Review Article

Hypothyroidism in pregnancy

Rakesh Kumar Sahay, V. Sri Nagesh

Department of Endocrinology, Osmania Medical College and Osmania General Hospital, Hyderabad, India

ABSTRACT

Pregnancy is a period that places great physiological stress on both the mother and the fetus. When pregnancy is compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense. While a lot of attention has been focused on the adverse fetal outcomes consequent to hypothyroidism, attention is also being gradually directed towards the adverse maternal outcomes of this disorder. Role of antibody positivity in influencing outcomes in a euthyroid woman, also needs further clarification. Prompt diagnosis and treatment of hypothyroidism in pregnancy is very essential. Subclinical hypothyroidism also needs to be detected and treated to prevent adverse outcomes, especially maternal. Since women with hypothyroidism during pregnancy, especially of the autoimmune variety might have a flare up of the disorder post-partum, or might continue to require thyroxine replacement post-partum, adequate follow-up is mandatory. While targeted case finding is generally practised, recent evidence seems to indicate that universal screening might be a better option. In conclusion, routine screening, early confirmation of diagnosis and prompt treatment. Allied with regular post-partum follow up, is required to ensure favourable maternal and fetal outcomes.

Key words: Hypothyroidism, pregnancy, subclinical hypothyroidism, targeted screening, universal screening

Introduction

Pregnancy is a period that places great physiological stress on both the mother and the fetus in the best of times. However, if pregnancy is compounded by endocrine disorders such as hypothyroidism, the potential for maternal and fetal adverse outcomes can be immense. Hypothyroidism is widely prevalent in pregnant women and the rate of detection, especially in a developing country like India, has not kept pace with the magnitude of the problem. Since hypothyroidism is easily treated, timely detection and treatment of the disorder could reduce the burden of adverse fetal and maternal outcomes, which are very commonly encountered.

Thyroid Physiology in Pregnancy

Thyroid physiology is perceptibly modified during normal pregnancy. These alterations take place throughout gestation, help to prepare the maternal thyroid gland to cope with the metabolic demands of pregnancy, are reversible post-partum and the interpretation of these changes can pose a challenge to the treating physician.

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The most notable change is the increase in thyroxine-binding globulin (TBG). This begins early in the first trimester, plateaus during midgestation, and persists until shortly after delivery. This is due to stimulation of TBG synthesis by elevated maternal estrogen levels, and more importantly, due to a reduced hepatic clearance of TBG because of estrogen-induced sialylation.[1] This increased TBG concentration leads to an expansion of the extra-thyroidal pool and results in elevated total T3 and T4 levels due to an increase in maternal thyroid hormone synthesis. Maternal thyroid hormone synthesis is also increased due to an accelerated renal clearance of iodide resulting from the increased maternal glomerular filtration rate.

Enhanced metabolism of T4 in the second and third trimesters, due to a rise in placental type II and type III deiodinases, which convert T4 to T3 and T4 to reverse T3 and T2 respectively, act as further impetus to T4 synthesis. Plasma iodide levels decrease due to both increased thyroxine metabolism and increased renal iodide clearance.

Corresponding Author: Dr. R. K. Sahay, 6-3-852/A, Ameerpet, Hyderabad-500 016, India. E-mail: sahayrk@gmail.com

All these changes lead to an increase in the size of the thyroid gland in 15% of pregnant women, which returns to normal in the post-partum period.

Serum hCG has intrinsic thyrotropic activity, which increases after fertilization and peaks at 10 to 12 weeks. Hence, in the first trimester, free T3 and T4 levels increase slightly and TSH levels decrease in the first trimester with a readjustment in the second and third trimesters, when hCG levels decrease. As a consequence, cut-offs to determine hypothyroidism in pregnancy are different in the first trimester and the rest of the pregnancy.

Physiology of the Fetal Thyroid

Fetal thyroid gland develops as an out pouching in midline of the anterior pharyngeal floor, migrates caudally, to reach its final position by 7 weeks of gestation. Fetal thyroid is capable of trapping iodine by 12 weeks and can synthesize thyroxine by 14 weeks of gestation. However, significant hormone secretion is not seen till 18–20 weeks of gestation. Thereafter, fetal TSH, T4, and TBG gradually rise to adult levels by 36 weeks gestation. But T3 and free T3 levels do not rise to adult levels, as placental type III deiodinase converts most fetal T4 to reverse T3; the fetal brain which has elevated levels of type II deiodinase, is an exception.

