CASE REPORT

Prenatal Diagnosis and Treatment Perspective of Fetal Hypothyroidism with Goiter

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ABSTRACT

We describe two cases of fetal goiter in women with no history of thyroid disease. Diagnosis of fetal goiter during antenatal care was made by ultrasound and MRI. Congenital hypothyroidism was confirmed by fetal blood sampling that was treated with weekly intra-amniotic injections of L-thyroxin. One fetus was initially treated with four weekly intra-amniotic injections of 200 µgms of L-thyroxin, later increased to 400 µgms. The other fetus was treated with only three weekly intra-amniotic injections of 400 µgms of L-thyroxin. Therapeutic response was monitored by repeated ultrasound and MRI along with fetal blood sampling. At birth, none of the babies had goiter and were put on oral thyroxin. Post-natal studies were suggestive of congenital hypothyroidism due to dyshormogenesis. No abnormality was detected at follow-up. These cases highlight the role of intra-amniotic thyroxine in management of fetal hypothyroidism with goiter.

Key words: *Fetal goiter. Hypothyroidism. Intra-amniotic. Thyroxine. Ultrasound. MRI.*

INTRODUCTION

Majority of fetal goiters are secondary to maternal thyroid disease. Advances have been made in pre-natal biochemical evaluation,[1] ultrasound, postnatal screening and therapeutic management. Motor and intellectual deficits of primary congenital hypothyroidism are likely in these children. Early intrauterine diagnosis and treatment have been advocated in order to avoid the long-term sequelae. The recent advances in ultrasound and MRI have facilitated the antenatal diagnosis of fetal goiter, thus offering a chance of intrauterine therapeutic intervention. This report describes ultrasound and MRI aided, biochemically confirmed diagnosis and monitoring of two fetuses with congenital hypothyroidism treated with intra-amniotic L-thyroxin therapy.

CASE REPORT

Case 1: A 25 years old lady at 30 weeks gestation subsequent to *in-vitro* fertilization (IVF) was referred after detection of a fetal neck mass on ultrasound. Based on the location of the mass, a provisional diagnosis of fetal goiter was made. The mother had no past or family history of thyroid disease and was not on any medications. Maternal thyroid function tests (TFTs) and anti-thyroid antibody profile were normal (Table I). A repeat ultrasound at 31 weeks revealed a hyper-extended fetal neck with an encapsulated, bilobed mass in front of trachea which was central and patent with no retro-sternal extension (Figure 1). The size of the right lobe was 24 x 16 mm and the left lobe was 26 x 17 mm. At 32 weeks, fetal MRI scan confirmed the presence of a homogeneous, bilobed mass measuring 36 x 36 mm in sagittal plane and 45 x 27 mm in axial plane engulfing the central patent trachea. Fetal TFTs obtained by cordocentesis at 32 weeks revealed a high TSH of 39.6 mu/L (normal range 10.2 $\pm$ 3.8 mu/L) and a T4 of 15.9

Table I: Maternal thyroid hormones of case no. 1.

Thyroid function test	Readings	Normal values
T4	17.0 pmol/L	12 – 22.0 pmol/L
TSH	2.37 mu/L	0.27 – 4.200 mu/L
T3 total	2.3 n mol/L	1.3 – 3.1 n mol/L
Anti-thyroglobin antibodies	14 U/ml	= < 115 U/ml
Anti-thyroid peroxidase antibodies	9 U/ml	= < 34 U/ml
Thyroid stimulating Ig	< 1.0 TSI	= < 1.3 TSI

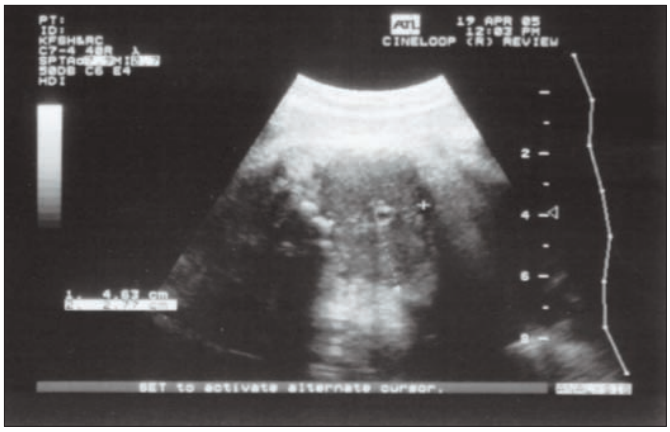

Figure 1: Ultrasound scan showing fetal goiter in cross section with a patent trachea.

