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Screening for thyroid disease in pregnancy

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Although gestational hyperthyroidism is uncommon (0.2%), hypothyroidism (autoimmune disease or suboptimal iodine intake) occurs in 2.5% of women and is predictive of reduced neonatal and child neuropsychological development and maternal obstetric complications. Postpartum thyroid dysfunction (PPTD) occurs in 5–9% of women and is associated with antithyroid peroxidase antibodies (antiTPOAb) in 10% of women in early pregnancy. Therefore, screening for thyroid dysfunction in pregnancy should be considered. T4 and thyroid stimulating hormone measurements could be used to screen for hypothyroidism, which would require levothyroxine intervention treatment. T4 supply is crucial to fetal nervous system maturation; currently, the recommended daily iodine intake is 200 µg, and this is not always achieved, even in the UK. At present, a randomised prospective trial is ongoing to provide the evidence base for this screening strategy. Meanwhile, it is reasonable to (a) optimise iodine nutrition during pregnancy; (b) ascertain women with known thyroid disease; (c) identify women at increased risk of thyroid disease—for example, those with other autoimmune diseases. PPTD can be predicted by measurement of antiTPOAb in early gestation.

data suggesting that some aspects of thyroid function during and after pregnancy are of sufficient clinical relevance, both to mother and child, to warrant consideration of routine screening of thyroid function in early pregnancy.

EPIDEMIOLOGY

Hyperthyroidism is found in 0.2% of all pregnancies. It is usually caused by Graves' disease and characterised by TSH receptor stimulating antibodies (TSHRAb), which usually decrease in titre throughout pregnancy.⁷ The clinical presentation of hyperthyroidism may not be obvious because symptoms of tachycardia, sweating, dyspnoea, and nervousness are seen in normal pregnancy, as are cardiac systolic flow murmurs. Maternal complications include miscarriage, placenta abruptio, and preterm delivery. Congestive heart failure and thyroid storm may also occur, and the risk of pre-eclampsia is significantly higher in women with poorly controlled hyperthyroidism.⁸ In addition, if high titres of TSHRAb are present at 36 weeks of gestation there is a high risk of neonatal thyrotoxicosis which, although transient, may cause considerable neonatal morbidity if unrecognised.⁹

“Important evidence has been presented during the past decade to show that the progeny of women with hypothyroxinaemia have psychoneurological deficits”

Changes in thyroid function tests occur during pregnancy as a result of physiological alterations in several factors controlling thyroid homeostasis at this time. Thyroxine binding globulin concentrations increase primarily because of decreased clearance resulting from increasing oestrogen concentrations and an increase in urinary iodine excretion, particularly in the first trimester.¹ Human chorionic gonadotrophin, a weak thyroid stimulating hormone (TSH) agonist, is raised at this time, and results in increased release of T4 and T3, which leads to low measurable TSH concentrations.² During the past two decades there has been an increasing awareness that thyroid dysfunction, particularly hypothyroidism, is common in gestation, and there are several reviews discussing the management of these conditions.^{3–5} Postpartum thyroid disease has also been found to occur frequently, particularly in predisposed women.⁶ This review will present the background information and

Hypothyroidism usually characterised by a high TSH value has been found to occur in around 2.5% of otherwise normal pregnancies.^{10–11} Again, untreated hypothyroidism may lead to obstetric complications, such as preterm delivery and fetal loss.¹² It has been known for over 10 years and recently re-emphasised that women who are taking levothyroxine at conception will require an increase in the dose during the pregnancy.¹³ Clearly, TSH should be measured in this group as early as possible. In addition, important evidence has been presented during the past decade to show that the progeny of women with hypothyroxinaemia have psychoneurological deficits. In a study by Haddow

Abbreviations: antiTPOAb, antithyroid peroxidase antibody; FT4, free T4; PPTD, postpartum thyroid dysfunction; TSH, thyroid stimulating hormone; TSHRAb, thyroid stimulating hormone receptor stimulating antibodies

