MOTHERISK ROUNDS

Fetal Pharmacotherapy 4: Fetal Thyroid Disorders

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INTRODUCTION

In this review we focus on advances in pharmacotherapy for fetal thyroid disorders. Because these disorders may affect fetal brain development, accurate and prompt diagnosis is critical. We will review fetal goitre, fetal hypothyroidism, and fetal hyperthyroidism.

FETAL GOITRE

Fetal goitre is an unambiguous indication of fetal thyroid dysfunction.[1] As fetal goitre has an incidence of 1:40 000 deliveries,[2] it is of the utmost importance for it to be included in the differential diagnosis of a sonographic anterior cervical mass.[3]

Untreated fetal goitre is often associated with both perinatal and long-term neurologic sequelae as a result of both the mechanical effects of the neck mass and the hormonal abnormalities involved. The goitrous mass may cause hyperextension of the fetal neck, obstruction of the trachea and esophagus, polyhydramnios, preterm labour, dystocia, asphyxia, and death at delivery. Thyroid deficiencies in the antenatal and neonatal periods are often associated with delays in motor and mental function, as well as hearing defects later in life. In comparison, congenital hyperthyroidism is associated with high morbidity and mortality due to the incidence of high-output cardiac failure, hydrops, growth restriction, advanced bone maturation, and mental retardation.[4–9]

Fetal goitre is diagnosed by ultrasound during the second or third trimester. It may be difficult to diagnose mild and moderate goitre, but it is essential to look for it carefully, especially in mothers with thyroid disorders. Goitre is typically the earliest sonographic sign of fetal thyroid dysfunction,[9] either hyperthyroidism or, more often, hypothyroidism.[1,2] Hence it is critical to determine fetal thyroid status accurately, either by using the gold standard of fetal blood sampling through cordocentesis,[10] or on the basis of maternal medical history, including the mother's medication and autoimmune diseases, and following up with further sonographic findings including tachycardia, skeletal maturation, hydrops, intrauterine growth restriction, and cardiac failure.[9,11]

FETAL HYPOTHYROIDISM

Congenital hypothyroidism is one of the most common curable causes of mental retardation.[12] However, despite early neonatal screening and treatment, approximately 10% of children with severe hypothyroidism require special education.[13] For this reason, antenatal treatment is essential to prevent the short- and long-term sequelae of hypothyroidism. While treatment of goitre associated with hypothyroidism is recommended because goitre is a clear indication of fetal thyroid dysfunction, the treatment of hypothyroidism without goitre remains controversial because it is still unclear whether the condition would affect the child's prognosis; in addition, it is difficult to diagnose.[1,4]

Fetal goitrous hypothyroidism might be caused by dyshormonogenesis, or it may be secondary to transplacental passage of maternal antithyroid drugs (commonly propylthiouracil or methimazole for the treatment of Grave's disease), or transport of antithyroid antibodies.[2]

In verified cases of fetal goitre with hypothyroidism, direct delivery of thyroid hormone to the fetus should be considered,[8,11] as well as reduction or discontinuation

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of maternal treatment with antithyroid drugs.[1,14,15] The standard treatment is levothyroxine through intra-amniotic administration; the fetus ingests this by swallowing it in the amniotic fluid and converting it primarily to triiodothyronine (T3),[2,4] because the placenta is relatively impermeable to the levothyroxine and T3 in maternal blood.[4]

Because pharmacokinetic data regarding fetal uptake and absorption of levothyroxine from amniotic fluid is lacking, different treatment regimens have been described. Dosing has ranged between 150 and 600 µg.[2–4,8,16–18] The number of injections have ranged from one to 10[3,11,19] at intervals of 7 to 21 days.[3,4,17] While in some cases timing of re-administration of levothyroxine has been based on re-enlargement of the fetal thyroid,[3] in others the interval was decided arbitrarily.[4,11] The optimal time to initiate treatment is also controversial. Some clinicians prefer not to inject the hormone intra-amniotically in order to minimize the risks of infection and preterm labour.[20] On the other hand, some clinicians have initiated treatment as early as 20 weeks of gestation and some as late as 37+4 weeks, believing that the hormonal deficiency should be corrected quickly to prevent negative effects on the fetal brain.[4,8,9,19]

Currently there are no clear guidelines for the timing of intra-amniotic injection of levothyroxine as treatment in addition to reducing maternal antithyroid medication in cases of fetal hypothyroidism. Invasive treatment is most commonly indicated when fetal goitre is diagnosed early in pregnancy, in cases of bulky goitre, with polyhydramnios, when there has been no response to a reduction in maternal antithyroid medication, or when fetal hypothyroidism is due to dyshormonogenesis.[1,21]

Monitoring fetal therapeutic efficacy remains difficult. Serial measures of thyroid hormone levels by cordocentesis (not by amniocentesis) is a reliable monitoring method, but it carries unacceptably high fetal risks.[8,9,19,22] The assessment of a therapeutic response is usually managed non-invasively by sonographic examination for follow-up of the goitre's size.[2,9,23] Additional follow-up strategies with less clinical evidence have also been recommended, such as a reduction in or disappearance of the colour Doppler signal[2,9] or MRI evaluation of the enlarged gland and airway.[24,25]

In most cases, rapid shrinking of the goitre has been observed within 0.5 to 2.5 weeks after the first injection.[1–3,19] In cases in which there is no response to treatment with intra-amniotic levothyroxine, it is important to recognize that as pregnancy progresses the fetal thyroid gland increases in size physiologically, and therefore no change in the size of the gland could mean a decrease in size relative to gestational age.[1] However, the injection dosage also could be insufficient, and therefore fetal thyroid status should be reconsidered.