TSH transfer across placenta is not significant, but T3 and T4 transport can be considerable. This is of special relevance in congenital hypothyroidism, where studies have shown that umbilical cord T4 levels in neonates with congenital hypothyroidism can be up to 50% of the normal.[2] This transferred T4 can play a crucial role in near normal fetal cognitive development in congenital hypothyroidism. Transplacental transfer of TRH, iodine, anti-thyroid drugs and thyroid stimulatory immunoglobulin (TSI) also occurs [Table 1].

Table 1: Transport of thyroid hormones and antibodies across placenta

Substance	Transfer across placenta
Iodine	Transferred avidly across placenta, both by passive diffusion and by active transport
Thyroxine	Some transfer is seen, especially in the first trimester
TSH	Poorly transferred
TRH	Avidly transported across placenta
Antibodies	Anti Tpo, Anti TG, TSI, TBII can all cause placenta freely and TSI can cause transient neonatal hyperthyroidism and TBII can cause transient neonatal hypothyroidism.

Maternal Aspects of Hypothyroidism

Women with hypothyroidism have decreased fertility; even if they conceive, risk of abortion is increased, and risk of gestational hypertension, anemia, abruptio placenta and postpartum hemorrhage is increased.[3] The risk of these complications is greater in women with overt, rather than subclinical hypothyroidism.

Fetal and Neonatal Aspects of Maternal Hypothyroidism

Untreated maternal hypothyroidism can lead to preterm birth, low birth weight, and respiratory distress in the neonate. Enough evidence has accumulated over the years about the role of thyroxine in normal development of the fetal brain. The presence of specific nuclear receptors and thyroid hormone found in fetal brain at 8 week of gestation, free T4 found in the coelomic and amniotic fluids and demonstration of the transfer of maternal thyroid hormones across the placenta, underline the role of thyroid hormones in fetal brain development. Complex interactions between the D2 and D3 iodothyronine deiodinases during gestation help to fine tune the supply of adequate amounts of T3 required for normal brain development.

A number of pioneering studies by Man *et al.*,[4] Haddow *et al.*,[5] and newer studies by Rovet *et al.*[6] and Pop *et al.*,[7] have conclusively proved that children born to mothers with hypothyroidism had a significantly increased risk of impairment in IQ scores, neuropsychological developmental indices and learning abilities. Children born to untreated hypothyroid women had an IQ score that was 7 points below the mean IQ of children born to healthy women and women given thyroxine supplements. This risk applies to children born not only of untreated women, but also women with suboptimal supplementation. A study by Rovet *et al.*,[6] found that such children had mild defects in global intelligence, but visual-spatial ability, language, fine motor performance, and preschool ability were unaffected. This study emphasizes the need to follow-up women adequately after initiating treatment.

Children born to mothers with iodine deficiency fared even worse, with a greater than 10-point average deficit in global IQ and quite a few also had attention deficit hyperactivity disorder.[8]

Etiology of Hypothyroidism in Pregnancy

The prevalence of hypothyroidism during pregnancy

is estimated to be 0.3−0.5% for overt hypothyroidism and 2−3% for subclinical hypothyroidism. Autoimmune thyroiditis is the commonest cause of hypothyroidism during pregnancy.[9] Other causes include radioiodine ablation of thyroid while treating hyperthyroidism or thyroid cancer, surgery of the thyroid tumors and rarely, central hypothyroidism including lymphocytic hypophysitis or ectopic thyroid and drugs like Rifampicin and phenytoin which accelerate thyroid metabolism. However, worldwide, iodine deficiency still remains one of the leading causes of hypothyroidism, both overt and subclinical.

Clinical Features

Hypothyroidism during pregnancy is usually asymptomatic, especially when subclinical. Signs and symptoms which suggest hypothyroidism include inappropriate weight gain, cold intolerance, dry skin and delayed relaxation of deep tendon reflexes. Other features like constipation, fatigue, and somnolence are usually attributed to pregnancy.

