



Update on the Management of Thyroid Disease during Pregnancy

Chang Hoon Yim

Department of Internal Medicine, Cheil General Hospital & Women's Healthcare Center, Dankook University College of Medicine, Seoul, Korea

Thyroid dysfunction during pregnancy can result in serious complications for both the mother and infant; however, these complications can be prevented by optimal treatment of maternal overt thyroid dysfunction. Although several studies have demonstrated that maternal subclinical hypothyroidism is associated with obstetric complications and neurocognitive impairments in offspring, there is limited evidence that levothyroxine treatment can improve these complications. Therefore, most professional societies do not recommend universal screening for thyroid dysfunction during pregnancy, and instead recommend a case-finding approach in which only high-risk women are tested. However, recent studies have estimated that targeted thyroid function testing misses approximately 30% to 55% of hypothyroidism cases in pregnant women, and some associations and researchers have recommended universal screening of pregnant women to facilitate the early detection and treatment of overt hypothyroidism. This review summarizes recent data on thyroid function test changes, thyroid functional disorder management, and thyroid screening during pregnancy.

Keywords: Pregnancy; Thyroid diseases; Hyperthyroidism; Hypothyroidism

INTRODUCTION

Thyroid dysfunction is a commonly encountered endocrine disorder during pregnancy. Overt thyroid dysfunction occurs in almost 1% of all pregnant women [1,2]. The management of thyroid disease during pregnancy has been reviewed in the guidelines of several societies including the American Thyroid Association (ATA) and the Endocrine Society and the European Thyroid Association (ETA) [3-5]. It is well documented that maternal overt thyroid dysfunction is associated with an increased risk in adverse maternal and fetal outcomes. However,

there is conflicting evidence as to whether subclinical hypothyroidism (SCH) is associated with adverse pregnancy outcomes, and whether universal thyroid screening during pregnancy is efficacious. Therefore, this review summarizes the management of thyroid disease during pregnancy with reference to several published guidelines and recent data.

THYROID CHANGES DURING PREGNANCY

Various hormonal changes and increased metabolic demands

Received: 17 July 2016, **Revised:** 22 July 2016, **Accepted:** 27 July 2016

Corresponding author: Chang Hoon Yim

Department of Internal Medicine, Cheil General Hospital & Women's Healthcare Center, Dankook University College of Medicine, 17 Seoae-ro 1-gil, Jung-gu, Seoul 04619, Korea

Tel: +82-2-2000-7248, **Fax:** +82-2-2264-1490,

E-mail: changhoon.yim@cgh.co.kr

Copyright © 2016 Korean Endocrine Society

This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0/>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

occur during pregnancy and profoundly affect thyroid function. It is important to understand both the expected changes in thyroid function test results during a normal pregnancy and the potential effects of pregnancy on preexisting thyroid diseases [6]. The major expected changes during normal pregnancy are an increase in the serum thyroxine-binding globulin (TBG) concentration and the stimulation of the thyrotropin (TSH) receptor by human chorionic gonadotropin (hCG) [7]. The serum TBG concentration rises almost two-fold during the first 20 weeks of gestation, and as a result, both serum total thyroxine (T4) and triiodothyronine concentrations increase [8]. The serum hCG concentration increases after fertilization and peaks at 10 to 12 weeks. During this peak, the thyrotropic activity of hCG reduces the concentration of serum TSH [9]. Later in pregnancy, the serum TSH concentration steadily returns to the normal range and the serum free T4 concentration declines [10].

Maternal thyroid hormones play an important role in fetal development. Because the fetal thyroid only produces thyroid hormones after 16 weeks of gestation, fetal development depends on the state of the maternal thyroid for the first half of pregnancy [11]. Therefore, maternal thyroid dysfunction can result in adverse outcomes for the fetus as well as the mother.

NORMAL RANGE OF TSH IN PREGNANCY

Due to the lack of typical symptoms of thyroid dysfunction during pregnancy, thyroid dysfunction must be diagnosed by a thyroid function test. The serum TSH concentration is the initial and most reliable measure of thyroid function during pregnancy [12]. Due to the physiologic changes in TSH levels during pregnancy, the ATA guidelines recommend using trimester-specific reference ranges for TSH [3]. If these reference ranges are not available in the laboratory, the following reference ranges can be used: first trimester, 0.1 to 2.5 mIU/L; second trimester, 0.2 to 3.0 mIU/L; third trimester, 0.3 to 3.0 mIU/L. Serum TSH concentration may also be affected by many other factors including analytical method, thyroid autoantibody status, ethnicity, and iodine nutrition. Since the reference range for the first trimester in the ATA guidelines was derived from studies during weeks 9 to 12 of gestation, this cutoff has been too low for pregnant women visiting the clinic before 8 weeks of gestation [13]. Also, different reference ranges for TSH in the first trimester have been reported for different populations [14]. Therefore, the correct interpretation of thyroid function tests requires knowledge of a woman's gestational week and the appropriate population-based reference interval [15,16].

