Özgün Araştırma Original Article

Jinekoloji - Obstetrik ve Neonatoloji Tıp Dergisi
The Journal of Gynecology - Obstetrics and Neonatology

Thyroid Functions Of Infants Born To Mothers With Thyroid Disease

Tiroid Hastalıklı Anne Bebeklerinin Tiroid Fonksiyonları

Nilgün ALTUNTAŞ, Serdar BEKEN, Hülya KOÇAK, Canan TÜRKYILMAZ, Ferit KULALI, Sezin ÜNAL, I. Murat HİRFANOĞLU, Esra ÖNAL, Ebru ERGENEKON, Esin KOÇ, Yıldız ATALAY

Gazi University, Faculty of Medicine, Department of Pediatrics, Division of Neonatology, Ankara, Turkey

ABSTRACT

Aim: Thyroid function abnormalities in pregnancy bear various risks for the mother, fetus and newborn. In this study, thyroid function tests of infants born to mothers with thyroid disease were evaluated.

Material and Methods: 237 mothers with thyroid disease hospitalized for birth between 2008 and 2010 and 237 newborn were included in this study. Of these cases, medical history, clinical features and laboratory values were retrospectively recorded.

Results: In the course of pregnancy, 95 mothers (40.1%) received thyroid replacement therapy for hypothyroidism, 5 mothers (2.1%) received anti-thyroid agents because of hyperthyroidism and 137 mothers (57.8%) were euthyroid, subclinical hypothyroidism or subclinical hyperthyroidism and did not receive any treatment. These 137 mothers were diagnosed with thyroid disorder and were received therapy before pregnancy. Postnatal first thyroid function tests showed TSH>20 μIU/mL (20-30 μIU/mL) in 5 cases. In 3 of these 5 cases, the thyroid function tests returned to normal values after the first week and 2 of them (0.8%) were diagnosed as congenital hypothyroidism (temporary or persistent) and received thyroid hormone replacement therapy in the first 2 weeks. In cases of TSH levels between 5-20 μIU/mL in the first week, there was no increase in the second week and neither hyperthyroidism nor hypothyroidism was detected.

Conclusion: Thyroid disease is most common in babies of mothers with thyroid disease. Examination of thyroid function in these infants in addition to the neonatal screening in the first week is important. Thus, treatment can be started earlier.

Key Words: Thyroid disease, newborn, neonatal screening.

ÖZET

Amaç: Gebelikte tiroid fonksiyon anormallikleri anne, fetüs ve yenidoğan için çeşitli riskler taşımaktadır. Bu çalışmada tiroid hastalıklı annelerin bebeklerinin tiroid fonksiyonları değerlendirildi.

Gereç ve Yöntemler: İki yıllık dönemde doğum için hastaneye başvuran 237 tiroid hastalıklı anne ve onların yeni doğmuş bebekleri (n: 237) çalışmaya alındı. Bu olguların tıbbi hikayeleri, klinik özellikleri ve laboratuvar değerleri geriye dönük olarak incelendi.

Bulgular: Gebelik süresince 95 annenin (%40.1) hipotroidi nedeniyle tiroid replasman tedavisi, 5 annenin (%2.1) hipertroidi nedeniyle antitiroid tedavi aldığı, 137 annenin (%57.8) ise gebelikte ötiroid, subklinik hipotiroidi veya hipertiroidi oldukları ve tedavi almadıkları tespit edildi. Bu 137 anneye gebelik öncesinde tiroid hastalığı tanısı konmuş ve tedavi verilmişti. Doğum sonrası alınan ilk tiroid fonksiyon testlerinde, 5 olguda TSH>20 μIU/mL (20-30 μIU/mL) saptandı. Ancak bu 5 olgunun 3'ünün tiroid fonksiyon testleri bir hafta sonra normale dönerken, ikisine (%0.8) konjenital hipotiroidi (geçici veya kalıcı) tanısıyla tiroid hormon replasman tedavisi başlandı. İlk hafta TSH düzeyleri 5-20 μIU/mL arasında olan hiçbir olguda ikinci hafta TSH düzeylerinde artış olmadı ve bu olgularda hipertiroidi veya hipotiroidi tespit edilmedi.

Sonuç: Tiroid hastalıklı anne bebeklerinde tiroid fonksiyon bozukluğu daha yaygındır. Yenidoğan tarama programına ek olarak bu bebeklerde ilk hafta içinde tiroid fonksiyonlarının değerlendirilmesi önemlidir. Böylece tedaviye daha erken başlanabilecektir.

