infertility in women. Alexander et al. (22) showed that infertility among women with TAI disease were significantly higher that healthy women. Quintino-Moro et al. (23) reported a significantly higher frequency of TAI disease among infertile women. There are contradictory discussions about the relationship between TAI and assisted reproductive methods. No definitive finding has been reached regarding TAI's adverse effect on in vitro fertilization outcomes (24).

Wasserman et al. (25) reported a significant association between TAI in the third trimester and children's intelligence quotient (IQ). The gap between the IQ of children in the control group at the age of four peaked in comparison with the children of euthyroid mothers. In another study, the same author found the higher risk of hearing deficits in children of euthyroid mothers (26). Another research also reported the relationship between TAI disease and respiratory distress in infants (27), perinatal mortality (28), and intrauterine growth retardation (28). The likely relationship between

maternal TAI disease and fetal neurodevelopmental disorder should be considered vague and awaits further investigations. There are also some studies concerning the effects of day of embryo transfer on aneuploidy tests (29,30).

Although the negative effects of TAI disease on various dimensions of the system are known, the findings of this study did not find the relationship between TAI disease and the first-trimester aneuploidy results. Based on findings, we recommend to do more research parents with abnormalities children in terms of the history of TAI disease. Therefore these results make more accurate findings about the impact of TAI disease on aneuploidy abnormalities.

Based on our findings, we believe several questions remain unanswered in effects of TAI disease on female reproductive system. For this reason, more interventional and observational trials should be done based on more comprehensive multiple-center randomized, and double blinded technique.

CONCLUSION

As a result, there is no statistically significant relationship between TAI diseases and the first-trimester aneuploidy results. TAI leads to infertility and neonatal and pregnancy complications. It is required to conduct more studies to raise our awareness of the possible adverse effects of TAI diseases on the fetus.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Bezmialem University Clinical Researchs Ethics Committee (Date:06.09.2022, Decision No:2022/262).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

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