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Received November 03, 2011; accepted May 31, 2012.

pmol/L, (normal range 6.0 – 143 pmol/L) confirming the diagnosis of hypothyroidism.[1] The fetus was treated initially by intra-amniotic L-thyroxin at dose of 200 µg/week (10 µg/kg/day) from 32 to 35 weeks. At week 35, ultrasound and MRI assessment revealed only a mild reduction in goiter size; however, a significant reduction in TSH levels (13.78 mu/L) was detected after a repeat cordocentesis. Subsequently, the dose of intra-amniotic L-thyroxin was increased to 400 µg/week for the next 2 weeks (20 µg/kg/day). A female baby was delivered by cesarean section at 38 weeks on maternal request. After the delivery, no mass was found on the anterior aspect of the fetal neck. The infant's serum TSH was 27 mu/L and free T4 was 14.8 pmol/L and TSH increased further on second day of life. Therefore, oral L-thyroxin was introduced, initially 50 µg L-thyroxin daily, reduced to 25 µg/day after a period of one week. I^{123} thyroid isotope scan of the neonate one week after delivery was consistent with thyroid dyshormogenesis. At 3 years of age, the child had been able to achieve normal physical and mental health with alternating oral dose of 25 and 12.5 µg/day of L-thyroxin.

Case 2: A 34 years old mother of 5 children, with no history of thyroid disease was referred at 34 weeks of gestation with anterior neck mass detected on ultrasound of the fetus. Two of her children aged 9 and 7 years were suffering from sequelae of congenital hypothyroidism due to delayed diagnosis and lack of treatment. The elder child was diagnosed at the age of 9 months and is now mentally retarded while the younger child had been diagnosed in the intra-uterine life but received no therapy until after birth. This child suffered from delayed speech and language difficulties. In the current pregnancy, fetal goiter was the most likely diagnosis by the ultrasound. Its dimensions were 50 x 30 mm with mild polyhydramnios. Maternal thyroid function tests were normal (Table II), whereas the fetal blood sampling revealed very high levels of TSH > 500 mu/L. Three doses of intra-amniotic L-thyroxin of 400 µgms/week were given at weekly intervals from 34 to 36 weeks. Goiter could not be detected by ultrasound and MRI scan at 36 weeks because of the prior treatment with L-thyroxin. At 37 weeks, patient went into spontaneous labour and a female baby was delivered with no apparent goiter. Postnatal thyroid function tests confirmed hypothyroidism and oral thyroxin was continued. Postnatal thyroid scan was suggestive of thyroid dyshormogenesis.

Table II: Maternal thyroid function tests of case no. 2.

Parameter	Readings	Normal range
T4	12.8 pmol/L	12.00 – 22.00 pmol/L
TSH	3.74 mu/L	0.27 – 4.20 mu/L
Thyroglobin	2.2 µg/L	1.4 – 7.8 µg/L
Anti-thyroglobin antibodies	24 u/ml	< 115 u/ml
Anti-thyroid peroxidase antibodies	< 5.4 u/ml	< 34 u/ml

DISCUSSION

Congenital hypothyroidism and associated fetal goiter is a rare pathological condition. It is known for its adverse effects on pre- and postnatal development particularly targeting intellectual performance. Early diagnosis and treatment is a key factor in ensuring normal growth and neurological development. In addition, the obstetrical complications due to enlarged goiter can also be avoided at the time of delivery.[2]

Fetal goiter is usually secondary to maternal thyroid dysfunction but rarely it may occur in infants delivered by otherwise normal and healthy women. The diagnosis is usually incidental and the availability of modern techniques in ultrasound imaging has now facilitated in utero detection of such conditions. Different modalities have been used for ultrasonographic evaluation of goiter. Whereas 3D ultrasound can accurately determine the volume, colour Doppler scan can detect the biological activity by means of patterns and changes in vascularity.[3] Assessment of these parameters is important for monitoring the therapeutic response. In these cases, ultrasound served as a useful tool for the diagnosis of fetal goiter. It also provided vital information regarding the position and patency of trachea and fetal neck extension. Although not applied in the present study, MRI assessment has been used in situations where the ultrasound findings were ambiguous particularly in cases of oligohydramnios. MRI is a useful tool not only in the detection of retro-sternal extension of the goiter but also in the assessment of goiter related obstructive effects on trachea and esophagus in the presence of massive polyhydramnios.[4] In these cases, sufficient information was obtained by ultrasound imaging which obviated the need for MRI aided assessment.