Autoimmune Thyroid Disease

Multiple studies have dwelt upon the risk of miscarriage in patients with autoimmune thyroid disease.[10] While causality has not been established and these antibodies may only be a marker for autoimmune mediated recurrent miscarriage, more evidence is needed before dismissing antibody positivity as a cause of adverse pregnancy outcomes. Increased perinatal mortality and large-for-gestational-age infants have also been observed in a few studies.

Euthyroid women with positive thyroid peroxidase (TPO) antibodies undergoing *in vitro* fertilization (IVF) have also been reported to have higher miscarriage rates. A study by Negro *et al.*, reported an association between thyroid antibody positivity and preterm delivery in euthyroid women and a possible association with neonatal respiratory distress.[11]

Another study by Mannisto *et al.*, found that thyroid dysfunction and antibodies during pregnancy seem to predict later thyroid disease. Moreover, overt hypothyroidism seemed to predict a later risk of diabetes.[12]

Negro *et al.*,[13] in a pioneering study, found that LT4 administration in euthyroid pregnant women with autoimmune thyroid disease decreased the rates of negative obstetric outcomes in women with a TSH value greater than 2.0 mIU/liter and/or a high titer of thyroid antibodies. In view of the negative maternal and fetal outcomes of hypothyroidism, carefully monitored thyroid hormone treatment of TPO antibody positive pregnant patients might be a prudent measure.

Subclinical Hhypothyroidism

Subclinical hypothyroidism is defined as increased TSH with normal concentrations of FT4 and FT3. The prevalence of subclinical hypothyroidism during pregnancy is estimated to be 2% to 5%.[14] It is almost always asymptomatic. Women with subclinical hypothyroidism are more likely than euthyroid women to have TPO antibody positivity (31% compared to 5%).[15] Etiology is similar to overt hypothyroidism. Since multiple studies have shown that subclinical hypothyroidism is associated with an adverse outcome for the mother and offspring, most guidelines recommend thyroxine replacement in women with subclinical hypothyroidism. However, while thyroxine treatment has been shown to improve obstetrical outcome, it has not been proven to modify long-term neurological development in the offspring.

Isolated Maternal Hypothyroxinemia

Isolated maternal hypothyroxinemia is defined as a low FT4 and normal TSH, which can be found in approximately 1% to 2% of pregnancies. In the FASTER study, among the women with hypothyroxinemia and normal TSH, there was an increased odds ratio for preterm labor (1.62, 95% CI 1.00−2.62), macrosomia (1.97, 95% CI 1.37−2.83), and gestational diabetes (1.70, 95% CI 1.02−2.84), but these results were not consistent.[16] A study by Casey *et al.*,[17] concluded that isolated maternal hypothyroxinemia in the first half of pregnancy has no adverse affects on pregnancy outcome.

In some studies,[18] infants and toddlers whose mothers had reduced serum free T4 concentrations (with normal TSH) during gestation (12 to 20 weeks) had lower mean intelligence, psychomotor, or behavioral scores compared with children born to women with normal thyroid function during gestation. However, till date, no study has shown benefit from levothyroxine treatment of isolated hypothyroxinemia during pregnancy, on pregnancy outcome or subsequent infant development.

Diagnosis [Figure 1]

Thyroid function tests are the mainstay. Serum TSH elevation indicates primary hypothyroidism, and serum free T4 levels subclinical and overt hypothyroidism. Free hormone levels are estimated, as total hormone levels are elevated due to changes in TBG levels. "Trimester-specific" ranges are in vogue for TSH with an upper limit of 2.5 μiu/ml in the first trimester (due to the stimulatory effects of hCG) and 3 μiu/ml in the second and third trimesters.[19]

