Screening for maternal thyroid disease in pregnancy: a review

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Abstract

Many changes occur in thyroid function as a result of the dynamics of serum thyroxine-binding globulin, estrogens and human chorionic gonadotropic hormone levels during pregnancy. Hyperthyroidism is defined as a thyroid stimulating hormone value below the normal range with elevated levels of free T3 and free T4. In opposition, hypothyroidism is defined as an elevated TSH level with a decreased level of free T3 or free T4. The most frequent adverse effects of hyperthyroidism are increased risk of spontaneous miscarriage, preterm birth and preeclampsia. Untreated hypothyroidism is associated to psychoneurological deficiency in offspring. The main causes of hypothyroidism are chronic autoimmune thyroiditis (Hashimoto' thyroiditis), iodine deficiency, or thyroidectomy while hyperthyroidism is often determined by Morbus Graves. However, there is an ongoing debate regarding the need for universal screening of thyroid disease during pregnancy. Therefore, this review discusses the clinical evidence related to thyroid dysfunction in pregnant women.
Keywords: *pregnancy, thyroid disease, hyperthyroidism, hypothyroidism, adverse effects*

1. Introduction

Since thyroid hormones have a crucial role both in the development of a healthy baby and in maintaining the health of the mother, investigation of thyroid function during pregnancy is often recommended. Thyroid diseases are disorders that affect the thyroid gland; sometimes too much or too little thyroid hormone is produced, but not every time clinical symptoms are manifest. Thyroid hormones are important to fetal nervous system development and severe hypothyroiditis could determine defectuous brain development of the offspring. During pregnancy significant changes in thyroid function occurs, and a subclinical dysfunction before pregnancy may became manifest during pregnancy.

The main changes are determined by two hormones: human chorionic gonadotropin (hCG) and estrogens. Thyroxine binding globulin (TBG) concentrations increases as a result of higher estrogen levels present during pregnancy[1]. Human chorionic hCG is a hormone produced by placenta and has some structural similarities to thyroid stimulating hormone (TSH). Human chorionic gonadotropin hormone mildly stimulates the thyroid function and the secretion of triiodothyronine (T3) and thyroxine (T4). In the past few years many pregnant women that suffer from hypothyroidism have been observed[2,3]. Hypothyroid dysfunction has also been noted in postpartum period, most commonly in predisposed women[4].

Because of reversible changes in homeostasis of thyroid hormones during pregnancy, the diagnosis of thyroid dysfunction could be easily confused. Serum TSH showed the highest significance in the diagnosis of thyroid dysfunction during pregnancy, but it is often necessary to complete diagnosis measurement of value of FT3 or FT4. In the first trimester the TSH value should be under 2.5 mIU/L[5]. Moreover, in the first trimester of pregnancy total T4 serum level is usually higher and free T4 is comparable to or lower than for non-pregnant or second or third trimester pregnant women. This is determined due to the increased TBG levels[6]. The present contribution highlights the basic information and clinical aspects of thyroid function during pregnancy as far as hyper- and hypothyroidism are concerned, and points out that further routine screening for thyroid function warrants consideration.

2. Clinical hyperthyroidism

Hyperthyroidism is defined as a serum TSH below the trimester-specific range with elevated levels of free T3 and T4. The causes for hyperthyroidism in pregnancy are represented by thyroiditis, excessive hormone intake, and transient gestational thyrotoxicosis or Graves diseases[7]. In the case of Graves disease, the diagnosis should take into account the hyperthyroid symptoms prior to pregnancy and the presence of antibodies against TSH receptor[8].

Many clinical signs of hyperthyroidism may not be so clear from the beginning, since symptoms such as tachycardia, sweating, dyspnoea, and nervousness can also be found in a normal pregnancy. Heart failure, the risk of preeclampsia, spontaneous miscarriage, fetal growth restriction and preterm birth are significantly higher in women with undiagnosed hyperthyroidism[9,10].

