Intrauterine diagnosis and treatment of fetal goitreous hypothyroidism

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Abstract

We present two cases of fetal hypothyroidism with goiter which were successfully diagnosed and treated in utero. In both cases, ultrasonographic examination demonstrated a bilobed solid anterior neck mass with increased vascularity compatible with enlarged thyroid gland. Fetal blood sampling revealed hypothyroidism. Intra-amniotic injection of L-thyroxin caused a reduction in thyroid gland size and enabled vaginal delivery without complication. In the first case, maternal thyroid hormone levels and autoantibodies were normal and the neonate had hypothyroidism suggesting the diagnosis of dyshormonogenesis. In the second case, the fetus had transient hypothyroidism, which resolved spontaneously after delivery. Maternal thyroid function tests and autoantibodies were normal and both the mother and neonate had normal urinary iodine, excluding the diagnosis of iodine deficiency or excess. Thus, we believe that transplacental transfer of undetermined factors might be a cause of transient congenital hypothyroidism. Also, we reviewed the literature and described controversial issues regarding the management of fetal goiter.

Key words: fetal goiter, fetal hypothyroidism, intra-amniotic thyroxin, intrauterine thyroxin treatment

Introduction

Fetal goiter is a very rare pathology with an incidence of one in every 40 000 deliveries.1 It can be diagnosed during the second or third trimester of gestation with the triad of anterior cervical mass, hyperechogenicity of head and polyhydramnios.1 Fetal goiter may cause: hyperechogenicity of head leading to malpresentation during delivery,2 high-output cardiac failure due to intrathyroid arteriovenous shunting,3 esophageal and tracheal compression which may cause polyhydramnios, preterm labor, and neonatal asphyxia and death,4 and motor or cognitive deficits or impaired intellectual development in cases of fetal hypothyroidism.1,5 Fetal goiter may be associated with hyperthyroidism, hypothyroidism or euthyroid state, hence, the assessment of fetal thyroid function is necessary to start early treatment.5 Since the assessment of amniotic fluid hormone levels is unreliable, cordocentesis is considered the gold standard for the evaluation of fetal thyroid hormone levels.4,5

Prenatal treatment of fetal hypothyroidism requires the direct administration of thyroid hormones to the fetus as the placenta is relatively impermeable to thyroxin (T4) and triiodothyronine (T3) in the mother's blood.4 Even though intravascular and intramuscular administration are available for direct delivery of medication to the fetus, intra-amniotic injection of L-thyroxin, with the aim of reaching the fetal circulation through the fetal gastrointestinal tract, has become the standard therapy for fetal goiterous hypothyroidism due to its ease, low rate of complications and administration at long intervals.1,4
In the present paper, we report two cases of fetal goiter due to hypothyroidism in which we applied intra-amniotic L-thyroxin treatment.

Case 1
A 26-year-old woman in her first pregnancy was referred to our medical center because of a cervical mass at a gestational age of 25 weeks. The detailed ultrasonography demonstrated a 3.25 x 3.8-cm, bilobed, symmetrical, homogenously solid tumor on the anterior neck, suggesting a fetal goiter. There was an increased amniotic fluid index (AFI: 28 mm) and there were no signs of cardiac insufficiency. No other major fetal anomalies were detected. Maternal physical examination and thyroid function were normal. Thyroglobulin antibody, serum thyroid-stimulating hormone (TSH) receptor antibody and urine iodine were within normal limits. To evaluate fetal thyroid function, cordocentesis was conducted at 26 weeks' gestation. Cord blood TSH level was 23.84 μIU/mL (normal 6.9 ± 3.34 μIU/mL) and free T4 level was 1.10 ng/dL (normal 0.98 ± 0.23 ng/dL). TSH receptor blocking antibody, thyroglobulin antibody and thyroxin binding globulin were within the normal limits. Based on these findings, fetal goitrous hypothyroidism was diagnosed and the treatment with 500 μg of intra-amniotic L-thyroxin was initiated in the 29th week of gestation. The follow up was performed with weekly sonographic assessment. The goiter progressively shrank from 4.6 x 3.5 x 2.4 cm (30 cm³) to 3.3 x 2.2 x 1.6 cm (4 cm³). At 33 weeks of gestation, the thyroid gland measured 10 cm³ and a second injection of 500 μg L-thyroxin administered intra-amniotically was repeated 3 weeks later. AFI decreased to normal levels after the second injection. The in utero treatment was uncomplicated without any signs of intrauterine infection or preterm labor. After a follow-up period of 13 weeks, the labor was induced at 38 weeks of gestation and a 2810-g, female infant was delivered vaginally with Apgar scores of 7 and 9 at 1 and 5 min, respectively. Thyroid hormone levels in umbilical cord blood at delivery were TSH 23.84 μIU/mL (normal 0.34-5.60 μIU/mL), free T4 0.89 pmol/L (normal 0.89-1.76 pmol/L) and free T3 2.04 pmol/L (normal 2.5-3.9 pmol/L). Physical examination revealed a small goiter without an evidence of airway obstruction and 37.5-μg daily L-thyroxin treatment was initiated to the neonate. The baby has been followed up in the Endocrinology Unit of our hospital with normal growth and neurological development.