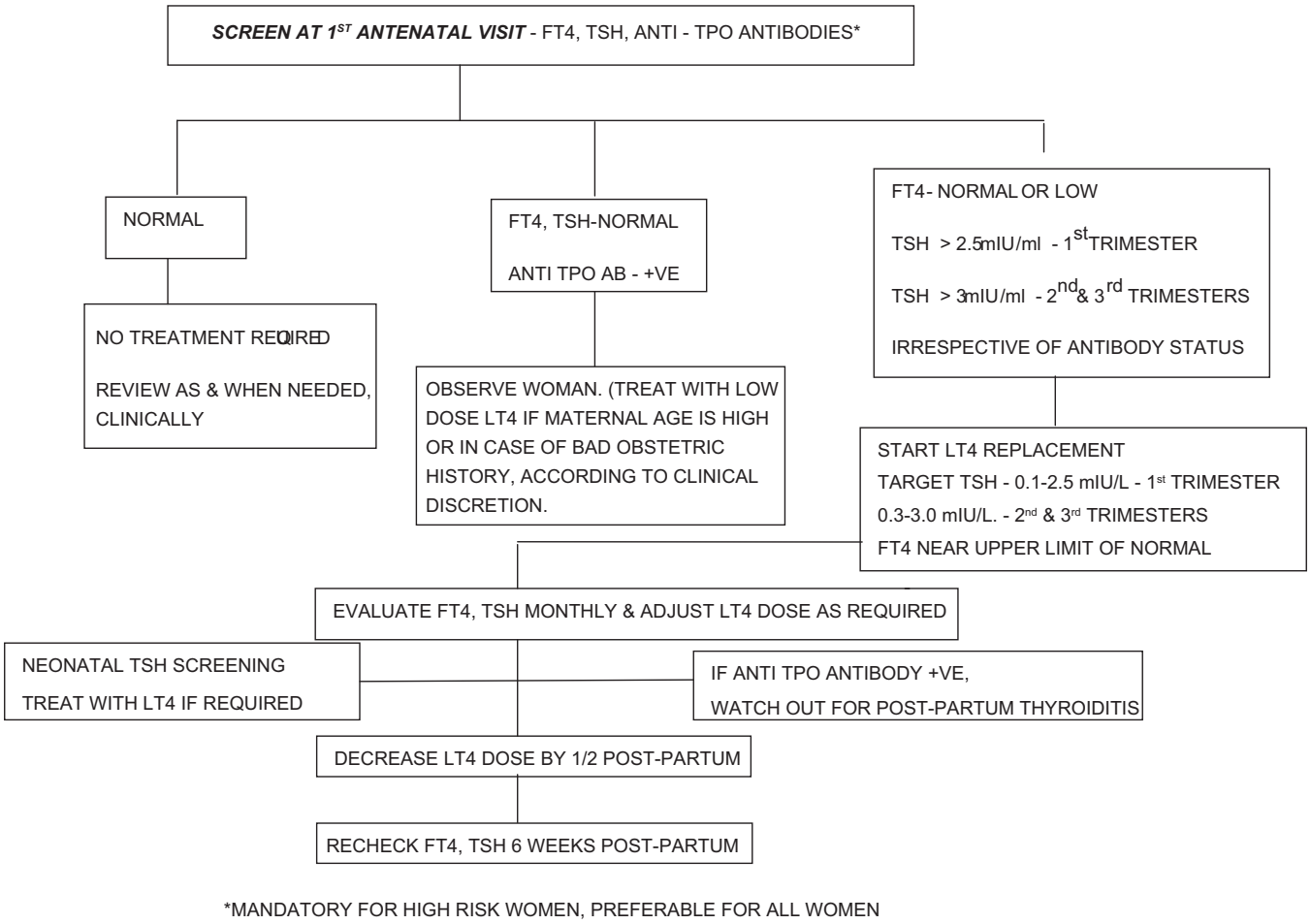

Figure 1: Algorithm for management of hypothyroidism in pregnancy

Autoimmune origin is confirmed by measuring TPO and thyroglobulin (TG) antibodies.

Treatment

Administration of levothyroxine is the treatment of choice for maternal hypothyroidism. Pregnant women need larger doses due to the rapid rise in TBG levels resulting from the physiological rise in estrogen, the increased placental transport and metabolism of maternal T4 and the increased distribution volume of thyroid hormones. During pregnancy, the full replacement thyroxine dose is around 2−2.4 μg/kg / day. In severe hypothyroidism, for the first few days, a thyroxine dose twice the estimated final replacement daily dose may be given, to rapidly normalize the extrathyroidal thyroxine pool before reducing to the final replacement dose. Women who already on thyroxine prior to pregnancy usually need to increase their daily dosage, on an average, by 30-50% above preconception dosage. Dose of thyroxine also depends on the etiology of hypothyroidism with disorders with very little residual tissue, like radioiodine ablation and extensive thyroid surgery requiring a greater increment in thyroxine dosage than women with Hashimoto's thyroiditis, who usually have some residual thyroid tissue.

