A Rare Case of Recurrent Fetal Goiter

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Established Facts
- Fetal goiter is a very rare congenital anomaly and may be associated with both hypo- and hyperthyroidism of the fetus.
- The assessment of TSH and thyroid hormone concentrations in amniotic fluid is a reliable method for evaluating the function of fetal thyroid gland.

Novel Insights
- The most important aim of intra-amniotic L-thyroxine injections is not the complete recovery of thyroid function of the fetus but the reduction of the goiter size and prevention of fatal complications including heart failure and fetal hydrops.

Key Words
Fetus · Goiter · Hypothyroidism · Thyroxine · Amniotic fluid

Abstract
We report the case of fetal goiter which occurred in two consecutive pregnancies in the same patients. The first one, due to too late diagnosis and no intrauterine treatment, contributed to the immediate postnatal death of the newborn; the second one was properly diagnosed at 19 weeks and then effectively treated prenatally which allowed to avoid the fatal complications for the fetus and the newborn.

Case Report
A 25-year-old woman, with no prior history of thyroid problems, was referred to our unit at 29 weeks of gestation because of signs of severe fetal hydrops. Ultrasound evaluation revealed abnormal umbilical artery, umbilical vein (pulsations) and ductus venosus blood flow as well as the presence of a big solid tumor of fetal neck (8 cm of diameter), the most probable cause of fetal hydrops in this case. Emergency cesarean section was performed on the day of admission to the hospital for repeated fetal heart rate decelerations. A 1,280-gram boy was delivered with Apgar scores 3 and 3 at 1 and 5 min, respectively. The baby died soon after birth because of acute respiratory failure as a consequence of inability to intubate the newborn due to severe tracheal compression by the neck mass.

Based on the antenatal findings and postnatal appearance, a teratoma, a goiter and an angioma were taken into considerations as a possible diagnosis – as parents denied the autopsy of the child.
Maternal serum thyroid function tests undertaken 6 months after delivery revealed decreased level of TSH which was $0.005 /H_9262 \text{IU/ml}$ (normal $0.27–4.2 /H_9262 \text{IU/ml}$) and no increased concentration of free-T4 (fT4) which was $0.135 \text{ng/dl}$ (normal $0.932–1.71 \text{ng/dl}$). She had no detectable thyroid antibodies, including thyroid stimulating hormone receptor antibodies (TRAb), antithyroperoxidase antibodies (anti-TPO), thyroid stimulation-blocking antibodies (TSBAb) and antithyroglobulin antibodies. Methimazole therapy was started with a significant improvement of patient’s thyroid gland function.

About one year after the initiation of therapy, the patient got pregnant again. She was noted to be euthyroid at the time of her first visit at 6 weeks of pregnancy. The patient remained euthyroid throughout the whole pregnancy.

The first-trimester ultrasound scan at 12 weeks revealed a normal development of the fetus.

A second ultrasound scan of the fetus at 19 weeks gestation showed homogenous solid mass of $3.5 \times 2.5 \text{cm}$ on the anterior of the fetal neck (fig. 1) and mild cardiomegaly. Because of maternal thyroid condition, the location and high vascularity of the mass, a goiter was considered. Other fetal anatomical structures were normal.

Amniocentesis was performed at 20 weeks gestation to assess the TSH and fT4 concentrations in amniotic fluid and the fetal karyotype. Increased concentration of TSH ($2.39 /H_9262 \text{IU/ml}$; normal $0.1–0.5 /H_9262 \text{IU/ml}$) and the decreased level of fT4 ($0.28 \text{mg/dl}$; normal $0.4–4.5 \text{ng/dl}$) were consistent with fetal hypothyroidism. Fetal karyotype was normal (46,XY).

Treatment with intra-amniotic injections of $100 /H_9262 \text{g L-thyroxine}$ was started at 21 weeks’ gestation ($150 /H_9262 \text{g/kg of estimated fetal weight}$) and increased to $300 /H_9262 \text{g}$ at 23 weeks for increasing goiter size ($200–800 \text{g/injection}$) [1, 2].

Ultrasound scan at 25 weeks revealed increase in the goiter size to $4.3 \times 3.1 \text{cm}$ (fig. 2, 3), poor fetal growth, cardiomegaly (heart index 0.42), tricuspid regurgitation and polyhydramnios (amniotic fluid index 26 cm). The transverse diameter of thyroid gland ($4.3 \text{cm}$) was much above 97.5th percentile, which is 1.72 at 25 weeks [3]. With these findings L-thyroxine dose was increased to $500 \text{g}$.

