Intra-amniotic thyroxine to treat fetal goiter

Min-Jung Kim¹, Yong-Hwa Chae², So-Young Park³, Moon-Young Kim¹

Department of Obstetrics and Gynecology, ¹Cheil General Hospital and Women’s Healthcare Center, Dankook University College of Medicine, Seoul; ²Bundang Cheil Women’s Healthcare Center, Seongnam; ³Division of Endocrinology and Metabolism, Cheil General Hospital and Women’s Healthcare Center, Dankook University College of Medicine, Seoul, Korea

A 35-year-old pregnant woman visited our department and had been treated with 100 μg of daily oral levothyroxine for hypothyroidism. An ultrasonography screening was performed at 25 weeks gestation and revealed a fetal goiter and an increased amniotic fluid volume. Fetal hypothyroidism was confirmed by cordocentesis and amniotic hormone levels at 26 weeks gestation. We treated the mother with 200 μg of daily oral levothyroxine to optimize the transplacental transfer. A total of four intra-amniotic injections of levothyroxine were administered, resulting in progressive reduction in the fetal thyroid volume of goiter as measured by 3D ultrasonography and increased amniotic fluid volume. Following birth, neonatal serum thyroid stimulating hormone level was within the normal range, but free T4 was reduced. Based on this case, we suggest that monitoring amniotic fluid thyroid hormone concentration and intra-amniotic levothyroxine injection can be used to reduce the thyroid volume of goiters and to prevent polyhydramnios.

Keywords: 3D ultrasonography; Goiter; Hypothyroidism; Intra-amniotic thyroxine
or postnatal period. The woman had been diagnosed with hyperthyroidism and underwent radioactive iodine uptake treatment at 12 years of age. She was treated for hypothyroidism after radioactive iodine uptake and took 100 μg of oral levothyroxine daily. Sonography screening for routine check-up was performed at 25 weeks gestation and revealed a 21×14 (right lobe), 26×22 (left lobe)-mm-sized fetal neck mass (Fig. 1A). The location and echotexture were suggestive of a fetal goiter. On color Doppler imaging, the area around the goiter showed increased peripheral vascularity. However, the amniotic single pocket was 6.8 cm, and the amniotic fluid volume was relatively high. No other abnormality was noted in the fetus. Fetal hypothyroidism was confirmed by cordocentesis at 26 weeks gestation. The results of fetal blood sampling were as follows: TSH 390 U/mL (reference range, 0.5 to 4.5) and free T4 6.7 pmol/L (reference range, 10 to 28). The level of amniotic fluid hormone was checked at 26 weeks for reference of levothyroxine injection (Table 1). Maternal thyroid function test was performed at 26 weeks gestation. Serum TSH was 3.8 U/mL (reference range, 0.5 to 4.5), free T4 was 12.1 pmol/L (reference range, 10 to 28), T3 was 113 ng/dL (reference range, 97 to 170), thyrotropin binding inhibitory immunoglobulin/thyroid stimulating immunoglobulin was 16%, anti-thyroglobulin antibody was 2.6 U/mL (reference range, 0 to 0.3), and antimicrosome antibody was 28 U/mL (reference range, 0 to 0.3).

The maternal dose of levothyroxin was increased to 200 μg/day from 100 μg/day at 26 weeks gestation. However, even with treatment, the fetal goiter size did not change on ultrasound. Therefore at 30+2 weeks, in-utero treatment was initiated with 200 μg of levothyroxine injected into the amniotic sac. The fetal goiter mass size had not changed. The fetus was assessed weekly by determining thyroid hormone levels via amniocentesis. At 32+1, 33+6, and 34+5 weeks, 400 μg levothyroxine was injected into the amniotic sac. At 32+1, 33+6, and 34+5 weeks, we did not treat with a levothyroxine injection because the amniotic TSH gradually decreased, and the free T4 was within the lower normal range (Table 1).

We measured the change in thyroid size by 3D ultrasonography. This was the first application of 3D ultrasonography to assess changes in fetal thyroid size in Korea. The thyroid volume was 6.6 cm³ at 29 weeks gestation (Fig. 1B) and 4.9 cm³ at 37 weeks gestation (Fig. 1C). The patient was admitted to the delivery room due to labor pain at 38+2 weeks. She delivered a healthy girl who weighed 2,495 g, with Apgar scores 8 at 1 minute and 9 at 5 minutes. The infant did not have any breathing difficulties and no palpable mass in the anterior neck. The infant was not intubated.

At 3 days after birth, thyroid ultrasonography and thyroid function tests were performed. The echogenicity of the thyroid gland was normal without definite focal lesions. No abnormally enlarged lymph node was observed on either anterior side of the neck. Neonatal serum TSH was 11.84 ulU/mL and was within the normal range (1 to 4 days; reference range, 10.0 to 18.0), but the free T4 17.9 pmol/L was low (1 to 4 days; reference range, 28.4 to 68.4). The infant and mother were discharged on the third day after delivery without any complications. During two months of follow-up, the baby was treated with daily oral thyroxine. Currently, three years after birth, the baby has not had any neurodevelopmental problems.

