

MOTHERISK ROUNDS

Hypothyroidism in Pregnancy

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J Obstet Gynaecol Can 2007;29(4):354–356

INTRODUCTION

Hypothyroidism is a relatively common illness in pregnancy. Between 2.2% and 2.5% of women have been found to have serum thyroid stimulating hormone (TSH) levels of 6 mU/L or greater at 15 to 18 weeks' gestation.^{1,2}

OBSTETRICAL COMPLICATIONS OF MATERNAL HYPOTHYROIDISM

Maternal hypothyroidism may place the mother at an increased risk of adverse obstetrical outcomes. Untreated hypothyroidism is associated with increased risk for preeclampsia, low birth weight, placental abruption, miscarriage, and perinatal mortality.^{3,4} Recently, Idris et al. found that in addition to an increased risk of low birth weight, hypothyroidism (as defined by increased serum TSH) early and late in pregnancy may also increase the rate of Caesarean section (CS).⁵ Raised maternal serum TSH in the second trimester is also associated with an increased rate of fetal death after 16 weeks' gestation.² Recent studies have found that although women treated for hypothyroidism may have higher rates of preeclampsia⁶ and CS⁷ than euthyroid women, they are not at any higher risk for adverse outcomes such as fetal anomalies, fetal demise, or preterm birth. In a study of 419 hypothyroid women, Tan et al. observed that women who are treated with levothyroxine (L-T4) in pregnancy were not at increased risk of maternal or neonatal morbidity.⁸

NEONATAL AND LONG-TERM COMPLICATIONS OF MATERNAL HYPOTHYROIDISM

In addition to adverse obstetrical outcomes, maternal hypothyroidism is associated with adverse neonatal outcomes. As the fetus does not begin to produce its own thyroid hormones until approximately 12 weeks' gestation, it is solely dependent on maternal thyroxine (T4) during early gestation.^{9,10} After 12 weeks, thyroid hormone in the fetus continues to be partly supplied by the mother.¹¹

Neuropsychological deficits in the offspring from as early as 3 weeks to 9 years of age have been observed. Recently, Kooistra et al. studied 108 neonates born to mothers with serum free thyroxine (fT4) levels below the 10th percentile at 12 weeks' gestation. Compared with control subjects, these infants had decreased neonatal behavioural assessment scores at three weeks of age.¹² Pop et al. studied 220 healthy infants and found that having maternal serum fT4 levels below the 10th percentile at 12 weeks' gestation was a significant risk for impaired psychomotor development at 10 months of age.¹³ A similar result was observed by Kasatkina et al.¹⁴ The finding of a low maternal serum fT4 level at five to nine weeks' gestation correlated significantly with a lower coefficient of mental development (which is thought to represent neuropsychological development) at 6, 9, and 12 months of age.¹⁴ In a study of 63 cases with matched controls, mothers with low serum fT4 at 12 weeks' gestation who continued to have low levels at weeks 24 and 32 were at risk of having a child with delays in mental and motor development at one and two years of age. This neurodevelopmental delay was even more profound when the mothers had a continuing decrease in serum fT4 as pregnancy progressed.¹⁵ Children born to women who were not treated for thyroid deficiency during pregnancy (as defined by increased serum TSH) had average IQ scores at

Key Words: Pregnancy, thyroid disease, hypothyroidism, therapy

seven to nine years of age that were 7 points lower than those of controls.¹⁶

Fortunately, treatment of maternal hypothyroidism decreases the risk of neurodevelopmental deficits in the offspring. The stage of development during which the lack of T4 in the fetus is most detrimental for neurodevelopment is thought to be the first trimester.¹⁷ However, Pop et al. showed that maternal treatment at a later stage in pregnancy is also beneficial for neonatal outcome. In this study, the offspring of women who had an ongoing increase in maternal serum fT4 from 12 to 32 weeks' gestation showed neurodevelopment at one and two years of age that was not significantly different from that of controls.¹⁵ Other investigators have noted similar benefits with treatment of maternal hypothyroidism. The offspring of mothers who had correction of serum fT4 by week nine of gestation using L-T4 had the same level of neurodevelopment at one year of age as control subjects.¹⁴ Interestingly, Haddow et al. observed that even when pregnant women were insufficiently treated for hypothyroidism (based on serum TSH measurements), the IQ scores of their offspring were not significantly different from those of controls.¹⁶

