Original Article

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Correlation of Adverse Pregnancy Outcomes with Postpartum Thyroid Function and Autoimmunity Status in Euthyroid Women

Fattaneh Bassami[1], Hossein Chiti[2*], Shahin Besharati Kivi[2], Farnaz Mohammadian,[3] Seyedeh Aisa Paknejad[1], Ramezan Fallah[4]

1. *Dept. of Internal Medicine, School of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*
2. *Zanjan Metabolic Diseases Research Center, Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences, Zanjan, Iran*
3. *Dept. of Obstetrics and Gynecology, Zanjan University of Medical Sciences, Zanjan, Iran*
4. *Dept. of Statistics and Epidemiology, Faculty of Medicine, Zanjan University of Medical Sciences, Zanjan, Iran*

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Corresponding Information:
Hossein Chiti, Zanjan Metabolic Diseases Research Center, Health and Metabolic Diseases Research Institute, Zanjan University of Medical Sciences, , Zanjan, Iran
E-Mail: h.chiti@yahoo.com

ABSTRACT

Background & Objective: Occurrence of maternal or fetal complications during pregnancy may be related to development of postpartum thyroid dysfunction based on the underlying thyroid autoimmune status. The purpose of this study wasto investigate the incidence of thyroid dysfunction after delivery in euthyroid mothers who have experienced adverse pregnancy outcomes.

Materials & Methods: Among 387 euthyroid pregnant women, 118 experienced adverse pregnancy outcomes out of which only 96 subjects completed the study. The level of thyroperoxidase antibody in the first week after delivery and thyroid function tests including Total T4, T3RU and TSH three months after delivery were measured by electrochemiluminescence immunoassay method. SPSS version 22 was used to analyze the data and the significance level was defined as $p<0.05$.

Results: Thyroperoxidase antibody was positive in 14 participants (14.6%). Overall maternal and fetal complications in the group with positive thyroperoxidase antibody were more than the group without this antibody ($p<0.001$). Total T4 level was significantly ($p=0.02$) higher in the group with negative thyroperoxidase antibody (8.03±1.91) comparing with the positive antibody group (6.72±1.96). Overt hypothyroidism was the only thyroid dysfunction that had a significant relationship with thyroid autoimmune status three months after delivery ($p=0.02$).

Conclusion: This study indicates the possible occurrence of thyroid dysfunction after delivery in euthyroid mothers who have experienced maternal or fetal pregnancy complications.

Keywords: Thyroid function tests, Postpartum, Pregnancy outcome, Autoimmunity

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Introduction

Pregnancy is associated with significant changes in metabolic processes, including the function of the thyroid gland (1). Adequate maternal thyroid function is essential for optimal fetal brain development (2). Preliminary studies have shown that hypothyroidism increases the risk of pregnancy complications and leads to growth delay in newborns (3).On the other hand, the fetus of a mother who suffers from Graves' thyrotoxicosis during pregnancy or have a previous history of this disease is at risk of hyperthyroidism and

its complications such as tachycardia, heart failure, goiter, prematurity and fetal hydrops (4).The most common complication of hyperthyroidism in pregnant mothers is increased arterial blood pressure, which increases the risk of gestational hypertension and preeclampsia (5).

Some studies also have emphasized on the relationship between thyroid dysfunction in women during pregnancy with other fetal or maternal complications, including premature birth, placental abruption, intrauterine fetal death, recurrent miscarriage, intrauterine growth retardation (IUGR), postpartum thyroiditis, and finally neurodevelopmental - psychological disorders in infants (6, 7). On the other hand, the available evidence has shown that thyroid autoimmunity can change the course and outcome of pregnancy (8). A prospective study which investigated the possibility of postpartum thyroid dysfunctions in pregnant mothers based on the presence or absence of TPO-Ab during early pregnancy has shown that the incidence of these disorders increased at about 12 weeks to 12 months after delivery in mothers with thyroid autoimmunity (9). Therefore, it seems that the presence or absence of thyroid antibodies in early pregnancy can probably predict the occurrence of pregnancy associated complications and maternal thyroid dysfunctions. Although the foot track of thyroid antibodies in patients with thyroid dysfunctions has been determined, their effects in euthyroid women has been yet a controversial issue (10, 11). In some studies, thyroid autoimmunity has been identified as an important risk factor for the onset and progression of maternal thyroid insufficiency, miscarriage and premature birth of the fetus (8, 9, 12). In the case of euthyroid pregnant mother, this question is always raises that if they experience a maternal or fetal complication of pregnancy, should they be checked for thyroid autoimmunity or dysfunction in the postpartum period or not**?**If a strong and significant relationship is found between the complications of pregnancies in euthyroid mothers with thyroid autoantibodies and the occurrence of thyroid dysfunction in the postpartum period, this hypothesis can be potentiated. To the best of our knowledge, there was no study that investigate the relationship between occurrence of maternal and fetal complications of pregnancy with the state of thyroid function and autoimmunity in euthyroid women, so the present study was carried out to uncover some aspects of this relationship.