Anahtar Kelimeler: Tiroid hastalığı, yenidoğan, yenidoğan taraması.

Yazışma Adresi/ Correspondence Address:
Nilgün Altuntaş
Gazi University, Faculty of Medicine, Department of Pediatrics,
Division of Neonatology, Beşevler, Ankara, Turkey
Tel/Phone: 90 312 202 6556
E-mail: nilgunaltuntas@hotmail.com

Geliş Tarihi/ Received: 30.10.2014
Kabul Tarihi/ Accepted: 09.01.2015

Introduction

Thyroid disorders are the second most common endocrine function abnormalities after diabetes mellitus among the fertile women.

Hyperthyroidism is detected in 0.2% of pregnant women and 95% of them are Graves's disease. Hyperthyroidism in pregnancy can promote abortion, growth retardation, prematurity, ablation placenta, hypertension, preeclampsia, heart failure, infection and perinatal mortality (1-2). Graves's disease increases fetal or neonatal thyrotoxicosis risk. Fetal thyrotoxicosis can trigger prematurity, fetal craniosinositozis, exophthalmia, heart failure, hepatosplenomegaly, thrombocytopenia, goiter and growth retardation (3). 10-20% of infants born to mothers treated with propylthiouracil in pregnancy can experience neonatal hypothyroidism. This picture of hypothyroidism may regress spontaneously until fifth postnatal day.

The frequency of subclinical or overt hypothyroidism in pregnant women is 0.3-2.5% (4-6). It was reported that hypothyroidism in pregnancy increases the risk of abortion, stillbirth, congenital malformation, pregnancy related hypertension, postpartum bleeding and fetal distress. However, some studies reported that pregnant women with hypothyroidism do not have risk for perinatal problems (7,8). Autoantibodies can cross placenta and cause neonatal or fetal hypothyroidism. Hypothyroidism detected during pregnancy can cause fetal neurological and growth abnormalities. This is the reason for necessity of L-thyroxin replacement therapy in pregnancy.

There is no consensus about how to follow-up thyroid function tests of babies born to mothers with thyroid diseases. These babies should be observed for temporary hypothyroidism. There is still no agreement about the duration of this observation and tests to be performed.

In this study, we aimed to evaluate the thyroid function tests and the frequency of thyroid disorders in infants of mothers with thyroid disease.

Material and Methods

Mothers diagnosed with thyroid disease in pregnancy or having history of thyroid disease in preconceptional period and their babies born in Gazi University Hospital between 2008 and 2010 were evaluated retrospectively.

The time of diagnosis, clinical features, treatment, risk factors about pregnancy (preeclampsia, anemia, etc.) abortion history, thyroid function tests in pregnancy period [free T3 (fT3), free T4 (fT4) and TSH levels] and autoantibodies [anti-thyroglobuline (anti-Tg), anti-thyroid peroxidase (anti-TPO), TSH-receptor antibody (TRAb)] of the mothers and prenatal, natal, postnatal features of the newborns (including age of pregnancy, gender, duration of pregnancy, labor type, presentation, Apgar score of first and fifth minutes, birth weight of newborn), clinical features, thyroid function tests [total T3 (tT3), total T4 (tT4), fT3, fT4 and TSH levels] and second week thyroid function tests of the cases with TSH >5 μIU/mL in the first week were recorded.

Thyroid function tests and autoantibodies were studied with chemiluminescence immunoassay (Siemens Advia Centaur XP). At the first week of the newborns normal values are 0.58-2.5 μg/mL for tT3, 2.6-9.4 pmol/L for fT3, 6.0-15.9 μg/dL for tT4, 9.0-22.5 pmol/L for fT4 and 0.35-18 μIU/mL for TSH normal values after two weeks are 0.74-1.52 ng/dL for fT4, 2.3-4.2 pg/mL for fT3, 0.55-4.78 μIU/mL for TSH, 0-60 U/mL for anti-Tg, 0-60 U/mL for anti-TPO, 0-14 U/L for TRAb (9).

Congenital hypothyroidism was diagnosed as TSH levels above 4.78 μIU/mL and fT4 levels below 0.74 ng/dL on the second weeks of life.