3. Clinical hypothyroidism

Hypothyroidism is defined as an elevated TSH levels with a decreased level of free T3 and freeT4[11]. Hypothyroidism was found in around 2.5% of normal pregnancies. The most frequent causes of hypothyroidism are chronic autoimmune thyroiditis (Hashimoto' thyroiditis), iodine deficiency (ID), or thyroidectomy. While endemic iodine deficiency can lead to hypothyroidism, mild to moderate ID can lead to isolated hypothyroxinemia. Isolated hypothyroxinemia is defined as the presence of a free thyroxine (FT4) value below the 2.5 the percentile with a thyrotropin level within the reference values. Nowadays, about thirty countries are iodine defici-

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ent[12]. The untreated cause could lead to increased risk for adverse pregnancy complications: premature birth, low birth weight, miscarriages or psychoneurological deficiency in the offspring[13,14,15,16]. Considering the association between hypothyroidism and the above presented risks, the treatment in these pregnant women becomes mandatory. The goal of the treatment is to normalize maternal serum TSH values to normal specific values, with respect to the first trimester[14].

Haddow and contributors[17] compared a group of 7 year-old children who were born from mothers with higher TSH and lower T4 levels, with a control group in which the mothers had normal TSH. The result of the study was that 19% of the first group had an IQ<85 compared to 5% of the control group. Other studies have been showed similar data when the mothers of the children had low T3 or T4 but normal TSH[18].

Many physiological and neurological deficiencies in children have been described in areas with iodine deficiency. Neurological deficiencies are the result of maternal hypothyroxinaemia rather than of high TSH[19]. Therefore, optimum iodine nutrition during pregnancy should be taken into account and measured. However, even in the areas where iodine intake is sufficient there is evidence of substantial gestational iodine deficiency[20]. The recommendation is a daily intake of 200 μ Iodine/day, which is not always achieved[21].

4. Screening for thyroid dysfunction in pregnant women

The abnormalities of measured thyroid hormone levels found in some pregnant women suggest that further screening for thyroid dysfunction in relation to pregnancy should be taken into consideration. Women with established overt thyroid dysfunction, including both hyper- and hypothyroidism, should be treated to maintain a euthyroid state during pregnancy because identification and treatment of pregnant women with thyroid dysfunction will improve maternal and infant outcomes[22,23].

Ever since 2007 The American College of Obstetricians and Gynecology (ACOG), has recommended thyroid testing only in high-risk pregnant women who are symptomatic or have a personal history of thyroid disease. The Society for Maternal-Fetal Medicine further supports the same recommendation implemented by ACOG[24].

The American Thyroid Association recommended in 2011 against universal screening of healthy pregnant women for thyroid dysfunction. The Endocrine Society Task Force could not reach any agreement on thyroid testing recommendation in pregnancy[25]. With all this, some members recommended screening of all pregnant women for TSH level in the 9th week or at the time of their first visit. Other members recommended against universal screening of pregnant women at the time of their first visit and supported the identification of high-risk women instead[26].

Considering the debate regarding the screening for such diseases in pregnant women, more epidemiological studies are necessary to clarify this issue. The potential risk of universal screening would include: cost of treatment, follow-up, possible misinterpretation of serum tests results, and inadequate treatment. However, screening may be pertinent given the high prevalence of thyroid dysfunction in pregnant women and long term consequences of these disturbances on fetal and child development.

5. Conclusions and Future Research

The strategy of the screening of thyroid dysfunction in pregnant women remains controversial. Observational studies have evaluated maternal and fetal outcomes in women with both hyper- and hypothyroidism. As more data will become available regarding the screening for thyroid dysfunction during pregnancy, the recommendation for thyroid testing will likely come to be applied. The present data shows the need for a targeted approach to case finding in pregnant women with thyroid disease and a better treatment which can improve outcomes. ■