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*et al.*¹⁴ a group of 7 year old children born to mothers known to have a high TSH during pregnancy (but normal T4 values) was compared with a control group whose mothers had normal TSH. The striking finding was that 19% of the first group had an IQ < 85 compared with 5% of the control group, a highly significant difference. Similar data have been recorded in the Netherlands¹⁵ in relation to children whose mothers had low T4 but normal TSH. In classic areas of iodine deficiency, a range of psychological and neurological deficits in children has been described during the past century,¹⁶ but in many of the mothers it is the maternal hypothyroxinaemia rather than high TSH that is the striking abnormality.¹⁷ In these areas, maternal iodine intake is often substantially less than the 200 µg/day currently recommended. Even in areas thought to be iodine sufficient, there is evidence of substantial gestational iodine deficiency,¹⁸ which may lead to low maternal circulating thyroxine concentrations. In addition, 6.7% of pregnant women were noted to have a urinary iodine excretion of less than 50 µg/litre in the USA between 1988 and 1994.¹⁹ Because maternal thyroxine is crucial to fetal nervous system maturation, even modest states of iodine deficiency could be deleterious.

Thyroid antibodies, particularly antithyroid peroxidase antibody (antiTPOAb), occur in 10% of women at 14 weeks of gestation. A proportion of these women will have subclinical hypothyroidism with a high TSH (see above), but most will be euthyroid. However, after delivery thyroid dysfunction will develop in 50% of antiTPOAb positive women, as ascertained in early gestation, clinically apparent as postpartum thyroiditis.²⁰ In addition to the childhood neuropsychological problems relating to low thyroxine values, there is evidence from a retrospective study that maternal antiTPOAb may result in intellectual impairment even when there is normal thyroid function.²¹ Postpartum Graves' disease also develops in predisposed women, although the prevalence of TSHRab during gestation is much less than that of antiTPOAb.

SCREENING IMPLICATIONS

The thyroid abnormalities during gestation described above suggest that screening for thyroid dysfunction in relation to pregnancy should be strongly considered. However, because of the low incidence of hyperthyroidism in pregnancy, the current cost of this strategy makes it impractical at least in the UK. If screening for hypothyroidism during gestation is offered, then treatment of hypothyroidism (even subclinical hypothyroidism) with thyroxine should be instituted. What screening tests should be used? Serum free or total thyroxine measurements have high sensitivity and specificity for the diagnosis of hypothyroidism, as has serum TSH measurement. Currently, a randomised study is being undertaken where pregnant women provide a blood sample before 16 weeks of gestation. The samples are randomised to a screen group (with immediate estimation of free T4 (FT4) and TSH) and a control group with estimation of these parameters occurring after delivery. Levothyroxine treatment is given to those in the screen group whose FT4 is in the lowest 2.5th centile or whose TSH is above the 97.5th centile. These values are derived from thyroid hormone measurements on previously collected antenatal sera from women whose gestational age was confirmed by scan. Subsequent adjustment is being made based on every two to three thousand samples collected during the study. This strategy will produce two groups of children whose development will subsequently be tested at 3 years of age; that is, those from treated hypothyroid mothers and those from untreated mothers (undiagnosed during gestation). Preliminary data from this study suggest that utilising both parameters results in two abnormal pregnant populations—namely, about half with a

low T4 and an equal number with a high TSH, with very few having both a low T4 and a high TSH (JH Lazarus *et al.* The controlled antenatal thyroid screening study (CATS)—first observations. *Endocrine Abstracts*. 22nd Joint Meeting of the British Endocrine Societies, Glasgow, UK, 24–26 March 2003). Further studies suggest that the abnormality in the high TSH group is predominantly autoimmune (with positive thyroid antibodies) in origin, whereas the aetiology of the low T4 group is not clear, but may be related to iodine deficiency. A disadvantage of screening during pregnancy is of course that the fetal brain is dependent on maternal T4 from conception, and that by the time testing is possible (probably at the first booking antenatal visit at around 14 weeks), damage may already have occurred. Nevertheless, maternal T4 is still an important source of thyroid hormone for the fetal brain during the rest of the pregnancy. Results from this study will provide evidence to decide whether a screening programme to detect gestational thyroid dysfunction is appropriate.