High levels of TSH and low levels of fT4 in pregnant women were accepted as clinical overt hypothyroidism, high levels of TSH and normal fT4 levels were subclinical hypothyroidism. Overt hyperthyroidism was diagnosed with low TSH levels and high fT4 levels, and subclinical hyperthyroidism was diagnosed with low TSH and normal fT4 levels (10).

Nationally, all the newborns are screened by the blood drawn from the heel to Gutrie paper on 3-5 days after birth as a part of united screening program. In cases with TSH >20 μIU/mL, test is repeated, if the result is again high then thyroid function tests are studied. In our newborn unit, as an institutional protocol, babies of mothers with thyroid disease are evaluated with thyroid function tests in their first week besides the united screening program.

Statistical analyses were made with SPSS 16.0 (for windows, USA). Frequencies and percentages were calculated for categorical variables. Mean and standard deviation (SD) were calculated for numerical variables.

Results

Medical history, clinical features and laboratory values of the mothers were reviewed. In pregnancy period, 95 mothers (40.1%) received thyroid replacement therapy for hypothyroidism, 5 mothers (2.1%) received anti-thyroid agents because of hyperthyroidism. 137 mothers (57.8%) did not receive any treatment in the pregnancy period, because their thyroid hormone status were euthyroid (n=94, 68.6%), subclinical hypothyroidism (n=6, 4.3%) or subclinical hyperthyroidism (n=37, 27%).

134 (57%) of 237 babies born to mothers with thyroid disease were girls and 103 babies (43%) were boys. 213 babies (89.9%) were term, 24 babies (10.1%) were premature. 73 babies (31%) were delivered vaginally and 164 babies (69%) with cesarean section. Demographic data of the patients are given in (Table 1).

95 mothers with hypothyroidism were diagnosed with Hashimoto's disease, nonspecific hypothyroidism, or operated for goiter; 5 mothers with hyperthyroidism were diagnosed with toxic nodular goiter, Hashimoto's disease, nonspecific hyperthyroidism; 137 mothers were diagnosed with simple nodular goiter, multinodular goiter and Hashimoto's disease before pregnancy. Mothers' and their babies' thyroid hormone status were given in (Table 2).

In terms of birth weight of the babies, 203 (86%) babies were normal for gestational age (AGA), 6 babies (2%) were small for gestational age (SGA), 28 babies (12%) were large for gestational age (LGA) (Table 1).

Table 1: Demographic features of newborns born to mothers with thyroid disease

Specialty	Total (n=237)	Euthyroid, Sub-clinical Hypo/ Hyperthyroidism (n=137)	Clinical Hypothy-roidism (n=95)	Clinical Hyperthy-roidism (n=5)
Sex:				
Male, n (%)	103 (43)	67 (49)	34 (36)	2 (40)
Female, n (%)	134 (57)	70 (51)	61 (64)	3 (60)
Gestational age ±SD, week	38.6±1.4	38.5±1.5	38.6±1.3	39.4±1.7
Mothers who had abortion story, n (%)	33 (13.9)	14 (10.4)	18 (18.3)	1 (20)
Preterm, n (%)	24 (10.1)	16 (12)	7 (7.4)	1 (20)
Term, n (%)	213(89.9)	121 (88)	88 (92.6)	4 (80)
Presentation abnormalities, n (%)	14 (5.9)	6 (4.4)	7 (7.4)	1 (20)
Preeclampsia or hyperten-sion, n (%)	17 (7.2)	10 (7.3)	7 (7.4)	-
Delivery way: Vaginal, n (%)	73 (31)	45 (32.3)	26 (27.4)	2 (40)
Cesarean, n (%)	164 (69)	92 (68)	69 (72.6)	3 (60)
Apgar score ± SD (5. min)	9.8±0.4	9.83±0.4	9.7±0.4	9.4±0.9
Birth weight ±SD, (gr)	3226±500	3199±504	3296±454	3272±101
AGA, n (%)	203 (86)	124 (90.5)	77 (81)	2 (40)
SGA, n (%)	6 (2)	4 (2.9)	1 (1.1)	1 (20)
LGA, n (%)	28 (12)	9 (6.5)	17 (17.9)	2 (40)

Table 2: Thyroid function test results of mothers with thyroid disease and newborns