At 27 weeks, two weeks after the first administration of $500 \mu g$ of L-thyroxine, the goiter size stabilized with improvement in fetal growth parameters. At 31 weeks, there were no signs of fetal heart failure (no cardiomegaly, no tricuspid regurgitation). At 33 weeks the goiter size relatively decreased to $4.6 \times 2.6 \text{cm}$ (the transverse diameter of $2.15 \text{cm}$ is 97.5th percentile at 33 weeks).
weeks [3]) and amniotic fluid concentrations of TSH and fT4 were within normal limits (TSH 0.15 μIU/ml, fT4 2.64 ng/dl). Most importantly, the fetal growth parameters were appropriate for gestation age. Fetus was closely monitored by ultrasound scans weekly until 37 weeks. During this time the goiter size was 4.8 × 3.0 cm with normal fetal growth and amniotic fluid index of 23–25 cm.

The last dose of 500 μg of L-thyroxine was given at 37 weeks. Three days later a live 3,250-gram male infant with Apgar score of 9 and 9 at 1 and 5 min, respectively, was delivered by elective cesarean section. Goiter was clinically evident at birth without any airway obstruction. Hypothyroidism was confirmed by neonatal blood sampling on the 7th day of life [TSH in the newborn was 19.4 μIU/ml (normal <6 μIU/ml)]. The baby was discharged home on the 8th day of life on 6.25 μg of thyroxine once a day. The child is now euthyroid with daily thyroxin therapy, with normal neurodevelopmental evaluation at 6 months of follow-up.

Discussion

Our case differs from those previously reported cases in that the diagnosis of large goiter occurred relatively early in gestation, at 19 weeks. To avoid possible adverse neurologic events, and with poor outcome in first pregnancy, we chose to treat antenatally for fetal hypothyroidism. Another potential benefit of treatment is that a goiter usually shrinks with treatment, avoiding the complications associated with mechanical obstruction of the esophagus and trachea. Additionally, normalization of fetal thyroid hormone levels may be beneficial to the developing fetal brain. Reference ranges have been established for thyroid hormone concentrations in amniotic fluid, most recently by Singh et al. [4] in 2003 and Baumann and Gronowski [5] in 2007. We think that we were able to monitor the fetal status adequately with amniocentesis and ultrasound scan. The number of injections have ranged from 1 to 9. In our case we used 8 intra-amniotic injections. The dose of L-thyroxine used by authors varied from 200 to 800 μg/injections which was comparable to our doses. There are 5 cases in the literature in which early treatment was undertaken, the earliest at 23 weeks [1, 6–10]. In our case the treatment was initiated at 21 weeks, as the previous fetus had full-blown hydrops by 29 weeks.

There are only few studies on several intra-amniotic injections of L-thyroxine as a treatment of fetal goitrous hypothyroidism [1, 2, 10]. In the case report published by Hanono et al. [10], a significant reduction in goiter size was achieved after 7 intra-amniotic injections of L-thyroxine (250–500 μg/injections). In the only study based on multiple cases of fetal goitrous hypothyroidism, published by Ribault et al. [2], 8 of 9 fetuses responded adequately to 1–6 intra-amniotic injections of L-thyroxine (20–1,200 μg/injections).

Goitrous hypothyroidism in fetus of euthyroid mothers is usually due to inborn errors of thyroid hormone synthesis [2, 11]. Another possible but rare cause of congenital goitrous hypothyroidism is transplacental passage of maternal antibodies such as anti-TPO, TSAB and antithyroglobulin antibodies [12, 13].

Ribault et al. [2] in their retrospective study of 12 prenatally treated fetuses described two siblings and another patient whose older sister had thyroid carcinoma at birth. They were heterozygous for a mutation in the thyroid peroxidase gene. All the babies in their study had hypothyroidism at birth despite antenatal treatment and were healthy with normal neurological and cognitive functions at 2.5–18 years of age.

Dyshormonogenetic cases are often recessively inherited, and recent cohort analyses estimated that approximately 2% of cases with thyroid dysgenesis are familial [14]. The possible candidate genes of dyshormonogenesis are: (1) thyroid peroxidase (TPO) gene; (2) thyroglobulin (TG) gene; (3) sodium iodide symporter (NIS) gene; (4) pendrin (PDS) gene, and (5) thyroid oxidase 2 (THOX2) gene [15]. Most of these mutations follow a recessive mode of inheritance [16]. We could not do testing for genetic basis of congenital hypothyroidism in our case.

Fig. 4. The three-dimensional image of fetal face and neck at 33 weeks; the significant reduction of fetal goiter is visible.
The case presented by us confirmed the necessity of intrauterine treatment of fetal goitrous hypothyroidism. The most important aim of the intra-amniotic L-thyroxine injection is not the complete recovery of thyroid function of the fetus but the reduction or stabilization of the goiter size, prevention of fetal hydrops and prevention of impaired postnatal neurological development. We conclude that early ultrasound evaluation and intra-amniotic treatment of high-risk fetus can avoid the most dangerous complications such as fetal heart failure, intrauterine fetal demise and acute respiratory failure in the newborn due to a compression of trachea.

References