

# Thyroid and Pregnancy

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**T**hyroid disease in pregnancy comprises conditions that affect both the mother and the fetus with potential important consequences for child development.<sup>1</sup> To inform the debate concerning the importance of thyroid disorders in pregnancy and the role of screening for thyroid function, it should be noted that the gestational incidence of hyperthyroidism is 0.2-0.3%, hypothyroidism 2.5% and thyroid antibody (mainly TPOAb) positivity around 10%.<sup>2</sup> Pregnancy has marked effects on thyroid physiology and autoimmune thyroid disease tends to ameliorate through gestation due to general immunosuppression seen in pregnancy. The presence of thyroid antibodies is associated with infertility and miscarriage.<sup>3</sup> The explanation for these findings is unknown and, unfortunately, thyroxine treatment in the euthyroid woman does not increase pregnancy rates.<sup>4</sup>

Transient gestational hyperthyroidism due to elevation in HCG – a weak thyroid stimulator – is common and presents as hyperemesis gravidarum.<sup>5</sup> It is more frequent in multiple pregnancies and in hydatidiform mole but normally does not require therapy. Around 5% of women require hospitalisation because

of ketosis and dehydration. They have an increased incidence of high thyroid hormone levels and suppressed TSH. The TSH receptor antibody should be measured if there is diagnostic confusion between hyperemesis and Graves' disease.

As mentioned, hyperthyroidism in pregnancy – usually due to Graves' disease – is not common; untreated or poorly managed disease may result in miscarriage, pre term delivery, hypertension and pre eclampsia in the mother and intra uterine growth retardation and even increased death rate in the fetus. In a compliant patient, a good outcome can be expected both for mother and child if treatment with anti-thyroid drugs (propylthiouracil is preferred because of the association of methimazole with aplasia cutis and methimazole embryopathy) is instituted.<sup>6</sup>

TSH receptor antibody should be measured at 36 weeks in such patients in order to predict the possibility of neonatal hyperthyroidism. Available evidence suggests that there is no significant effect of antithyroid drugs in utero on the long-term health of the neonate or child<sup>7</sup> even if the dose during gestation has caused iatrogenic fetal hypothyroidism.<sup>8</sup> Radioiodine therapy is contraindicated in pregnancy but thyroid surgery may be performed safely in the 2nd trimester.

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***Problems associated with hypothyroidism in pregnancy:***

Women who are taking levothyroxine at conception (either for autoimmune thyroid disease or following thyroidectomy) will require an increase in the dose during the pregnancy and it should normally be increased by 50 to 100 micrograms per day.<sup>9</sup> TSH should be measured in this group about one month after the increase in dose so as to obtain meaningful hormone concentrations.

Hypothyroidism, usually evident as subclinical hypothyroidism, occurs in around 2.5% of otherwise normal pregnancies and, although relatively asymptomatic, is associated with pre-term delivery as well as an increased incidence of abortion, obstetric complications, fetal abnormalities and fetal death if untreated.<sup>2</sup> There is now compelling evidence from retrospective and prospective controlled observational studies demonstrating that the progeny of hypothyroxinaemic women have psychoneurological deficits. Haddow et al<sup>10</sup> showed that in a group of 7 year old children born to mothers known to have a high TSH during pregnancy (but normal T<sub>4</sub> levels) 19% had an IQ < 85, compared to 5% of a carefully matched control group, a highly significant difference. In the Netherlands,<sup>11</sup> children whose mothers had low T<sub>4</sub> but normal TSH during pregnancy also have decrements in IQ compared to those whose mothers had normal T<sub>4</sub> during gestation. These findings are similar to those seen in iodine deficient areas where thyroxine levels are known to be low in gestation. Recently, the WHO has recommended an increase in the daily iodine requirement from 200 to 250 micrograms.<sup>12</sup> As maternal thyroxine is critical to the fetal nervous system maturation even modest states of iodine deficiency could be deleterious.<sup>13</sup> Thyroid antibodies, particularly anti thyroid peroxidase antibody (antiTPOAb), occur in 10% of women at 14 weeks gestation. A proportion of these will have subclinical hypothyroidism with a high TSH (see above) but most will be euthyroid. However, following delivery thy-

roid dysfunction will develop in 50% of TPOAb positive women as ascertained in early gestation, clinically apparent as postpartum thyroiditis.<sup>14</sup> As well as the childhood neuropsychological problems relating to low thyroxine levels, there is evidence from a retrospective study that maternal antiTPOAb may result in intellectual impairment even when there is normal thyroid function. Postpartum Graves' disease also develops in predisposed women although the prevalence of TSHRAb during gestation is much less than that of TPOAb.

Thyroid abnormalities during gestation suggest that screening for thyroid dysfunction in relation to pregnancy should be strongly considered.<sup>15</sup> However, due to the low incidence of hyperthyroidism in pregnancy, the current cost of this strategy makes it impractical in most, if not all, countries. If screening for hypothyroidism during gestation is offered then treatment of hypothyroidism - even subclinical - with thyroxine should be instituted. However there are many current uncertainties; what screening tests should be used? Serum free or total thyroxine have high sensitivity and specificity for diagnosis of hypothyroidism, as does serum TSH. What cut off levels of T<sub>4</sub> and TSH are relevant during early gestation? There is a need for normative hormonal gestational reference ranges. What dose of T<sub>4</sub> should be given and what should be the desired T<sub>4</sub> concentration in early to mid gestation to allow adequate placental transfer to the developing fetus? Some studies have addressed these problems but more data are required including prospective randomised trials discussed in the Atlanta meeting convened by the CDC.<sup>16</sup> A drawback of screening during pregnancy is of course that the fetal brain is dependent on maternal T<sub>4</sub> from conception and that by the time testing is possible (probably at the first antenatal visit at around 14 weeks) damage may already have occurred. Nevertheless maternal T<sub>4</sub> is still an important source of thyroid hormone for the fetal brain during the remainder of the pregnancy.