TREATMENT

Given the increased risk for adverse obstetrical and neonatal outcomes in untreated patients, it is prudent to treat all pregnant women who have hypothyroidism. Levothyroxine is the treatment drug of choice. As L-T4 is a synthetic drug, the hormonal content is standardized and more reliable.⁴ It is considered safe to use in pregnancy and has not been shown to have teratogenic potential.^{18,19} Clinicians should also bear in mind that some medications, including iodine, lithium, carbamazepine, phenytoin, rifampin, amiodarone, aluminum hydroxide, cholestyramine, sucralfate, glucocorticoids, and propranolol have the potential to interfere with L-T4 requirements. Mechanisms involved include inhibition of thyroid hormone synthesis or release, inhibition of T4 conversion to T3, increase of thyroxine clearance, interference with binding of T4 or T3 to transport proteins, and interference with intestinal absorption of L-T4.^{4,20} As many pregnant women take vitamin supplementation, it is also important to note that ferrous sulfate²¹ and calcium carbonate²² can each reduce the absorption of L-T4 if taken concurrently.

It is evident that treatment of maternal hypothyroidism during pregnancy greatly improves both obstetrical⁶⁻⁸ and neonatal¹⁴⁻¹⁶ outcomes. In fact, treating maternal hypothyroidism is beneficial to the offspring, even if treatment is insufficient.¹⁶ Nonetheless, women should be made euthyroid as quickly as possible after the diagnosis of hypothyroidism, and all attempts should be made to

maintain thyroid balance. The dose of L-T4 usually needs to be increased as pregnancy progresses.^{5,23-25} This increase can be as great as 47% of the pre-pregnancy dosage.²⁴ Some authors have even suggested that women who are taking L-T4 prior to conception should increase the dosage (by 30-60%) once pregnancy is confirmed.^{5,20,23,24} Because of this increased requirement of L-T4, thyroid status should be monitored frequently throughout pregnancy.

MONITORING

There is no consensus about whether it is better to monitor the serum level of fT4 or TSH in maternal hypothyroidism, as it is not clear which of these better represents the T4 supply to the fetus.²⁶ Several investigators have suggested that TSH levels should be monitored to assess the adequacy of thyroid hormone replacement during pregnancy^{4,24,27}; Montoro et al. have even suggested the time intervals at which TSH should be measured (at 6-8 weeks, at 16-20 weeks, and at 28-32 weeks).⁴ However, others have argued that serum fT4 levels should be monitored, because these more closely reflect the hormone available to cross the placenta.²⁸

Currently there are also no clear reference ranges for serum levels of fT4 and TSH in pregnancy.²⁶ This deficiency is complicated by the fact that human chorionic gonadotropin (hCG) is a weak thyroid stimulator and thus will cause maternal serum TSH levels to decline.²⁹ Additionally, iodine insufficiency may cause a decrease in serum fT4 levels without a measurable change in TSH.¹⁰ In a review, Soldin has presented some trimester-specific reference ranges for serum levels of both TSH and fT4.²⁰ However, more research in larger populations is required to confirm these reference ranges as valid.²⁴ Several placebo-controlled randomized trials are currently in progress to evaluate the fetal effects of L-T4 in pregnant women who have an increased level of serum TSH without clinical signs of hypothyroidism. At present, it is left to the clinician to decide the ideal serum levels of fT4 and TSH during pregnancy. That being said, the correction of an isolated low level of fT4 (without elevation of TSH) has more potential for benefit than harm, given the adverse obstetrical and neonatal outcomes of maternal hypothyroidism.²⁶

CONCLUSION

Treatment of maternal hypothyroidism is essential, because adverse outcomes for both mother and baby are greatly reduced, if not eliminated, when patients are treated. Even when treatment is initiated later in pregnancy or is insufficient to restore a euthyroid state, the babies of treated mothers will show more normal neurodevelopment than the babies of non-treated mothers. Clinicians must follow

hypothyroid women closely during pregnancy and increase the dose of L-T4 as required.

Neurodevelopmental follow-up of the babies of hypothyroid mothers is also recommended in order to identify cognitive deficiencies as early as possible and provide appropriate management.

ACKNOWLEDGEMENTS

The preparation of this manuscript was supported by a grant from the Canadian Institute for Health Research. Facundo Garcia-Bournissen has received funding from the Clinician Scientist Training Program, which is funded, fully or in part, by the Ontario Student Opportunity Trust Fund–Hospital for Sick Children Foundation Student Scholarship Program.

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