“Optimum iodine nutrition during pregnancy should be ensured”

Meanwhile, several interim measures can be proposed. First, optimum iodine nutrition during pregnancy should be ensured. The recommended daily intake is 200 µg/day and there is evidence that this is not always achieved. Second, it is reasonable to identify women with known thyroid disease to make them aware of the potential problems of low thyroid function during pregnancy. Third, there is a strong case for the identification of women at increased risk for thyroid disease—for example, those with type 1 diabetes and those with a positive family history of thyroid disease and other autoimmune conditions, such as vitiligo and Addison's disease. A recent evidence based panel examining the evaluation and treatment of subclinical thyroid disease advocated aggressive case finding for thyroid disease during pregnancy,²² although systematic screening was not recommended. The benefits of screening in this setting are the high incidence of thyroid failure in pregnancy, the high specificity of FT4 and TSH for the detection of thyroid failure, and the (presumed) benefit of T4 treatment on fetal brain development. The disadvantages include inevitable maternal anxiety at the time of testing and during the childhood period. Concern about deleterious effects of T4 administration during gestation may be expressed and overdose of the drug may occur. In practice, overdosing is very unlikely and can easily be tested for. Excess T4 can adversely affect neuronal maturation in animals, but this is rare in humans. However, a recent study²³ did document adverse fetal effects of high maternal circulating thyroid hormone concentrations in women with thyroid hormone resistance (caused by a mutation in the thyroid hormone β receptor). Finally, the cost of such a programme must be appreciated. However, experience from the neonatal hypothyroid screening service²⁴ (now routine in the UK) suggests that the costs of the reagents and administration may provide a value for money return. Although we appreciate the necessity of an evidence base in this area, we hope that experience of screening strategies will be developed in different centres.

POSTPARTUM THYROID DISEASE

Postpartum Graves' disease is known to occur,⁷ and accounts for about 10% of postpartum thyroid disease. Detection of postpartum Graves' hyperthyroidism has been undertaken in Japan by testing for TSHRab,²⁵ but it is not cost effective to screen for this condition. However, the development of hyperthyroidism, hypothyroidism, or both, around 13 to

Table 1 Time of antibody sampling, sensitivity, specificity, and PPV for predicting PPTD

Time of sampling	Sensitivity	Specificity	PPV
Early pregnancy	0.67–1.00	0.62–0.93	0.31–0.55
3 rd trimester	0.71	0.92	0.52
Delivery/early postpartum	0.45–0.89	0.91–0.97	0.4–0.73
Late postpartum	0.46–0.86	0.9–0.98	0.52–0.78

Sensitivity, specificity, and PPV of thyroid antibody (antimicrosomal and antithyroid peroxidase) in PPTD prediction derived from published studies. Sampling times varied. Early pregnancy: 1st and 2nd trimesters; early postpartum: from delivery to 5 months after delivery; late postpartum: 6 or more months after delivery. Adapted from Premawardhana *et al.*³¹ PPTV, postpartum thyroid dysfunction; PPV, positive predictive value.