References

1. Glinoer D, The regulation of thyroid function in pregnancy: pathways of endocrine adaptation from physiology to pathology, Endocr.Rev., 1997, 18, 404-33.
2. Lazarus JH, Kokandi A, Thyroid disease in relation to pregnancy. A decade from change. Clin.Endocrinol., 2000, 53, 265-78.
3. Glinoer D, Management of hypo- and hyperthyroidism during pregnancy. Growth Horm IGF Res, 2003, 13, S45-54.
4. Stagno-Green A, Postpartum thyroiditis, Best Pronat Res Clin Endocrinol Metabol, 2004, 18, 303-16.
5. Stagnaro-Green A., Abalovich M, Alexander E et al. Guidelines of the American Thyroid Association for the diagnosis and management of thyroid disease during pregnancy and post-partum, Thyroid, 21, 10, 2011.
6. Lee RH, Spencer CA, Mestman JH et al., Free T4 immunoassays are flawed during pregnancy, Americal Journal of Obstetrics and Gynecology, 200, 3, 2009, 260.e1-260. e6.
7. Glinoer D., Thyroid hyperfunction during pregnancy, Thyroid, 8, 9, 1998, 859-864.
8. Goodwin TM, Montaro M, Mestman JH, Transient hyperthyroidism and hyperremesis gravidarum: clinical aspects, American Journal of Obstetrics and Gynecology, 167, 3, 1992, 648-652.
9. Millar LK, Wing DA, Leung AS, Koonings PP, Montoro MN, Mestman JH, Low birth weight and pre-eclampsia in pregnancies complicated by hyperthyroidism, Obstetrics and Gynecology, 84, 6, 1994, 946-949.
10. Casey BM, Dashe JS, Wells CE et al., Subclinical hypothyroidism and pregnancy outcomes, Obstetrics and Gynecology, 105, 2, 2005, 239-245.
11. Davis LE, Leveno KJ, Cunninghans FG, Hypothyroidism complicating pregnancy, Obstetrics and Gynecology, 72, 1, 1998, 108-112.
12. Soldin OP, Tractenberg RE, Hollowell JG, Jonklaas J, Janicic N, Soldin SJ, Trimester-specific changes in maternal thyroid hormone, thyrotropin, and thyroglobulin concentrations during gstation: trends and associations across trimesters in iodine sufficiency, Thyroid, 14, 2004, 1084-1090.
13. Glinoer D, Fernandez Soto M, Bourdoux P et al., Pregnancy in patients with wild thyroid abnormalities: maternal and neonatal repercussions, J Clin Endocrinol Metabol, 1991, 73, 421-7.
14. Suks MI, Ortiz E, Daniels GH, Subclinical thyroid disease: scientific review and guidelines for diagnosis and management, JAMA, 2004, 291: 228-38.
15. Benhadi N, Wiersinga WM, Reitsma JB, Wrijkotte TG, Bousel GJ, Higher maternal TSH levels in pregnancy are associated with increased risk for miscarriage, fetal or neonatal death, Eur J Endocrinol, 2009, 160, 985-991.
16. Haddow JE, Knight GJ, Palomaki GE, McClain MR, Pulkkinen AJ, The reference range and within person variability of thyroid stimulating hormone during the first and second trimester of pregnancy, J Med Screen, 11, 2004, 170-174.
17. Haddow JE, Padomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child, The New England Journal of Medicine, 341, 8, 1999, 549-555.
18. Allan WC, Haddow JE, Palomaki GE, Williams JR, Mitchell ML, Hermos RJ, Faix JD, Klein RZ, Maternal thyroid deficiency and pregnancy complications: implications for population screening, J Med Screen, 7, 2000, 127-130.
19. Pop VJ, Brouwers EP, Vader HL et al., Maternal hypothyroxiconaemia during early pregnancy and subsequent child development: a 3-year follow-up study, Clin. Endocrinol 2003, 59, 282-8.
20. Pearce EN, Bazrafshan HR, Hex et al, Dietary iodine in pregnant women from the Boston, Massachusetts area. Thyroid, 2004, 14, 327-8.
21. Pearce EN, Andersson M, Zimmermann M, Global iodine nutrition-where do we stand in 2013? Thyroid, 23, 5, 2013, 523-524.
22. Delange FM, Endemic cretinism. In: Braverman LE, Utiger RD eds., Werner and Ingbar's the thyroid. Philadelphia: Lippincott Williams & Wilkins, 2000, 743-54.
23. Allen WC, Haddow JE, Palomaki GE et al., Maternal thyroid deficiency and pregnancy complications: implications for population screening, J Med Screen 2000, 7, 127-30.
24. Committee on Patient Safety and Quality Improvement and Committee on Professional Liability, ACOG Committee Opinion No.381: subclinical hypothyroidism in pregnancy, Obstetrics and Gynecology, 110, 4, 2007, 959-960.
25. 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, 1699-1707.
26. Springer D, Zima T, Limanova Z, Reference intervals in evaluation of maternal thyroid function during the first trimester of pregnancy, Eur J Endocrinol, 2009, 160, 791-797.