### Discussion

Fetal goiter is defined as a circumference or diameter above the 95th percentile for fetal thyroid gland size. The fetal thyroid gland can be accurately assessed by serial ultrasound from 20 to 36 weeks [8]. Although we identified fetal goiter with sonography, we could not make a specific diagnosis until after birth. In many cases, cordocentesis enables a more accurate diagnosis [2]. Serial fetal blood sampling is necessary

| Table 1. Thyroid hormone levels in amniotic fluid during pregnancy |
|-----------------|---------------|--------------|------------|--------------|----------------|---------------|
|                  | 26+0 wk       | 30+2 wk      | 31+1 wk    | 32+1 wk     | 33+6 wk       | 34+5 wk       | 35+6 wk      | 36+5 wk      |
| Intra-amniotic thyroxin injection (μg) | -             | 200          | 400        | No          | No            | No            | 400          | 400          |
| TSH (ulU/mL)     | 11.6          | 2.3          | 1.0        | 0.4         | 0.1           | <0.1          | <0.1         | <0.1         |
| Free T4 (pmol/L) | 8.5           | 8.6          | 46.5       | 44.1        | 6.7           | 10.2          | 5.9          | 8.7          |
| T3 (ng/dL)       | 21.0          | 86.0         | 85.9       | 93.0        | 80.0          | 79.0          | 74.8         | 85.3         |

TSH, thyroid stimulating hormone.
Fig. 1. Measurement of fetal goiter volume change using 2D and 3D ultrasonography. (A) Fetal goiter size at 25 weeks using 2D ultrasonography. Right (Rt) lobe (21×14) and left (Lt) lobe (26×22). (B) Fetal thyroid volume (6.6 cm³) at 29 weeks’ gestation using 3D ultrasonography. (C) Fetal thyroid volume (4.9 cm³) at 37 weeks’ gestation using 3D ultrasonography.
to accurately determine fetal thyroid hormone concentration. However, this procedure has a high risk of adverse events such as fetal cord blood vessel contraction and bleeding, cord hematoma, feto-maternal bleeding, premature rupture of membranes, preterm birth, sepsis, and fetal death. The correlations between amniotic fluid and fetal serum levels of TSH, T3, and free T4 remain unclear [9]. However, amniocentesis is used to assess fetal thyroid function because it is easier to perform and safer than cordocentesis.

Therefore, we confirmed fetal hypothyroidism through cordocentesis and serially evaluated thyroid hormone levels through amniocentesis, because measuring thyroid hormone levels in amniotic fluid is reflecting fetal rather than maternal thyroid function [10]. In our case, when cordocentesis was performed at 26 weeks gestation, the TSH level was significantly elevated compared with the amniotic TSH concentration. Although amniotic fluid TSH value clearly underestimated the degree of hypothyroidism, therapy was adjusted based on the results of the amniocentesis.

In 1980, the first intra-amniotic levothyroxine administration was performed as an in utero fetal goitrous hypothyroidism treatment. Until now, intra-amniotic replacement therapy has been used as the standard treatment in fetal goitrous hypothyroidism.

In our case, intra-amniotic therapy was started at 30 weeks gestation; as soon as the intra-amniotic levothyroxine was administered, the amniotic TSH level decreased. Therefore, we found that TSH level rapidly responded to intra-uterine treatment [11]. However, amniotic free T4 level was similar to the level before intra-amniotic levothyroxine therapy, whereas the T3 level was increased after serial levothyroxine administration.

The number of cases treated in utero is currently too small to outline clear recommendations for optimal doses of free T4. Effective doses have varied from 250 μg levothyroxine in a single intra-amniotic injection to more than 3,000 g in repeated injections. There were no complications at birth from goiter size, in any of the cases. In our case, in utero treatment was initiated when 200 μg of levothyroxine was injected into the amniotic sac, and three additional intra-amniotic injections of 400 μg levothyroxine were administered between 30 and 37 weeks gestation. Intra-amniotic levothyroxine therapy was feasible and induced no adverse events.

The prenatal thyroid state is determined mainly by indirect assessment of fetal size, fetal heart rate, and thyroid goiter. Because non-invasive procedures are preferable for treatments, three-dimensional sonography can be used to evaluate and manage fetal goiters [12].

The first report of three-dimensional sonography of fetal goiter was introduced in 2005. This technique allowed measurement of fetal thyroid volume and blood flow and monitoring of the increase in size prior to therapy, in addition to regression after intra-amniotic thyroxine injections [12,13]. In our case, 3D ultrasonography indicated progressive reduction in volume of the goiter; this is the first case to use 3D ultrasonography to assess fetal thyroid volume in Korea.

It is difficult to determine if a fetus will have a goiter, therefore, it is important to use non-invasive techniques, such as continuous thyroid sonographic evaluation, to assess mothers with thyroid diseases, regardless of current treatment regimen. Additionally, specialists can be trained to perform intra-amniotic levothyroxine injections or cordocentesis in order to assess, diagnose, and treat similar conditions.

In conclusion, monitoring of amniotic fluid hormonal concentrations and intra-amniotic levothyroxine injection were useful for reducing the volume of the goiter and to prevent polyhydramnios. And 3D ultrasonography can be a good alternative tool for assessing a change of fetal goiter.

Conflict of interest

No potential conflict of interest relevant to this article was reported.

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