Numerous cases with good neonatal outcomes after intra-amniotic levothyroxine injections have been reported.[1,3,8,9,16,26–28] According to the largest systematic review, 16 of 22 neonates (73%) were euthyroid after antenatal reduction of maternal antithyroid drug dose in addition to intra-amniotic injection of levothyroxine, while six of 22 (27%) were hypothyroid.[1] Even severe cases with hydrops fetalis resolved with intra-amniotic levothyroxine treatment.[29] Unfortunately, follow-up information is sparse in these publications. In reports with neonatal follow-up there has been no marked delay in bone maturation or neurodevelopmental issues, although it is possible there is bias in reporting results.[1,3,9,29]

While intra-amniotic injection of levothyroxine is considered standard treatment because of the low complication rates and wide administration intervals,[3,4] fetal intramuscular injection or umbilical cord injection of levothyroxine should be considered in cases in which swallowing is critically impaired by extreme pressure on the esophagus by the goitrous mass.[2,30]

An alternative treatment is to administer tri-iodothyronine, either as an intra-amniotic injection or as a maternal oral treatment.[19] Intra-amniotic T3 may reduce the goitrous mass size faster and with a smaller dose than levothyroxine, because the fetal effects of T3 begin within 4 to 8 hours. T3 has a half-life of 1 to 2 days, while levothyroxine has a half-life of 6 to 7 days.[19] The oral maternal medication tiratricol is a T3-derived analogue that binds to thyroid hormone receptors with higher affinity than T3, and has rapid transplacental transfer that could be effective in decreasing fetal TSH concentrations and fetal goitre size without the need for invasive procedures.[31–34] Further research is needed to determine whether these alternative treatments can optimize fetal outcome better than intra-amniotic injections of levothyroxine.

FETAL HYPERTHYROIDISM

Congenital hyperthyroidism is less common than congenital hypothyroidism, but the growth and developmental sequelae can be as serious.[35] Transient neonatal hyperthyroidism is the more common form, most often caused by either active or inactive maternal Graves' disease, as a result of transplacental passage of maternal TSH-receptor antibodies (TRAb). These antibodies can

cause overstimulation of the fetal thyroid gland beginning in the second trimester, even several years after maternal thyroidectomy or ablation.[36–38] Several cases of persistent congenital hyperthyroidism have been described, including cases of familial neonatal Graves' disease and sporadic cases of neonatal hyperthyroidism due to mutations in the TSH receptor.[35]

When fetal goitre is diagnosed in a mother with Graves' disease, it is critical to evaluate whether the goitre is a result of transplacental passage of thyroid-stimulating antibodies. In cases of concomitant fetal hyperthyroidism, the mother will usually require an increase in the doses of antithyroid drugs. If the fetal goitre is found in a euthyroid mother, it is usually possible to treat the mother with antithyroid drugs and have a favourable response in the fetus. However, the mother will usually need levothyroxine supplementation during this treatment.[9]

Propylthiouracil (PTU) has been considered a first-line drug for treatment of fetal hyperthyroidism, and is preferred to methimazole or carbimazole because these drugs have been associated with esophageal or choanal atresia, aplasia cutis, and embryopathy that includes developmental delay, hearing loss, and dysmorphic facial features.[38,39] Because these abnormalities have been described mainly with exposure during the first trimester of pregnancy, and because thyroid goitre appears only in the second half of pregnancy, treatment with carbimazole[40] or methimazole alone[39] or intermittently with Lugol's solution (potassium iodide and iodine)[36] have been described with good results in post-thyroidectomy cases with positive TRAb. Propranolol can also be used for the treatment of fetal hyperthyroidism, but it is not recommended because it is less effective and because it may be associated with fetal growth restriction.[39] Other treatment modalities, such as using human monoclonal autoantibody to the thyrotropin receptor (5C9) to inhibit stimulation,[41] have been studied and may be treatment options in the future.

Fetal hyperthyroidism is treated with the lowest effective dose of PTU in order to minimize the risk of fetal hypothyroidism.[37] The dose range is usually from 100 mg/day to 450 mg/day depending on goitre size and treatment response.[9,42]

Response to the treatment of fetal hyperthyroidism can also be assessed by cordocentesis or sonographically. However, cordocentesis follow-up may be more important because PTU overdose can cause fetal hypothyroidism.[42] Moreover, in one study goitre shrinkage was less clear in cases of fetal hyperthyroidism than in fetal hypothyroidism, despite improved fetal thyroid outcome.[9] Maternal TRAb may have caused a direct trophic effect on the fetal thyroid.[9]

While there are no large cohorts reporting the outcome of fetal treatment, the available studies have generally reported satisfactory outcomes, with only mild thyrotoxicosis[9,39] or hypothyroidism[9,43] or euthyroidism[40,42] at birth and significant improvements over previous untreated pregnancies.[9,36]

Adverse effects of fetal hyperthyroidism treatment may occur, especially when the mother is euthyroid clinically but needs antithyroid drugs. Thus, serial maternal thyroid function assessments at two week intervals after initiation of antithyroid treatment is recommended, in addition to fetal surveillance.[42,43]

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