Materials and Methods

Study design

In this prospective cohort study, pregnant women aged 18 to 35 years admitted to pregnancy care at obstetrics and gynecology clinic of Zanjan University of Medical Sciences, monitored for thyroid function tests. In women whom were euthyroid the occurrence of maternal or neonatal complications including miscarriage, mild and severe pre-eclampsia, placental abruption, premature delivery, premature rupture of membranes, intrauterine growth retardation, intrauterine fetal death, meconium excretion, and low birth weight were determined. Pregnant mothers who had a history of known autoimmune disease, any form of thyroid disorder, diabetes, chronic systemic disease, miscarriage, structural disorder of the uterus and cervical insufficiency (monitored from week 16 trough week 24), use of assisted reproductive methods, critical illness during pregnancy, multiple births, or unwillingness to participate in the study; were excluded. Euthyroid mothers who cooperated until the end of the study, evaluated for thyroid autoimmunity status in the first week after delivery and their thyroid function tests also performed three months later. Based on the presence or absence of thyroid autoimmunity, subsequent comparisons were made between the two groups regarding thyroid function changes and their possible association with maternal or fetal complications.

Laboratory indices

TSH and T4 levels were initially checked by electrochemiluminescence assay for all pregnant mothers and their initial serum samples were kept in a refrigerator at -20°C to check thyroid autoimmunity in selected euthyroid mothers, based on Iranian trimester-specific criteria (13), in the first week after delivery. The ELISA method was used to measure the level of anti-thyroid peroxidase antibody (Anti-TPO Ab).TPO Ab levels less than 16 IU were classified as negative and levels higher than it were classified as positive. Thyroid function tests including TSH, Total T4 and T3RU were measured again three months after delivery by electrochemiluminescence assay. Based on the results obtained from these postpartum tests, patients were sub-classified into euthyroid, subclinical hypothyroid, overt hypothyroid, subclinical hyperthyroid and overt hyperthyroid categories (Table1).

Statistical analysis

We used SPSS.V22 software for data analysis. Chi-square test and one-way analysis of variance were used to compare the demographic and basic characteristic data of the participants. Paired t-test was used to compare the changes in thyroid function tests. Quantitative data were indicated by “mean ± SD" and qualitative data by "Number (%)". A P-value above 0.05 was considered significant.

Ethical issues

The research plan of this study was approved by the Research Ethics Committee of Zanjan University of Medical Sciences with code: IR.ZUMS.REC.1398.190.

Results

Among 387 euthyroid pregnant women, 118 experienced at least one adverse pregnancy or fetal complication. Only 96 of these mothers cooperated to complete the study and checking their thyroid function three months after delivery. Based on the presence (n=14) or absence of TPO Ab (n=82), subsequent comparisons were made between the two groups regarding thyroid function changes and their association with maternal or fetal complications. In general, a significant difference was seen in terms of overall maternal and fetal complications of pregnancy between the groups ($p<0.001$); although this was not true for each of the complications alone.

The most common maternal complications in the negative TPO Ab group were placental abruption (28%) and premature delivery (25.6%) while in the positive TPO Ab group they included premature delivery (35.7%) and mild preeclampsia (28.6%). The most common fetal complications in negative vs positive TPO Ab group included meconium excretion (19.5% and 28.6%, respectively) and the need to admit the baby to the NICU (18.3% and 21.4%, respectively) (Table2).

