To Screen or not to Screen for Subclinical Hypothyroidism in Pregnancy?

Abstract:

Not unlike screening for gestational diabetes, controversy prevails over the value of screening for thyroid disease in pregnancy. Fortunately, overt hypothyroidism is rare in pregnancy (0.3-0.5%) because it is associated with infertility and increased rates of first trimester miscarriage. Studies suggest that obstetric complications such as hypertension, placental abruption, preterm delivery, perinatal morbidity and mortality are increased in women with hypothyroidism in pregnancy[1] and there is evidence that the offspring of untreated mothers have neuropsychological and cognitive impairment. Subclinical hypothyroidism (Elevated TSH and normal Free T4) is estimated to be present in 2 â 2.5% of pregnant women. It is not as clearly associated with adverse obstetric and neonatal outcome but there is some evidence that maternal subclinical hypothyroidism is associated with impaired psychomotor development in the offspring[2].

Most expert groups advise targeted screening of mothers who have risk factors for thyroid disease e.g. If symptomatic, residence in an area of iodine deficiency, family or personal history of thyroid disease, known Thyroid Peroxidase antibodies, Type I diabetes mellitus, history of preterm labour or miscarriage, history of head or neck radiation, BMI > 40 kg/m[2], infertility and Age >30 years[3]. It is estimated, however, that one third of cases will be missed with targeted screening and some experts are calling for universal screening claiming that this will be more cost effective with an estimated saving of more than 8 million dollars for every 100,000 women screened[4]. This estimate is based on the assumption that detection and treatment of the 2.5% women with subclinical hypothyroidism will impact on the neurocognitive development of their offspring.

This does not appear to be the case, however. A paper in the NEJM in 2010 reports the results of a well conducted trial where 21,846 women less than 16 weeks gestation had serum taken and were randomized to be tested for TSH and T4 immediately or following delivery[5]. Those that were tested in early pregnancy and had TSH levels above the 97.5th centile, free T4 less than the 2.5th centile or both were deemed screen positive and treated with thyroxine. Bloods were repeated six weeks later and dose adjusted to a target TSH of 0.1 â 1.0 mIU/L. The primary study outcome was IQ at 3 years of age in the children of the women who tested positive.

4.6% of the screening group tested positive and 5% of the control group and about 5% of these cases had both a high TSH and low free T4. Both groups were comparable in terms of baseline and socioeconomic characteristics and had similar gestational age at delivery, rates of preterm birth and birth weight. The analysis based on intention to treat showed a mean standardized IQ at 3 years of age of 100 in the screening group and 99.2 in the control group (p=0.40) and the proportions of children with an IQ of less than 85 was 12.1% compared to 14.1% (p=0.39). There was no difference between groups in other psychological assessments (CBCL and Brief-P scores). 79% of women in the screening group were compliant with medication and the results were unchanged when on-treatment analysis was performed.

At approximately 10 to 12 weeks gestation the fetal thyroid can concentrate iodine and synthesise iodothyronines but hormonal synthesis is limited until the 18th to 20th week. For this reason, the fetus is thought to be dependent on maternal T4 and T3 in the first trimester when neurodevelopment is occurring. It is possible that screening for and treatment of maternal subclinical hypothyroidism occurred too late in gestation (median 13 weeks 3 days) in this study but, in practical terms, this is the time that women present for antenatal care. Preconceptual screening may be of benefit in women planning pregnancy or attending infertility clinics. Major deficits in our understanding of fetal and placental thyroid physiology remain, however. Thyroid hormone receptor is not expressed in fetal tissue until 8-10 weeks and the placenta is rich in T III deiodinase that converts maternal thyroxine to inactive rT3 such that a large percentage of maternal thyroxine never reaches the fetus. Thus, the hypothesis that administration of thyroxine to a mother with subclinical hypothyroidism may impact on the neurocognitive development of her fetus may be too simplistic.

Perhaps the primary end point of this study, namely IQ at 3 years, did not have the sensitivity to detect subtle differences in outcome between the two groups. It is reassuring, however, to note that the mean IQ in the children born to the women with subclinical hypothyroidism was not different from that of the normal population. Hypothyroidism has been associated with psychomotor deficits, delays in language development, orientation, vision abnormalities and behavioural changes[5]. This study was not designed to examine for all of these end points. There is currently another RCT examining the impact of screening and treatment on IQ at 5 years of age[6]. This study focusing on the intellectual function of offspring at five years of age will hopefully shed more light on the subject. Secondary outcomes include motor and psychomotor development, behavioural and social competencies and some obstetric complications.

The paper by Lazarus et al[5] is important in the interim because it provides randomized controlled data on neurocognitive outcome following screening for subclinical hypothyroidism and thyroxine supplementation in pregnancy. It clearly shows that there is no influence on infant outcome in terms of IQ at 3 years of age. At the present time screening for and treating subclinical hypothyroidism in early pregnancy has no proven maternal and fetal benefit and the results of the ongoing NICHD study will not be available until 2015.

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