Parameters	
Maternal age ± SD (year)	31 ± 5.1
Maternal thyroid functions	
Euthyroid, n (%)	94 (39.6)
Subclinical hypothyroidism, n (%)	6 (2.5)
Clinical hypothyroidism n (%)	95 (40)
Subclinical hyperthyroidism, n (%)	37 (15.6)
Clinical hyperthyroidism, n (%)	5 (2.1)
Neonatal thyroid function tests (in the first week)	
Free T4 ± SD (ng/dL)	1.6±0.4
Total T4 ± SD (μg/dL)	13.8±2.9
TSH ± SD (μIU/mL)	5.7±4.5
TSH >20 μIU/mL, n (%)	5 (2.1%)

When first thyroid function tests were evaluated in first postnatal week, five babies had TSH>20 μIU/mL levels. Thyroid functions of the mothers of these five babies revealed that three of them took L-thyroxin for hypothyroidism; two of them received propylthiouracil (PTU) for hyperthyroidism. One of the mothers with hypothyroidism was diagnosed as Hashimoto disease. Three of these five cases were followed-up, thyroid function tests returned to normal after one week but two cases (0.8%) were diagnosed with congenital hypothyroidism and thyroid hormone replacement therapy was started. Mothers of these two cases were treated with levothyroxine during pregnancy and one of them had Hashimoto disease. In two babies diagnosed with congenital hypothyroidism urine iodine levels and thyroid ultrasonography were normal and any thyroid autoantibody were not detected in their serum.

Hashimoto's disease was detected in 33 mothers (13.9%). In all of them one or more thyroid autoantibodies (anti-thyroglobulin antibody, thyroid peroxidase antibody) were positive. Nineteen Hashimoto's patients (57.5%) who had clinically hypothyroid were treated with L-Thyroxin replacement therapy. Ten mothers (30.5%) were euthyroid, three mothers (9%) were subclinical hyperthyroidism and one (3%) mother was subclinical hypothyroidism and these 14 mothers were not treated. Five of 33 babies born to mothers with Hashimoto's disease were LGA (15.2%), one of them was SGA (3%). Only one of the babies born to mothers with Hashimoto's disease (3%) had congenital hypothyroidism (temporary or persistent).

Hyperthyroidism during pregnancy was diagnosed in five cases (2.1%) and they received propylthiouracil treatment during pregnancy. Two of the 5 babies born to mothers with hyperthyroidism had TSH levels >20 μIU/mL in first postnatal week; but TSH levels returned to normal value in the second week. None of these newborns had congenital abnormalities.

Fifteen babies (6.3%) (one of them had congenital hypothyroidism) were hospitalized because of indirect hyperbilirubinemia, 13 babies (5.4%) for transient tachypnea of newborn, 4 babies (1.6%) for low birth weight and feeding problems. All of them were discharged with full recovery.

Discussion

We evaluated the thyroid function tests of the newborns born to mothers with thyroid diseases retrospectively. Two of 237 babies (0.8%) had congenital hypothyroidism. Wikner et al. reviewed 8504 women treated for hypothyroidism and their 8669 babies for 10 years and only 8 babies were diagnosed with overt hypothyroidism (11). On the other hand, Ogundele et al. did not detect any thyroid diseases in 47 babies born to mothers with thyroid disease (12).

The most common etiology of hypothyroidism is autoimmune thyroiditis, known as Hashimoto's disease. In North America, the incidence of temporary congenital hypothyroidism in infants born to mothers with autoimmune thyroid disease is 1:180.000 and 2% of these babies were diagnosed with congenital hypothyroidism (13). Another study found the incidence as 1:310.000 (14). Authors noticed that they had some concerns about overuse of the thyroid function tests (15,16). In our study, only one baby (%3) born to mothers with Hashimoto's disease had congenital hypothyroidism (temporary or persistent). The reason of the higher incidence of congenital hypothyroidism in this study could be the smaller patient population. This is why larger prospective studies are needed.

Ogivy-Stuart et al. reported that timing of thyroid function test screening for the babies born to the mothers with hypothyroidism was the second week (17). We evaluated 237 mothers with thyroid diseases and their 237 babies on the first week. TSH levels of the 5 babies (2.1%) were above 20 μIU/mL (20-30 μIU/mL), but 3 of the babies' TSH levels returned to normal values on the second week. The rest of the babies had to receive treatment for hypothyroidism (0.8%). One of the mothers of the latter two babies was diagnosed with Hashimoto's disease and both of them received levothyroxine for hypothyroidism during pregnancy. Frequency of overt hypothyroidism in babies of the mothers with hypothyroidism was 2.1% (2/95). This is a higher ratio compared to literature (11,12). None of the cases with TSH levels 5-20 μIU/mL in the first week had an increase in the second week.