Serum free T4 and TSH levels should be measured 1 month after the initiation of treatment. The thyroxine dose should be titrated to reach a serum TSH value less than 2.5 mIU/liter, while maintaining free T4 levels in the high normal range. Women should be followed up every 4−6 weeks with free T4 and TSH value, till delivery, to facilitate periodic adjustment of LT4 supplementation. If hypothyroidism has not been diagnosed until the end of the first trimester, offspring may display impairment in final intellectual and cognitive abilities, thus underscoring the importance of early diagnosis and treatment.

Post-Partum Follow-up [Figure 1]

After delivery, most women should decrease thyroxine dosage received during pregnancy, over a period of approximately 4 wk postpartum. Post-partum, two patterns of thyroid dysfunction can be discerned: (i) postpartum

thyroiditis characterized by transient hyperthyroidism or transient hyperthyroidism followed by transient or rarely permanent hypothyroidism, (ii) and a postpartum exacerbation of chronic Hashimoto's thyroiditis leading to transient or permanent hypothyroidism. The hyperthyroid phase of postpartum thyroiditis, is treated with a beta-adrenergic antagonist drugs. Transient hypothyroidism is treated with T4, which may be continued till six months and then tapered to determine if the hypothyroidism is permanent. Thyroid function tests should be monitored for at least 6 months after delivery.

Universal Screening vs. Targeted Case Finding

This debate has raged since the identification of hypothyroidism as a cause of maternal and fetal distress. Targeted case finding has been the preferred method due to its practicality, cost-effectiveness, and lack of any studies which conclusively demonstrate the superiority of universal screening over targeted case finding. Women screened usually have either a positive family history, goitre Type I diabetes, pre-existing thyroid disorder, preterm delivery, antibody positivity, or prior therapeutic head or neck irradiation, and so on.[20] Currently, position statements issued by the Thyroid, Endocrine and Obstetric organizations do not recommend universal screening.[21-23] However, recent research has highlighted the adverse effects of mild to moderate maternal hypothyroidism on maternal health in addition to fetal cognitive development, bringing universal screening into sharp focus once again.

A recent study by Vaidya *et al.*,[24] reported that screening only women considered "high risk" would miss 30% of women with overt or subclinical hypothyroidism**,** suggesting that universal screening is better than screening only high risk women. Another study by Negro *et al.*,[25] evaluated reduction in adverse pregnancy outcomes following treatment in those women identified by universal screening vs. targeted case finding for thyroid dysfunction in pregnancy. Universal screening, compared with case finding did not result in a decrease in adverse outcomes. Ostensibly, this study does not seem to be in favour of universal screening, but a closer examination reveals otherwise. This study divided women into two arms; universal screening arm, in which all the women were screened, (482 women with high risk and 1798 women with low risk) and the targeted case finding arm, in which only high-risk cases were investigated (454 women in high-risk group and 1828 women in the low-risk group). All the women identified to have hypothyroidism received levothyroxine replacement. Consequently, high risk women in both the universal screening and targeted case finding arms received treatment, while low risk women received treatment only in the universal screening arm. Low risk women in targeted case finding arm were not investigated and hence not treated.

In keeping with the predefined objective of the study, viz. "whether treatment of thyroid disease during pregnancy decreases the incidence of adverse outcomes and compare the ability of universal screening vs. case finding in detecting thyroid dysfunction", Negro *et al.*, included outcomes of both the high risk and low risk women from both the arms, in the analysis of the study. This did not show any statistically significant reduction in adverse outcomes.[26]

However, comparison of only the 3600 "low-risk" patients across both the arms of the study reveals that rates of pregnancy-related adverse events were reduced by nearly 40% after detection and treatment, i.e., considerable benefit was derived by the low-risk women in the universal screening arm when compared to the low-risk women in the targeted case finding arm. This effect was large enough that approximately 40 low-risk women would require screening (and intervention) to prevent a single adverse pregnancy outcome, a number which is significant enough.[26] This once again indicates that universal screening followed by appropriate treatment of those detected to have hypothyroidism has an impact of reducing adverse pregnancy outcomes.