Three months after delivery, TOTAL T4 level showed a significant difference between the two groups; with higher level of T4 in negative TPO Ab individuals. No meaningful difference was seen about the TSH and T3RU levels between the two groups (Table3).

At the end of the third month after delivery, 9 (64.3%) of the mothers with a positive anti-TPO test and 66 (80.5%) of the mothers with a negative anti-TPO test remained euthyroid. The only pattern that showed a significant difference in two groups was overt hypothyroidism ($p=0.02$). Subclinical hypothyroidism was the most functional abnormality in both groups regardless of thyroid autoimmunity status (Table4).

All mothers with severe preeclampsia, as well as whose babies had intrauterine growth retardation or intrauterine death; showed normal thyroid function three months after delivery. Although thyroid dysfunctions were mainly observed in mothers who had miscarriages (30%) and mild preeclampsia (27.3%), or their babies had low birth weight (28.6%) and meconium excretion (30%); but, no association was seen between the type of thyroid dysfunction and maternal (Figure1) or fetal (Figure2) complications.

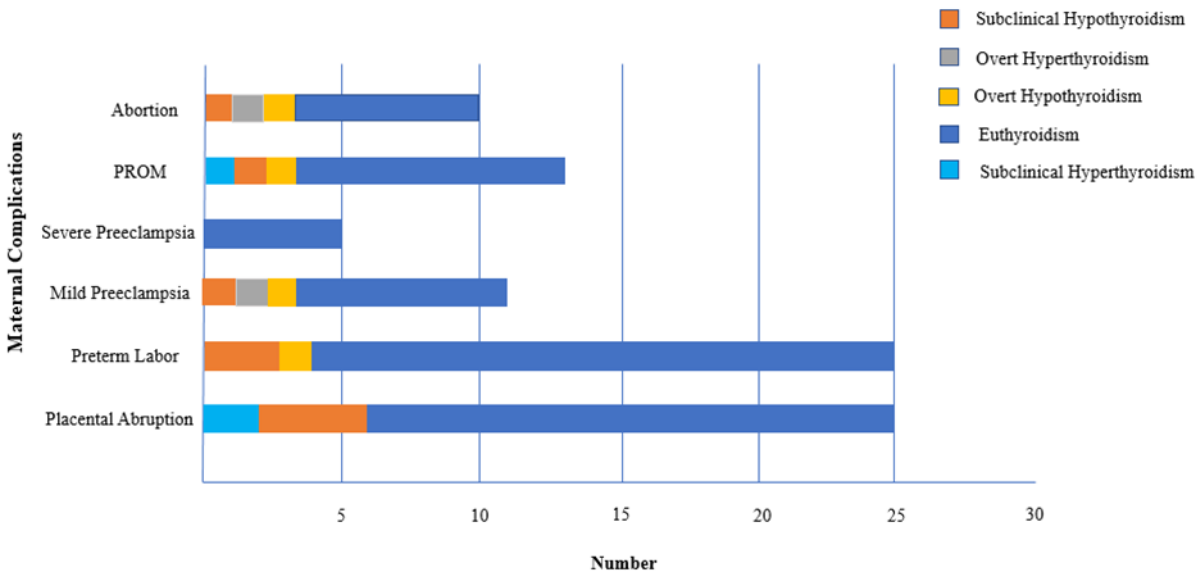

Figure 1.The frequency of thyroid function changes in each of the maternal complication