Meanwhile several interim measures can be proposed. Firstly optimum iodine nutrition during pregnancy should be ensured. The recommended daily intake is now 250µg/day and there is evidence that this level is not always achieved. Secondly it is reasonable to identify women with known thyroid disease in order to appraise them for the potential problems of low thyroid function during pregnancy. Thirdly there is a strong case for identification of women at increased risk for thyroid disease for example with Type 1 diabetes, a positive family history of thyroid disease and other autoimmune conditions such as vitiligo and Addison's disease. A recent evidenced-based panel examining evaluation and treatment of subclinical thyroid disease advocated aggressive case-finding for thyroid disease during pregnancy although systematic screening was not recommended.<sup>17</sup> The benefits of screening in this setting are the high incidence of thyroid failure in pregnancy, the high specificity of FT<sub>4</sub> and TSH for detection of the thyroid

failure and the (presumed) benefit of T<sub>4</sub> therapy 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 T<sub>4</sub> administration during gestation may be expressed and overdose of the drug may occur. In practice the latter is very unlikely but can easily be tested for. Excess T<sub>4</sub> can adversely affect neuronal maturation in animals but this is rare in humans although adverse fetal effects of high maternal circulating thyroid hormone concentrations in women with thyroid hormone resistance do occur.<sup>18</sup> The cost of screening programs is high and appropriate cost benefit analyses are required. A wealth of experience has been gained from screening strategies for neonatal hypothyroidism and it is to be hoped that with increasingly cheaper biochemical testing the possibility of thyroid screening in pregnancy will be realised.

## References

1. Glinoe D. Thyroid disease during pregnancy. In: Breverman LE, Utiger RD, editors. Werner and Ingbar's The Thyroid A Fundamental and Clinical Text. Philadelphia: Lippincott, Williams and Wilkins, 2005. P. 1086-1108
2. Lazarus JH. Thyroid Disorders Associated with Pregnancy: Etiology, Diagnosis and Management. *Treat Endocrinol* 2005;4:31-41.
3. Prummel MF, Wiersinga WM. Thyroid autoimmunity and miscarriage. *Eur J Endocrinol* 2004;150:751-755.
4. Negro R, Mangieri T, Coppola L et al. Levothyroxine treatment in thyroid peroxidase antibody-positive women undergoing assisted reproduction technologies: a prospective study. *Human Reproduction* 2005;20(6):1529-1533
5. Verberg MF, Gillott DJ, Al-Fardan N, Grudzinskas JG. Hyperemesis gravidarum, a literature review. *Hum Reprod Update* 2005; 11: 527-39.
6. Lazarus JH. Hyperthyroidism during pregnancy: etiology, diagnosis and management. *Women's Health* 2005; 1: 105-114
7. Azizi F, Khoshniat M, Bahrainian M, Hedayati M. Thyroid function and intellectual development of infants nursed by mothers taking methimazole. *J Clin Endocrinol Metab* 2000;85:3233-3238.
8. Azizi F. Thyroid function in breast-fed infants is not affected by methimazole-induced maternal hypothyroidism: results of a retrospective study. *J Endocrinol Invest* 2003;26:301-304
9. Mandel SJ. Hypothyroidism and chronic autoimmune thyroiditis in the pregnant state: maternal aspects. *Best Pract Res Clin Endocrinol Metab* 2004;18(2):213-224
10. Haddow JE, Palomaki GE, Allan WC et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med* 1999;341:549-555
11. Pop VJ, Vulsma T. Maternal hypothyroxinaemia during (early) gestation. *Lancet* 2005;365:1604-1606.
12. The prevention and control of iodine deficiency in pregnant and lactating women and in children less than two years old. WHO Geneva. Draft discussion in press 2005.
13. Delange F. Optimal iodine nutrition during pregnancy, lactation and the neonatal period. *Int J Endocrinol Metab* 2004;2:1-12.

14. Lazarus JH. Sporadic and postpartum thyroiditis. In: Braverman LE, Utiger RD, editors. *The Thyroid: A Fundamental and Clinical Text*. (Eds). 9th Edition. New York: Lippincott Williams and Wilkins, 2005 pp524-535.
15. Lazarus JH, Premawardhana LDKE. Screening for Thyroid Disease in Pregnancy. *J Clin Pathol* 2005;58:449-452.
16. LaFranchi SH, Haddow JE, Hollowell JG. Is thyroid inadequacy during gestation a risk factor for adverse pregnancy and developmental outcomes? *Thyroid* 2005;15:60-71.
17. Surks MI, Ortiz E, Daniels GH et al. Subclinical thyroid disease: scientific review and guidelines for diagnosis and management. *JAMA* 2004;291:228-233.
18. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *JAMA* 2004; 292:691-695.