The "Controlled Antenatal Thyroid Screening Study," (CATS)[27] by Lazarus *et al.*, in the United Kingdom, is an ongoing 8-year prospective intervention trial seeks to determine whether universal screening of pregnant women (and levothyroxine treatment**,** when hypothyroid) prevents adverse outcomes. In this study, serum samples are obtained before 16 week**s** gestation, with half of the sera analyzed immediately for free T4 and TSH, and the other half frozen until delivery. Women with a free T4 below the 2.5th percentile and/or TSH above the 97.5th percentile would be given levothyroxine therapy. The main outcome measure is the development of the unborn child, measured at 3 yr of age. Once, the outcome data from this study filters in, it may perhaps give us a better understanding to the contentious issue of universal screening vs. targeted case finding. However, the recent spate of reports highlighting the advantages of universal screening and the propensity of targeted case finding to miss a sizeable number of cases, seem to give universal screening a definite edge over targeted case finding.

Congenital Hypothyroidism

Congenital hypothyroidism, which occurs in approximately 1:2000 to 1:4000 newborns, is the most common

treatable cause of mental retardation. There is an inverse relationship between the age at diagnosis and IQ.[28] Most newborn babies with congenital hypothyroidism have few or no clinical manifestations of thyroid deficiency. The most common cause of congenital hypothyroidism is thyroid dysgenesis, followed by dyshormoogenesis, resistance to TSH, disorders in hormone transport, central hypothyroidism and transient congenital hypothyroidism.[29]

Screening of all newborns is now mandatory in the developed world and is catching on in most of the developing countries. Blood for screening is collected onto filter paper cards after heel prick, usually two to five days after delivery and sent to a centralized laboratory for testing. Two major screening strategies have evolved: (i) initial blood T4 assay, with follow-up TSH assay if the blood T4 value is below a certain cut-off (usually less than the 10th percentile); (ii) an initial blood TSH assay. Whatever may be the screening method, mandatory screening of all newborns, further evaluation where appropriate, and prompt initiation of treatment is absolutely essential.

Iron and Maternal Thyroid Function

Recently, attention is being focused on utility of poor maternal iron status in predicting high TSH and low total T4 concentrations during pregnancy, especially in areas of borderline iodine deficiency. While causality has not been established, it is postulated that iron deficiency decreases the thyrotropic response to TRH, serum T3 and T4 levels, slows turnover of T3, and may reduce T3 nuclear binding.[30] Iron deficiency might cause impairment of the heme-dependent enzyme thyroid peroxidase, thereby limiting synthesis of thyroid hormones, which can lead to a reduction in circulating levels of total T3 and total T4.[30] Iron repletion may reverse this hypothyroidism. More work is needed to elucidate a link between anemia, iodine, deficiency, autoimmune thyroid disease, and adverse outcomes in the mother and the fetus.

Conclusion

In conclusion, maternal hypothyroidism is a disorder with great potential to adversely affect maternal and fetal outcomes and is also associated with multiple other conditions which can affect maternal and fetal health. If the condition is detected early, it is easy to treat, with very little detriment to the mother and the fetus. Hence, this condition needs early detection, prompt initiation of treatment, adequate follow-up and most importantly, sufficient education of the doctors and the patients regarding these objectives, the importance of this condition and the ease and advantages of prompt management.