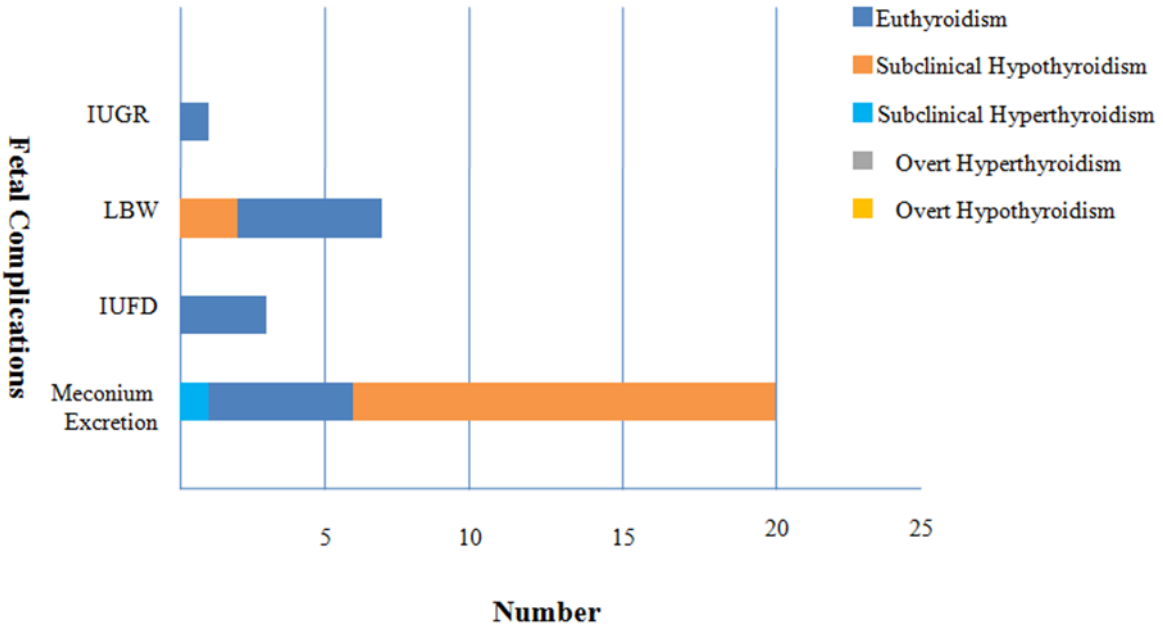

Figure 2. **The frequency of thyroid function changes in each of the fetal complication**

Table1. **Definition of different types of thyroid functions three months after deliver**

Category / Test	Normal	Subclinical hypothyroid	Overt hypothyroid	Subclinical hyperthyroid	Overt hyperthyroid
TSH (µIU/ml)	0.27-4.2	4.2-<10	≥10	<0.27	<0.27
T3RU (%)	24-37	24-37	Low to Subnormal	24-37	>37
T4 (µg/dl)	4.5-10.8	4.5-10.8	Low to Subnormal	4.5-10.8	>10.8

Table2. Basic information of the mothers participating in the study according to the thyroid autoimmune status

Variables	Anti-TPO test		P value
	Negative (N=82)	Positive (N=14)	
Age (Year/Mean± SD)	27.2 7±.0	30.±0 6.3	0.161
Sonographic estimation of fetal age (weeks/ Mean±SD)	36.2 ± 5.0	37.0 ± 2.7	0.580
Parity (Number / Mean±SD)	2.2 ± 1.3	1.8 ± 0.8	0.274
Maternal complications [number/ (%)]	**70 (85.3)**	**14 (100)**	**<0.001**
Placental abruption	23 (28.0)	2 (14.3)	0.344
Preterm delivery	21 (25.6)	5 (35.7)	0.517
Mild preeclampsia	7 (8.5)	4 (28.6)	0.052
Severe preeclampsia	5 (6.1)	0 (0)	0.599
Premature rupture of membrane	10 (12.2)	3 (21.4)	0.351
Abortion	4 (4.9)	0 (0)	0.159
Fetal complications [number (%)]	**27 (32.9)**	**5 (35.7)**	**<0.001**
Meconium excretion	16 (19.5)	4 (28.6)	0.481
Intrauterine death	3 (3.7)	0 (0)	0.467
Low birth weight	7 (8.5)	1 (7.1)	0.862
Intrauterine growth retardation	1 (1.2)	0 (0)	0.678
Need for NICU admission	15(18.3)	3(21.4)	0.781
Congenital hypothyroidism	4 (4.9)	0 (0)	0.399

Table 3. **Thyroid function tests of participants three months after delivery based on TPO Ab status.**

Variables (Mean±SD)	TPO Ab status		P value
	Negative (N=82)	Positive (N=14)	
Total T4(µg/dl)	8.03 ±1.91	6.72 ±1.96	0.020
TSH(µIU/ml)	3.18 ±1.99	7.50±9.83	0.125
T3RU (%)	1.00 ±0.10	0.98 ±0.10	0.381

Table4. **Different types of thyroid function three months after delivery based on thyroid autoimmunity**