In our country, all newborns are screened for hypothyroidism with Guthri card for TSH levels between third to fifth postnatal days. But central hypothyroidism can not be detected by the screening programs with TSH (18). In our study, the mothers of 2 babies with congenital hypothyroidism were treated with thyroxine because of hypothyroidism, and their thyroid hormone levels were kept in normal ranges during pregnancy period.

One of the studies that focused on the effect of hypothyroidism on pregnancy morbidity suggested that the frequency of gestational hypertension [eclampsia (22%), preeclampsia (15%) and pregnancy related hypertension (7.6%)] were higher in overt or subclinical hypothyroidism than normal population (19). In our series, 17 of the 237 mothers (7.2%) were diagnosed as preeclampsia or hypertension. Seven of these mothers were receiving levothyroxine for hypothyroidism. The incidence of preeclampsia or gestational hypertension in the mothers with hypothyroidism was 7.3% (7/95). Preeclampsia or HT was not seen in mothers with hyperthyroidism. Tkija Manisto et al. found higher incidence of preterm birth in mothers with overt hypothyroidism. But the same results were not found in mothers with subclinical hypothyroidism. Autoantibodies were detected in 50% of mothers with overt hypothyroidism and it was suggested to be related to preterm birth (10). In the same trial, low birth weight frequency was higher in mothers who had anti-TPO antibody and 65% of infants with low birth weight were preterm. It was not reported increased risk in rate of SGA or LGA.

In our trial 24 of the 237 babies (10.1%) were preterm. Premature birth frequency in mothers with overt hypothyroidism was 7.4%. Only one of the autoantibody positive cases had premature birth (3%). There was no premature birth in patients with subclinical hypothyroidism. It was not found association between autoantibody and premature birth in mothers with overt or subclinical hypothyroidism.

When birth weights were evaluated 6 babies were SGA (2%), 28 babies were LGA (12%) and 203 babies were AGA (86%). Only one of 95 babies born to mothers with hypothyroidism was SGA (1.1%), 17 of them were LGA (17.9%). Two of 5 babies born to mothers with hyperthyroidism were LGA (40%), 1 of them was SGA (20%). Five of 33 babies born to mothers with Hashimoto's disease were LGA (15.2%), one of them was SGA (3%). Thyroid hormones or presence of autoantibodies did not have effect on being SGA.

In the Tuija Mannistö's study perinatal mortality was found to be 2-3 times higher in autoantibody positive mothers (10). In our study, it was not found any association positive autoantibody and perinatal mortality.

In neonatal period, thyrotoxicosis is seen less than 2% and resulted with 22% mortality. 10-20% of babies born to mothers who were treated with propylthiouracil during pregnancy, developed neonatal hypothyroidism (20). This type of neonatal hypothyroidism usually regresses within 5 days after delivery (21). Lian et al. evaluated 35 babies that born from mothers with hyperthyroidism. In this study, abnormal thyroid function ratio was 48% and this ratio was statistically significant in the babies born to untreated mothers. It was noted that primary hypothyroidism ratio was 29.4%, subclinical hypothyroidism ratio was 29.4%, hypothyroxinemia ratio was 35.3% and central hypothyroidism was 5.9% (22). Another study reported that subclinical hyperthyroidism was a temporary situation and has no adverse effect (23). In our study, there was no adverse finding on 37 babies that born to mothers with subclinical hyperthyroidism. Thyroid function tests were totally normal. Two of 5 (%40) babies whose mothers had clinical hyperthyroidism had >20 μIU/mL TSH levels within the first week. But TSH levels of these two cases were return to normal in second week. This frequency is consistent with Lian XL's study results. The mothers with hyperthyroidism did not have thyroid stimulant antibodies and all of them were treated with propylthiouracil during pregnancy. LGA incidence was as high as 40% in babies born to mothers with hyperthyroidism. We found that maternal hyperthyroidism did not increase SGA risk and perinatal mortality. We did not encounter any morbidity.

Infants of mothers with thyroid disorders have increased risk for thyroid function abnormalities. Treatment of these infants can be started earlier by examination of thyroid function in the first week.

References

1. Burrow GN. Tyroid function and hyperfunction during gestation. Endocr Rev 1993; 14:194-202.
2. Smith C, Thomsett M, Choong C, Rodda C, McIntyre HD, Cotterill AM. Congenital thyrotoxicosis in premature infants. Clin Endocrinol 2001; 54:371-376.