For the assessment of the functional state of fetal goiter, fetal blood sampling is regarded as the gold standard but is associated with complications. Laboratory diagnosis of congenital hypothyroidism is based on increased TSH level, while T4 generally remains normal.[5] Serum levels of fetal TSH at which goiter may develop are variable. Case No. 2 had fetal serum TSH of > 500 mu/L, which, to the best of our knowledge, has never been reported before.

Under normal circumstances, thyroxin cannot cross placenta, however, in fetal hypothyroidism small amounts of maternal thyroxin can cross placenta but it is insufficient to treat fetal pathology. Intramuscular injections of L-thyroxin have been administered without any clear evidence of benefit in situations where large goiters were found to interfere with swallowing.[6] Weekly administration of L-thyroxin by intra-amniotic route has been advocated and considered as a treatment of choice for congenital hypothyroidism. The main benefits of intra-amniotic route have been the low rate of

complications and relatively longer intervals between injections. There is, however, no agreement on the intra-amniotic dose of L-thyroxin. In some cases, only one dose of 200-300 µg of L-thyroxin has proven sufficient to correct fetal thyroid dysfunction and goiter whereas in other instances upto eleven intra-amniotic injections of 250 – 500 µg of L-thyroxin have to be administered.[7] Here, 4 weekly intra-amniotic doses of 200 µg failed to achieve a significant reduction in the thyroid mass, despite reduction in fetal TSH levels from 39.6 mu/L to 13.7 mu/L. Intra-amniotic administration of 400 µg (20 µg/kg/day) L-thyroxin in both the cases resulted in satisfactory response and it appears to be a sufficient dosage for the treatment of congenital hypothyroidism. However, the dose needs to be adjusted according to the size of goiter, the time available for treatment until birth and response to therapy.

For the diagnostic and therapeutic purposes, assessment of amniotic fluid TSH and T4 levels is considered to be unreliable.[8] Fetal blood TSH and T4 levels may confirm the diagnosis of fetal goiter but are not recommended frequently because of the high risk associated with the procedure. In the first patient, it was performed twice, initially to diagnose and then at 35 weeks to assess the therapeutic response. In the second case, fetal blood sampling was performed once only at the time of diagnosis and the therapeutic response was assessed by imaging only. Single intervention for the assessment of fetal TSH and T4 appears to be sufficient as each invasive procedure carries the risk of pre-mature labour.[4] For the same reason, Nicoline *et al*. proposed maternal oral therapy with triac as an effective alternative to avoid multiple invasive procedures.[9] Triac is a T3-derived analog, which binds to thyroid hormone receptors and has high trans placental transfer but it needs more experience to determine proper dosage for fetal response without causing untoward maternal effects. Intra-amniotic tri-iodo-thyroxin (T3) has also been used in the treatment of congenital hypothyroidism. It was found that T3 is more potent and had a short duration of action requiring frequent injections. It has, therefore, been recommended to be used in acute symptoms of esophageal obstruction and polyhydramnios either alone or in combination with T4.[10] The present study shows that L-thyroxin in higher doses administered at the same frequency was able to achieve the desired therapeutic response in comparatively shorter time with less number of invasive procedures.

Dyshormogenesis, as a cause of congenital hypothyroidism, was evident in the present study. It is believed to be a recessively inherited biochemical defect in thyroid hormone synthesis and secretion. Affected women can have several babies with congenital hypothyroidism, therefore, close monitoring in future pregnancies is mandatory. This was evident in the second case where two affected siblings were already present in the family due to delayed diagnosis and treatment. We intend to conduct future follow-ups of all 3 children in this family in an attempt to evaluate the long-term benefits of early ante-natal diagnosis and treatment.

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