Thyroid Function, Number (%)	Anti-TPO test		P value
	Negative (N=82)	Positive (N=14)	
Euthyroidism	66 (80.5)	9 (64.3)	0.175
Overt Hypothyroidism	0 (0)	2 (14.2)	0.02
Overt Hyperthyroidism	1 (1.2)	0 (0)	0.173
Subclinical hypothyroidism	11 (13.4)	3 (21.5)	0.432
Subclinical hyperthyroidism	4 (4.9)	0 (0)	0 .713

Discussion

This study showed a significant relationship between overall pregnancy complications in euthyroid mothers with their thyroid autoimmunity status. Overt hypothyroidism was the only thyroid dysfunction that had a significant relationship with thyroid autoimmune status three months after delivery, but no relationship was seen with other types of thyroid dysfunctions. Thyroid autoimmune disorder is the most common cause of hypothyroidism in women of reproductive age (14). Although the prevalence of overt hypothyroidism in pregnancy is less common nowadays, subclinical hypothyroidism is still seen in a significant percentage of pregnant women (15). Of course, the difference in diagnostic criteria may mask the true prevalence of thyroid disorders in pregnancy (16). About mothers suffering from overt hypothyroidism, previous studies have often investigated a relationship between thyroid autoimmunity or TSH levels with the occurrence of maternal or fetal complications (17, 18). However, some of these studiesconducted in women with subclinical hypothyroidism have not shown any significant association between thyroid autoimmunity or TSH levels with pregnancy associated complications (18). In our study, although the level of Total T4 in cases with thyroid autoimmunity was obviously lower than cases without autoimmunity, but the levels of TSH and T3RU did not show any significant difference between the two groups. Some studies have not observed a clear effect of treatment with levothyroxine on the occurrence of maternal or fetal complications in pregnant mothers with hypothyroxinemia and precisely for this reason there is no consensus about the treatment of hypothyroxinemia (19, 20). In a case-control study, the frequency of thyroid autoimmunity in women with and without pregnancy complications was compared. They concluded that thyroid autoimmunity was more common in women with recurrent pregnancy loss(21). These results are consistent with the findings of our study. Thyroid autoimmunity also has a relatively high prevalence in euthyroid women. The prevalence of thyroid autoimmunity in the present study was between the values reported in two previous studies (22, 23). One of these researchers have commented that the risk of premature delivery and miscarriage increases in euthyroid mothers with thyroid autoimmunity (22). It is hypothesized that if there is a maternal or fetal complication of pregnancy in euthyroid women, it is likely that postpartum thyroid dysfunction will occur, especially in mothers with thyroid autoimmunity. Although previous studies have been emphasized that postpartum thyroiditis is the most common endocrine disorder associated with pregnancy (24) and happens with a prevalence of about fifty percent in pregnant mothers with thyroid autoimmunity (25). However, the present study did not prove a relationship between the thyroid function related to postpartum thyroiditis with pregnancy complications and thyroid autoimmune status. The relatively small sample size of euthyroid mothers with pregnancy complications and the short duration of their follow-up regarding changes in thyroid function can be one of the limitations of this study and the reason for the obtained results, but the novelty of this study was the follow-up of the thyroid function in euthyroid mothers who experienced one of the maternal or fetal complications.

Conclusion

In current study, the incidence of overt hypothyroidism was higher than the other types of thyroid dysfunctions in euthyroid mothers with thyroid autoimmunity and pregnancy complications. Due to the existence of agreement on the role of thyroid autoimmunity in the occurrence of pregnancy complications and the possibility of thyroid dysfunction after childbirth, it seems logical to pay attention to the autoimmune status and postpartum follow up of thyroid function of this subgroup of mothers. It is suggested to conduct other studies with larger sample size and a longer follow-up period.

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None

Conflict of Interest

The authors declared no conflict of interest.

Authors' Contributions

H.Chiti and Sh.Besharati Kivi conceptualized and designed the study. F.Bassami, SA.Paknejad and F.Mohammadian provided the data. R.Fallah conducted the statistical analysis and interpretation of the data. H.Chiti contributed to the writing and revision of the manuscript. All authors read and approved the final version of the manuscript.

Ethics Approval and consent to participate

The research plan of this study was approved by the Research Ethics Committee of Zanjan University of Medical Sciences with code: IR.ZUMS.REC.1398.190.

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