HYPOTHYROIDISM IN PREGNANCY

In iodine-sufficient areas, the most common cause of hypothyroidism during pregnancy is chronic autoimmune thyroiditis. The diagnosis of hypothyroidism is based on an elevated serum TSH concentration. When serum TSH is elevated, measurement of the serum free T4 concentration is required to classify the patient's status as either SCH or overt hypothyroidism (OH) [3]. OH is defined as an elevated trimester-specific TSH concentration with a reduced free T4 concentration, or an elevated TSH concentration (>10 mIU/L) irrespective of the free T4 level. The prevalence of OH during pregnancy has been estimated to be 0.3% to 0.5% [2]. Untreated OH is associated with an increased risk of adverse pregnancy complications, including premature birth, low birth weight, and miscarriage [17,18]. Haddow et al. [19] indicated that untreated OH during pregnancy may have detrimental effects on the neuropsychological development of the unborn child. SCH is defined as an elevated trimester-specific serum TSH concentration with a normal free T4 level. Early studies reported the prevalence of SCH to be 2% to 2.5% in pregnant women [20]. However, recent studies utilizing the ATA criteria for SCH (TSH >2.5 mIU/L) have reported that the prevalence may be as high as 27.8% [13,21,22].

In many observational studies, SCH in pregnancy has been found to be associated with adverse outcomes for both the mother and the offspring, including gestational diabetes, gestational hypertension, placental abnormalities, miscarriage, preterm labor, and low birth weight [20,23]. However, other studies have not found any association between SCH and pregnancy complications [24,25]. At present, the harmful effects of maternal SCH on fetal neuropsychological development are less clear. Some studies have found an association of SCH in early pregnancy with poor intellectual and motor development in the offspring [26,27]. However, other studies have not found any association between SCH in mothers and the neuropsychological development of their children [28-30].

Because of the clear association between OH and adverse outcomes for both the mother and the offspring, OH in pregnancy should be treated. However, the treatment of SCH is not universally recommended, since there are limited data demonstrating the beneficial effects of levothyroxine (LT4) treatment on obstetric outcomes. One randomized control study demonstrated that treatment of SCH pregnant women with LT4 reduced the occurrence of adverse events in both the mother and the fetus [31]. Subgroup analysis of the Controlled Antenatal Thyroid Screening (CATS) study revealed that maternal abnor-

mal thyroid function was associated with certain adverse obstetric outcomes, while LT4 treatment may improve these outcomes [32]. In a randomized controlled trial to assess the effects of LT4 treatment on cognitive function, LT4 treatment for maternal SCH did not improve the cognitive function of children at 3 years of age [33]. In addition, in another randomized, double-blinded, placebo-controlled trial, treatment for maternal SCH did not improve cognitive outcomes in offspring at 5 years of age [34].

While ATA guidelines recommend the treatment of pregnant women who have SCH and positive thyroid peroxidase (TPO) antibodies, the guidelines of the Endocrine Society and the ETA recommend LT4 treatment for all pregnant women with SCH, irrespective of their TPO antibodies [3-5]. The goal of hypothyroidism treatment is to maintain the serum TSH levels within the trimester-specific reference range. Thyroid function tests should be conducted every 4 to 6 weeks during the first trimester and once during the second and third trimesters, and the dose of LT4 should be adjusted [3].

Women being treated for hypothyroidism before pregnancy need to increase their LT4 dose during pregnancy [35]. The dose requirement may increase by 30% to 50% during pregnancy and as early as 4 to 6 weeks of gestation, and may gradually increase through 16 to 20 weeks of gestation [3,36].