References

1. Ain KB, Mori Y, Refetoff S. Reduced clearance rate of thyroxine-binding globulin (TGB) with increased sialylation: A mechanism for estrogen-induced elevation of serum TBG concentration. J Clin Endocrinol Metab 1987;65:689-702.
2. Vulsma T, Gons MH, deVijlder JJ. Maternal-fetal transfer of thyroxine in congenital Hypothyroidism due to total organification defect or thyroid agenesis. N Engl J Med 1989;321:13.
3. Abalovich M, Gutierrez S, Alcaraz G, Maccallini G, Garcia A, Levalle O. Overt and subclinical hypothyroidism complicating pregnancy. Thyroid 2002;12:63-6.
4. Man EB, Jones WS, Holden RH, Mellits ED. Thyroid function in human pregnancy, 8, Retardation of progeny aged 7 years: Relationships to maternal age and maternal thyroid function. Am J Obstet Gynecol 1971;111:905-16.
5. 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.
6. Rovet JF. Neurodevelopmental consequences of maternal hypothyroidism during pregnancy (abstract 88;annual Meeting of the American Thyroid Association). Thyroid 2004;14:710.
7. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, *et al*. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149-55.
8. Vermiglio F, Lo Presti VP, Moleti M, Sidoti M, Tortorella G, Scaffidi G, *et al*. Attention deficit and hyperactivity disorders in the offspring of mothers exposed to mild-moderate iodine deficiency: A possible novel iodine deficiency disorder in developed countries. J Clin Endocrinol Metab 2004;89:6054-60.
9. 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.
10. Pratt DE, Kaberlein G, Dudkiewicz A, Karande V, Gleicher N. The association of antithyroid antibodies in euthyroid nonpregnant women with recurrent first trimester abortions in the next pregnancy. Fertil Steril 1993;60:1001-5.
11. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Thyroid antibody positivity during pregnancy. J Clin Endocrinol Metab 2011;96:E920-4.
12. Mannisto T, Vääräsmäki M, Pouta A, Hartikainen AL, Ruokonen A, Surcel HM, *et al*. Thyroid dysfunction and maternal morbidity. J Clin Endocrinol Metab 2010;95:1084-94.
13. Negro R, Formoso G, Mangieri T, Pezzarossa A, Dazzi D, Hassan H. LT4 in autoimmune thyroid disease during pregnancy. J Clin Endocrinol Metab 2006;91:2587-91.
14. Woeber KA. Subclinical thyroid dysfunction. Arch Intern Med 1997;157:1065-8.
15. Jayme JJ, Ladenson PW. Subclinical thyroid dysfunction in elderly. Trends Endocrinol Metab 1994;5:79-86.
16. 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.
17. 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.
18. Pop VJ, Kuijpens JL, van Baar AL, Verkerk G, van Son MM, de Vijlder JJ, *et al*. Low maternal free thyroxine concentrations during early pregnancy are associated with impaired psychomotor development in infancy. Clin Endocrinol (Oxf) 1999;50:149.
19. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-

Green A. Increased pregnancy loss rate in thyroid antibody negative women with TSH levels between 2.5 and 5.0 in the first trimester of pregnancy. J Clin Endocrinol Metab 2010;95:E44.
20. Abalovich M, Amino N, Barbour LA, Cobin RH, De Groot LJ, Glinoer D, *et al*. Management of thyroid dysfunction during pregnancy and postpartum: An endocrine society clinical practice guideline. J Clin Endocrinol Metab 2007;92(Suppl):S1-47.
21. Davies TF. Time for the American thyroid association to lead on thyroid screening in pregnancy. Thyroid 2007;17:697-8.
22. Subclinical hypothyroidism in pregnancy - ACOG Committee Opinion. Obstet Gynecol 2007;110:959-60.
23. Gharib H, Cobin RH, Dickey RA. Subclinical hypothyroidism during pregnancy: Position statement from the American Association of Clinical Endocrinologists. Endocr Pract 1999;5:367-8.
24. Vaidya B, Anthony S, Bilous M, Shields B, Drury J, Hutchison 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.
25. Negro R, Schwartz A, Gismondi R, Tinelli A, Mangieri T, Stagnaro-Green A. Universal screening vs. case-finding for detection and treatment of thyroid hormonal dysfunction during pregnancy. J Clin Endocrinol Metab 2010;95:1699-707.
26. Alexander EK. Here's to you, baby: A step forward in support of universal screening of thyroid function during pregnancy. J Clin Endocrinol Metab 2010;95:1699-707.
27. Lazarus JH, Premawardhana LD. Screening for thyroid disease in pregnancy. J Clin Pathol 2005;58:449-52.
28. Klein AH, Meltzer S, Kenny FM. Improved prognosis in congenital hypothyroidism treated before age three months. J Pediatr 1972;81:912.
29. Devos H, Rodd C, Gagné N, Laframboise R, Van Vliet G. A search for the possible molecular mechanisms of thyroid dysgenesis: Sex ratios and associated malformations. J Clin Endocrinol Metab 1999;84:2502-6.
30. Zimmermann MB, Burgi H, Hurrell RF. Iron deficiency predicts poor maternal thyroid status during pregnancy. J Clin Endocrinol Metab 2007;92:3436-40.

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