3. Peleg D, Cada S, Peleg A, Ben Ami M. The relationship between maternal serum thyroid-stimulating immunoglobulin and fetal and neonatal thyrotoxicosis. Obstet Gynecol 2002; 99:1040-1043.

4. Glinoer D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. Endocr Rev 1997; 18:404-433.

5. Kamijo K, Saito T, Sato M, Yachi A, Mukai A, Fukusi M, et al. Transient subclinical hypothyroidism in early pregnancy. Endocrinol Jpn 1990; 37:397- 403.

6. Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RT, Pulkkinen A, et al. Prevalence of thyroid deficiency in pregnant women. Clin Endocrinol (Oxf) 1991; 35:41-46.

7. Montoro M, Collea JV, Frasier SD, Mestman JH. Successful outcome of pregnancy in women with hypothyroidism. Ann Intern Med 1981; 94:31-34.

8. Balen AH, Kurtz AB. Successful outcome of pregnancy with severe hypothyroidism. Case report and literature review. Br J Obstet Gynaecol 1990; 97:536-539.

9. Nicholson JF, Pesce MA. Laboratory medicine and reference tables. In: Behrman RE, Kliegman RM, Arvin AM (eds). Nelson Textbook of Pediatrics (15th ed). Philadelphia: WB Saunders 1996: 2031-2084.

10. Mannistö T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, et al. Perinatal Outcome of Children Born to Mothers with Thyroid Dysfunction or Antibodies: A Prospective Population-Based Cohort Study. J Clin Endocrinol Metab 2009; 94:772-779.

11. Wikner BN, Sparre LS, Stiller C, Källén B, Asker C. Maternal use of thyroid hormones in pregnancy and neonatal outcome. Acta Obstet Gynecol Scand 2008; 87:617-627.

12. Ogundele MO, Quinn MW, Salzmann M. Investigation of infants born to mothers with thyroid disorders: an ongoing search for consensus. J Eval Clin Pract 2010; 16:206-208.

13. Brown RS, Bellisario RL, Botero D, Fournier L, Abrams CA, Cowger ML, et al. Incidence of transient congenital hypothyroidism due to maternal thyrotropin receptor-blocking antibodies in over one million babies. J Clin Endocrinol Metab 1996; 81:1147-1151.

14. Pasquier S, Torresani T, Werder E, Gnehm HE. Transitory neonatal hypothyroidism caused by transplacental transfer of anti-receptor antibodies of hypophyseal thyroid stimulation: case report and estimated incidence. Schweiz Med Wochensch 1997; 127:1824-1828.

15. Roti E, Gardini E, Magotti MG, Pilla S, Minelli R, Salvi M, et al. Are thyroid function tests too frequently and inappropriately requested? J Endocrinol Invest 1999; 22:184-190.

16. Volpe, R. Rational use of thyroid function tests. Crit Rev Clin Lab Sci 1997; 34:405-438.

17. Ogilvy-Stuart AL. Neonatal thyroid disorders. Arch Dis Child Fetal Neonatal Ed 2002; 87:165-171.

18. Higuchi R, Miyawaki M, Kumagai T, Okutani T, Shima Y, Yoshiyama M, et al. Central hypothyroidism in infants who were born to mothers with thyrotoxicosis before 32 weeks' gestation: 3 cases. Pediatrics 2005; 115:623-625.

19. Leung AS, Millar LK, Koonings PP, Montoro M, Mestman JH. Perinatal outcome in hypothyroid pregnancies. Obstet Gynecol 1993; 81:349-353.

20. Momotani N, Noh JY, Ishikawa N, Ito K. Effects of propylthiouracil and methimazole on fetal thyroid status in mothers with Graves hyperthyroidism. J Clin Endocrinol Metab 1997; 82:3633-3636.

21. Cheron RG, Kaplan MM, Larsen PR, Selenkow HA, Crigler JF. Neonatal thyroid function after propylthiouracil therapy for maternal Graves's disease. N Engl J Med 1981; 304: 525-528.

22. Lian XL, Bai Y, Xun YH, Dai WX, Guo ZS. Effects of maternal hyperthyroidism and antithyroid drug therapy on thyroid function of newborn infants. Zhongguo Yi Xue Ke Xue Yuan Xue Bao 2005; 27:756-60.

23. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. Obstet Gynecol 2006; 107:337-341.