THYROTOXICOSIS IN PREGNANCY

Overt thyrotoxicosis occurs in 0.2% to 0.4% of all pregnancies [1,18,37]. The diagnosis of overt hyperthyroidism during pregnancy should be based on a reduced serum TSH value and an elevated free T4 level that exceeds the normal range for pregnancy [3]. The most common cause of autoimmune hyperthyroidism in pregnancy is Graves' disease. However, in the first half of gestation, gestational transient thyrotoxicosis may occur in 2% to 3% of all pregnancies [7,11,38]. It is important to differentiate Graves' hyperthyroidism from gestational transient thyrotoxicosis, since the two diseases have distinct clinical courses and are managed differently [39]. The findings of a history of thyroid disease, goiter, ophthalmopathy, and TSH receptor antibody (TRAb) positivity favor the diagnosis of Graves' hyperthyroidism [40]. Gestational transient thyrotoxicosis does not require antithyroid treatment, since the serum T4 level returns to normal by 14 to 18 weeks gestation [1].

Subclinical hyperthyroidism is defined as a reduced serum TSH concentration, with free T4 levels within the normal reference range. It has not been associated with adverse pregnancy

outcomes; therefore, the treatment of pregnant women with subclinical hyperthyroidism is not required [41].

Overt hyperthyroidism can adversely affect the mother and child, depending on the severity of the disease. Inadequately treated maternal hyperthyroidism has been associated with a high risk of preeclampsia, heart failure, preterm delivery, low birth weight, and fetal loss [42,43]. Propylthiouracil or methimazole can be used to treat pregnant women with overt hyperthyroidism to minimize the risk of adverse outcomes. However, the use of an antithyroid drug in early pregnancy is associated with birth defects in 3.4% of exposed children [44]. Propylthiouracil has been the preferred treatment for overt hyperthyroidism in pregnancy because it crosses the placenta less readily than methimazole, and the birth defects associated with propylthiouracil (mainly aplasia cutis, choanal or esophageal atresia, and dysmorphic facies) seem less severe than those associated with methimazole [45,46]. However, the U.S. Food and Drug Administration warned about the risk of hepatotoxicity associated with the use of propylthiouracil [47]. Correspondingly, most professional societies have recommended propylthiouracil therapy during the first trimester followed by a switch to methimazole in the second and third trimesters [3,4,48].

The goal of overt hyperthyroidism treatment is to maintain the serum free T4 concentration in the upper normal range. Serum free T4 and TSH levels should be assessed every 2 to 4 weeks with dose adjustment. Once euthyroidism is achieved, patients should be monitored every 4 to 8 weeks [3]. The natural course of Graves' hyperthyroidism gradually improves in late pregnancy, so antithyroid drug dose adjustment is needed in the second and third trimesters [49]. β -Blocker treatment may be used to control hypermetabolic symptoms in severe hyperthyroidism. However, this agent should be discontinued within 2 weeks, since long-term use of β -blockers has been associated with intrauterine growth restriction, fetal bradycardia, and neonatal hypoglycemia [50].

The prevalence of fetal hyperthyroidism is 1% to 5% in pregnant women with Graves' hyperthyroidism [51]. Persistently high levels of maternal serum TRAb have been associated with fetal hyperthyroidism [52]. Therefore, it is recommended that the TRAb test be performed by 24 to 28 weeks of gestation to predict the risk of fetal thyroid dysfunction [53]. Fetal thyroid assessment by ultrasound is recommended in women with uncontrolled hyperthyroidism or high TRAb titers. Fetal tachycardia (>170 beats per minute), growth restriction, goiter, accelerated bone maturation, heart failure, and hy-

drops are suspicious ultrasound findings of fetal hyperthyroidism [51,52].

THYROID SCREENING IN PREGNANCY

Although the adverse maternal and fetal effects of untreated overt thyroid dysfunction have been well described, the association between untreated SCH and adverse pregnancy outcomes are less well defined. Therefore, performing thyroid function screening for all asymptomatic pregnant women is controversial. Negro et al. [31] demonstrated that the treatment of thyroid dysfunction detected by universal screening prevented adverse outcomes in pregnant women. However, in the CATS study, antenatal universal thyroid screening and treatment of maternal thyroid dysfunction did not improve Intelligence Quotient (IQ) scores in offspring [36]. Large prospective randomized controlled trials for the universal screening and treatment of pregnant women with SCH are underway, but the results of these trials have not yet been published [54,55].

Because there is insufficient evidence favoring universal thyroid screening in pregnant women, most professional societies recommend a case-finding approach targeting thyroid function testing in high-risk groups [3-5,48]. Targeted screening includes women who have a personal history, symptom, or sign of a thyroid disorder, a positive family history, and thyroid antibody positivity [3,4]. However, some recent studies have estimated that targeted thyroid function testing would miss about 30% to 55% of pregnant women with hypothyroidism [31,56,57]. Additionally, universal thyroid screening could detect 200 to 300 women with undiagnosed OH per 100,000 pregnancies [58]. Therefore, some endocrinologists have argued for the universal screening of pregnant women for overt thyroid disease based on the results of the early detection and treatment of OH during pregnancy [57,59].