Case 2
A gravida 2 para 1 24-year-old woman was referred to our hospital at a gestational age of 22 weeks due to a 2.8 x 1.8 x 2.2-cm (6 cm³) fetal neck mass with increased vascularity. AFI was normal and there were no signs of cardiac insufficiency. Maternal thyroid hormone levels and physical examination were normal. Thyroid peroxidase antibody, TSH receptor antibody, and thyroglobulin antibody were all negative. Urinary iodine level was also normal. Fetal blood sampling revealed severe fetal hypothyroidism with TSH 296.7 μIU/mL (normal 6.5 ± 1.81 μIU/mL) and free T4 0.30 ng/dL (normal 0.65 ± 0.23 ng/dL). Umbilical blood thyroid peroxidase antibody was <5 IU/mL (normal <34 IU/mL), thyroglobulin antibody was 124.6 IU/mL (normal <115 IU/mL) and TSH receptor antibody was 0.96 U/L (normal <1.1 U/L). With a diagnosis of fetal goitrous hypothyroidism, intra-amniotic injection of L-thyroxin was administered with a 2-weekly dose of 500 μg seven times between 24 and 36 weeks' gestation. The response to the treatment was followed up by 2-weekly sonographic evaluation of thyroid gland, which showed a progressive decrease in size (Fig. 1). AFI returned to normal level after the first injection. The intraterine treatment was free of complications. Due to oligohydramnios, labor was induced at 38 weeks of gestation and a 3140-g, male infant was delivered with an Apgar score of 8 at 1 min and 9 at 5 min. There was no goiter and the baby had normal results on thyroid studies on day 5 of TSH 3.48 μIU/mL (normal 0.34-5.6 μIU/mL) and free T4 1.04 pmol/L (normal 0.61-1.12 pmol/L). Urinary iodine level of the neonate was within normal limits. Thyroid ultrasound demonstrated a normal-sized thyroid gland. The follow up of the infant for 6 months revealed normal thyroid hormone levels without goiter and abnormal neurological development.

Discussion
Neonatal goitrous hypothyroidism is associated with maternal hyperthyroidism in most cases. Antithyroid medication, especially propylthiouracil (PTU) and rarely maternal thyroid-binding inhibitory immunoglobulin, cross the placenta causing hypothyroidism in the fetus. Endemic iodine deficiency or iodine-rich products, and fetal thyroid dysmornogenesis are other less-frequent causes. Dysmornogenesis is caused by gene mutations which are generally inherited in an autosomal recessive way resulting in biochemical
defects in one or more of the steps in iodothyronine synthesis and secretion. In the first case we present here, congenital hypothyroidism with normal maternal thyroid function tests and thyroid autoantibodies suggested the diagnosis of dys hormonogenesis.

In the second case, despite the normal maternal thyroid functions, the fetus had transient hypothyroidism which resolved spontaneously after delivery. Maternal ingestion of goitrogens, such as iodine-containing vitamins and iodine-rich products, are considered to be responsible for fetal hypothyroidism. However, both maternal and neonatal urinary iodine levels were detected as normal in our case. Furthermore, none of the thyroid autoantibodies were detected in maternal or neonatal serum, which is another possible cause of transient fetal hypothyroidism. Furthermore, the mother did not have a history of thyroid disease or thyrostatic medication use. Matsumoto et al. reported a case of fetal goitrous hypothyroidism followed by transient neonatal hyperthyroidism in the absence of thyroid autoantibodies in neonatal serum. They speculated that the transplacental transfer of undetermined factors might be involved in neonatal transient hyperthyroidism. Similarly, since none of the known factors, such as iodine deficit or excess, anti-thyroid medication or autoantibodies, seem to be the reason for the transient congenital hypothyroidism in our case, we believe that transplacental transfer of undetermined factors, such as maternally ingested unknown dietary goitrogens, may be responsible for fetal goitrous hypothyroidism.

The dose and frequency of L-thyroxin administration have been variable in the literature. Since thyroxin overdosage may result in fetal tachycardia, heart failure, growth restriction and perinatal death, Hashimoto et al. suggested to start with an initial dose as low as 150 μg of L-thyroxin and gradually increase the dose as necessary in order to prevent such adverse effects. Furthermore, Perelman et al. successfully treated a fetus with goitrous hypothyroidism with 500 μg of L-thyroxin at intervals of 10–14 days. Davidson et al. recommended weekly injections of 250 μg of L-thyroxin, which would approximate the requirement of a neonate with hypothyroidism (10 μg/kg/day). While Miyata et al. administered a weekly dose of 15 μg/kg/day L-thyroxin for severe congenital hypothyroidism. We preferred intra-amniotic injection of 500 μg L-thyroxin in our cases and detected a progressive regression of goiter. In the first case we administered the second dose when we detected a re-enlargement in fetal thyroid gland size. In the second case, we opted to inject L-thyroxine on a regular basis with 2-week intervals.

In conclusion, we reported two prenatally treated congenital goitrous hypothyroxin cases, one of which was an atypical case of transient fetal hypothyroidism with unknown cause. Fetal goiter is a rare disease which should be considered in the differential diagnosis of anterior cervical mass, and its prenatal diagnosis is very important as it is curable with intrauterine L-thyroxin injection, which prevents both obstetric complications at delivery and neurologic sequelae.
Disclosure

The authors declare that there are no conflicts of interest.

References