19 weeks postpartum^{6 19 20 26 27} occurs in 5–9% of women, and is strongly associated with the presence of antiTPOAb. Of the 10% of women who are found to be antiTPOAb positive in early gestation, 50% will develop postpartum thyroid dysfunction (PPTD), whereas the other 50% will remain euthyroid but still have antiTPOAb. The condition is transient, but 20–30% will develop permanent hypothyroidism. Longterm follow up studies show that 50% of those whose thyroid function recovers after an episode of PPTD will become hypothyroid at seven years, compared with about 5% of antibody positive patients who were PPTD negative (that is, euthyroid postpartum).²⁸ In addition, there is a higher rate of postpartum psychiatric symptomatology in all antiTPOAb positive women compared with controls.^{29 30} There is also considerable morbidity associated with the hypothyroid phase of PPTD. However, levothyroxine treatment results in a satisfactory clinical state. Although the sensitivity of antiTPOAb measured during early pregnancy is only 50% for postpartum thyroid dysfunction, there is evidence that the gestational titre of antibody is also predictive of disease.³¹ Proponents of screening for PPTD justify it on the basis that it is relatively common, causes considerable morbidity, and can be diagnosed with freely available tests that are inexpensive. Effective treatment is available if required. Screening may also be pertinent in view of the high prevalence of longterm thyroid dysfunction in these women. However, there is a lack of consensus about the timing of screening or the screening test for PPTD prediction. AntiTPOAb or TSH measurements have all been suggested as possible screening tools. Opponents of screening cite the lack of good prospective cost–benefit analyses to support their view. A review of published data on PPTD prediction using thyroid antibodies in different population groups reveals several reasons for this lack of consensus, such as variability of the antibody measured (microsomal or antiTPOAb), variations in assay methodology, and different times of screening during pregnancy and the postpartum period. However, the influence of disease definition and the effects of variability of genetic predisposition, frequency of blood testing, and study design should not be ignored, although antiTPOAb measurement remains the leading candidate for PPTD screening. The sensitivity, specificity, and positive predictive value of antiTPOAb measurement in PPTD prediction are highly variable, and are dependent to some extent upon the above factors (table 1).

Further refinements to the screening strategy have been suggested to improve its positive predictive value. A variable degree of enthusiasm for screening for this condition has been expressed,³² and a compromise would seem to be the targeted screening of individuals at the highest risk of developing PPTD, such as those with previous PPTD and type 1 diabetes mellitus. Nearly 70% of subjects who had PPTD

had a recurrence in a subsequent pregnancy.³³ Similarly, patients with type 1 diabetes mellitus have a 25% prevalence of PPTD.³⁴ The cost of testing is relatively high but new assay techniques will reduce this. The high incidence of the disease suggests that a considerable reduction in postpartum morbidity will be derived from this strategy.

“Proponents of screening for postpartum thyroid dysfunction justify it on the basis that it is relatively common, causes considerable morbidity, and can be diagnosed with freely available tests that are inexpensive”

In conclusion, screening for disease is an area often open to argument, emotion, and criticism, as the history of screening for cervical and breast cancer in the UK shows. Nevertheless, evidence based medical information has been gathered to justify screening for these diseases. In the area of thyroid disorders, neonatal screening for hypothyroidism has also been amply justified during the past 25 years as a cost effective strategy. As described here, evidence has been presented, largely from retrospective studies, to suggest that low circulating maternal thyroid hormone concentrations are associated with impaired neurointellectual performance in early childhood. In addition, impaired performance in school age children was associated with high maternal TSH and normal T4 concentrations in another study. An appropriate prospective randomised trial is being performed that should provide the evidence on which to decide whether screening for thyroid function with thyroid hormone interventional treatment is justified. In this study, the neurointellectual performance of the offspring of two groups, one with normal maternal T4 and high TSH and the other with low T4 and normal TSH, will be assessed. Because there is a lack of adequately documented trimester specific normative ranges for thyroid hormone concentrations, the lowest 2.5th centile for FT4 and the highest 2.5th centile for TSH are being used to define low and high FT4 and TSH. A large body of data exists that documents the incidence, morbidity, and response to treatment of postpartum thyroiditis. Screening for this disorder is strongly advocated, but prospective controlled trials are as yet not available. Nevertheless, the present evidence suggests the need for a targeted approach to case finding in early pregnancy for those women with known thyroid disease or a family history of thyroid or other autoimmune diseases.

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