CONCLUSIONS

Maternal overt thyroid dysfunction is associated with an increased risk of adverse outcomes. To date, there has been conflicting evidence regarding the association of SCH with adverse pregnancy outcomes and the efficacy of universal thyroid screening during pregnancy. Large prospective randomized controlled trials are needed to resolve these controversies. Results from these studies have the potential to greatly change the management of pregnant women with thyroid dysfunction.

CONFLICTS OF INTEREST

No potential conflict of interest relevant to this article was reported.

ORCID

Chang Hoon Yim <http://orcid.org/0000-0002-9019-4907>

REFERENCES

- Glinoe D. Thyroid hyperfunction during pregnancy. *Thyroid* 1998;8:859-64.
- Klein RZ, Haddow JE, Faix JD, Brown RS, Hermos RJ, Pulkkinen A, et al. Prevalence of thyroid deficiency in pregnant women. *Clin Endocrinol (Oxf)* 1991;35:41-6.
- Stagnaro-Green A, Abalovich M, Alexander E, Azizi F, Mestman J, Negro R, et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and postpartum. *Thyroid* 2011;21:1081-125.
- De Groot L, Abalovich M, Alexander EK, Amino N, Barbour L, Cobin RH, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab* 2012;97:2543-65.
- Lazarus J, Brown RS, Daumerie C, Hubalewska-Dydejczyk A, Negro R, Vaidya B. 2014 European Thyroid Association guidelines for the management of subclinical hypothyroidism in pregnancy and in children. *Eur Thyroid J* 2014;3:76-94.
- Werner SC, Ingbar SH, Braverman LE, Utiger RD. *Werner & Ingbar's the thyroid*. 9th ed. Philadelphia: Lippincott Williams & Wilkins; 2005. p. 1086.
- Glinoe D, de Nayer P, Bourdoux P, Lemone M, Robyn C, van Steirteghem A, et al. Regulation of maternal thyroid during pregnancy. *J Clin Endocrinol Metab* 1990;71:276-87.
- Baloch Z, Carayon P, Conte-Devolx B, Demers LM, Feldt-Rasmussen U, Henry JF, et al. Laboratory medicine practice guidelines. Laboratory support for the diagnosis and monitoring of thyroid disease. *Thyroid* 2003;13:3-126.
- Ballabio M, Poshychinda M, Ekins RP. Pregnancy-induced changes in thyroid function: role of human chorionic gonadotropin as putative regulator of maternal thyroid. *J Clin Endocrinol Metab* 1991;73:824-31.
- Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic

- N, Soldin SJ. Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gestation: trends and associations across trimesters in iodine sufficiency. *Thyroid* 2004;14:1084-90.
11. Glinoe D. The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology. *Endocr Rev* 1997;18:404-33.
 12. Glinoe D, Spencer CA. Serum TSH determinations in pregnancy: how, when and why? *Nat Rev Endocrinol* 2010;6:526-9.
 13. Li C, Shan Z, Mao J, Wang W, Xie X, Zhou W, et al. Assessment of thyroid function during first-trimester pregnancy: what is the rational upper limit of serum TSH during the first trimester in Chinese pregnant women? *J Clin Endocrinol Metab* 2014;99:73-9.
 14. Brabant G, Peeters RP, Chan SY, Bernal J, Bouchard P, Salvatore D, et al. Management of subclinical hypothyroidism in pregnancy: are we too simplistic? *Eur J Endocrinol* 2015;173:P1-11.
 15. McNeil AR, Stanford PE. Reporting thyroid function tests in pregnancy. *Clin Biochem Rev* 2015;36:109-26.
 16. Medici M, Korevaar TI, Visser WE, Visser TJ, Peeters RP. Thyroid function in pregnancy: what is normal? *Clin Chem* 2015;61:704-13.
 17. Stagnaro-Green A. Overt hyperthyroidism and hypothyroidism during pregnancy. *Clin Obstet Gynecol* 2011;54:478-87.
 18. Casey BM, Leveno KJ. Thyroid disease in pregnancy. *Obstet Gynecol* 2006;108:1283-92.
 19. Haddow JE, Palomaki GE, Allan WC, Williams JR, Knight GJ, Gagnon J, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341:549-55.
 20. Casey BM, Dashe JS, Wells CE, McIntire DD, Byrd W, Leveno KJ, et al. Subclinical hypothyroidism and pregnancy outcomes. *Obstet Gynecol* 2005;105:239-45.
 21. Blatt AJ, Nakamoto JM, Kaufman HW. National status of testing for hypothyroidism during pregnancy and postpartum. *J Clin Endocrinol Metab* 2012;97:777-84.
 22. Stagnaro-Green A. Postpartum management of women begun on levothyroxine during pregnancy. *Front Endocrinol (Lausanne)* 2015;6:183.
 23. Maraka S, Ospina NM, O'Keeffe DT, Espinosa De Ycaza AE, Gionfriddo MR, Erwin PJ, et al. Subclinical hypothyroidism in pregnancy: a systematic review and meta-analysis. *Thyroid* 2016;26:580-90.
 24. Cleary-Goldman J, Malone FD, Lambert-Messerlian G, Sullivan L, Canick J, Porter TF, et al. Maternal thyroid hypofunction and pregnancy outcome. *Obstet Gynecol* 2008;112:85-92.
 25. Mannisto T, Vaarasmaki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, et al. Thyroid dysfunction and autoantibodies during pregnancy as predictive factors of pregnancy complications and maternal morbidity in later life. *J Clin Endocrinol Metab* 2010;95:1084-94.
 26. Li Y, Shan Z, Teng W, Yu X, Li Y, Fan C, et al. Abnormalities of maternal thyroid function during pregnancy affect neuropsychological development of their children at 25-30 months. *Clin Endocrinol (Oxf)* 2010;72:825-9.
 27. Su PY, Huang K, Hao JH, Xu YQ, Yan SQ, Li T, et al. Maternal thyroid function in the first twenty weeks of pregnancy and subsequent fetal and infant development: a prospective population-based cohort study in China. *J Clin Endocrinol Metab* 2011;96:3234-41.
 28. Javed Z, Sathyapalan T. Levothyroxine treatment of mild subclinical hypothyroidism: a review of potential risks and benefits. *Ther Adv Endocrinol Metab* 2016;7:12-23.
 29. Henrichs J, Bongers-Schokking JJ, Schenk JJ, Ghassabian A, Schmidt HG, Visser TJ, et al. Maternal thyroid function during early pregnancy and cognitive functioning in early childhood: the generation R study. *J Clin Endocrinol Metab* 2010;95:4227-34.
 30. Behrooz HG, Tohidi M, Mehrabi Y, Behrooz EG, Tehrani-dooost M, Azizi F. Subclinical hypothyroidism in pregnancy: intellectual development of offspring. *Thyroid* 2011;21:1143-7.
 31. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening versus case finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. *J Clin Endocrinol Metab* 2010;95:1699-707.
 32. Taylor PN, Thayer D, Lacey A, Boelaert K, Ludgate ME, Rees A, et al. Controlled antenatal thyroid screening study: obstetric outcome. *Thyroid* 2015;25(Suppl 1):A358.
 33. Lazarus JH, Bestwick JP, Channon S, Paradise R, Maina A, Rees R, et al. Antenatal thyroid screening and childhood cognitive function. *N Engl J Med* 2012;366:493-501.
 34. Casey B. Effect of treatment of maternal subclinical hypothyroidism or hypothyroxinemia on IQ in offspring. *Am J Obstet Gynecol* 2016;214(1 Suppl):S2.
 35. Mandel SJ, Larsen PR, Seely EW, Brent GA. Increased need for thyroxine during pregnancy in women with primary hy-

- pothyroidism. *N Engl J Med* 1990;323:91-6.
36. Alexander EK, Marqusee E, Lawrence J, Jarolim P, Fischer GA, Larsen PR. Timing and magnitude of increases in levothyroxine requirements during pregnancy in women with hypothyroidism. *N Engl J Med* 2004;351:241-9.
 37. Patil-Sisodia K, Mestman JH. Graves hyperthyroidism and pregnancy: a clinical update. *Endocr Pract* 2010;16:118-29.
 38. Glinoe D, De Nayer P, Robyn C, Lejeune B, Kinthaert J, Meuris S. Serum levels of intact human chorionic gonadotropin (HCG) and its free alpha and beta subunits, in relation to maternal thyroid stimulation during normal pregnancy. *J Endocrinol Invest* 1993;16:881-8.
 39. Goodwin TM, Montoro M, Mestman JH. Transient hyperthyroidism and hyperemesis gravidarum: clinical aspects. *Am J Obstet Gynecol* 1992;167:648-52.
 40. Tan JY, Loh KC, Yeo GS, Chee YC. Transient hyperthyroidism of hyperemesis gravidarum. *BJOG* 2002;109:683-8.
 41. Casey BM, Dashe JS, Wells CE, McIntire DD, Leveno KJ, Cunningham FG. Subclinical hyperthyroidism and pregnancy outcomes. *Obstet Gynecol* 2006;107(2 Pt 1):337-41.
 42. Davis LE, Lucas MJ, Hankins GD, Roark ML, Cunningham FG. Thyrotoxicosis complicating pregnancy. *Am J Obstet Gynecol* 1989;160:63-70.
 43. Aggarawal N, Suri V, Singla R, Chopra S, Sikka P, Shah VN, et al. Pregnancy outcome in hyperthyroidism: a case control study. *Gynecol Obstet Invest* 2014;77:94-9.
 44. Andersen SL, Olsen J, Laurberg P. Antithyroid drug side effects in the population and in pregnancy. *J Clin Endocrinol Metab* 2016;101:1606-14.
 45. Andersen SL, Olsen J, Wu CS, Laurberg P. Birth defects after early pregnancy use of antithyroid drugs: a Danish nationwide study. *J Clin Endocrinol Metab* 2013;98:4373-81.
 46. Yoshihara A, Noh J, Yamaguchi T, Ohye H, Sato S, Sekiya K, et al. Treatment of graves' disease with antithyroid drugs in the first trimester of pregnancy and the prevalence of congenital malformation. *J Clin Endocrinol Metab* 2012;97:2396-403.
 47. Bahn RS, Burch HS, Cooper DS, Garber JR, Greenlee CM, Klein IL, et al. The role of propylthiouracil in the management of Graves' disease in adults: report of a meeting jointly sponsored by the American Thyroid Association and the Food and Drug Administration. *Thyroid* 2009;19:673-4.
 48. American College of Obstetricians and Gynecologists. Practice bulletin no. 148: thyroid disease in pregnancy. *Obstet Gynecol* 2015;125:996-1005.
 49. Hamburger JI. Diagnosis and management of Graves' disease in pregnancy. *Thyroid* 1992;2:219-24.
 50. Rubin PC. Current concepts: beta-blockers in pregnancy. *N Engl J Med* 1981;305:1323-6.
 51. Polak M, Le Gac I, Vuillard E, Guibourdenche J, Leger J, Toubert ME, et al. Fetal and neonatal thyroid function in relation to maternal Graves' disease. *Best Pract Res Clin Endocrinol Metab* 2004;18:289-302.
 52. McKenzie JM, Zakarija M. Fetal and neonatal hyperthyroidism and hypothyroidism due to maternal TSH receptor antibodies. *Thyroid* 1992;2:155-9.
 53. Matthews DC, Syed AA. The role of TSH receptor antibodies in the management of Graves' disease. *Eur J Intern Med* 2011;22:213-6.
 54. Hales C, Channon S, Taylor PN, Draman MS, Muller I, Lazarus J, et al. The second wave of the Controlled Antenatal Thyroid Screening (CATS II) study: the cognitive assessment protocol. *BMC Endocr Disord* 2014;14:95.
 55. Eunice Kennedy Shriver National Institute of Child Health and Human Development (NICHD). Thyroid therapy for mild thyroid deficiency in pregnancy (TSH) [Internet]. Bethesda: National Library of Medicine; 2000 [cited 2016 Jul 26]. Available from: <http://www.clinicaltrials.gov/ct/show/NCT00388297>.
 56. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchinson S, et al. Detection of thyroid dysfunction in early pregnancy: universal screening or targeted high-risk case finding? *J Clin Endocrinol Metab* 2007;92:203-7.
 57. Horacek J, Spitalnikova S, Dlabalova B, Malirova E, Vizda J, Svilius I, et al. Universal screening detects two-times more thyroid disorders in early pregnancy than targeted high-risk case finding. *Eur J Endocrinol* 2010;163:645-50.
 58. Laurberg P, Andersen SL, Pedersen IB, Andersen S, Carle A. Screening for overt thyroid disease in early pregnancy may be preferable to searching for small aberrations in thyroid function tests. *Clin Endocrinol (Oxf)* 2013;79:297-304.
 59. Stagnaro-Green A. Screening pregnant women for overt thyroid disease. *JAMA* 2015;313:565-6.