A Rare Case of Dyshormonogenetic Fetal Goiter Responding to Intra-Amniotic Thyroxine Injections

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What Is Known about This Topic?

- Defects in thyroid hormonogenesis can produce fetal goiter and congenital hypothyroidism of varying severity. Intra-amniotic administration of thyroxine is of benefit in treatment; widely varying dose regimens have been used.

What Does This Case Report Add?

- It gives detailed information on a case of fetal goiter inadvertently detected early in pregnancy in a euthyroid mother, and presents the response to repeated intra-amniotic thyroxine injections as monitored by ultrasound, and amniotic TSH and thyroid hormone levels.

Key Words

Dyshormonogenetic fetal goiter · Thyroxine injections · Cordocentesis · Intra-amniotic TSH

Abstract

Fetal goiter was detected by routine ultrasound in early pregnancy, gestational week (GW) 18, in a 28-year-old woman with no thyroid history, normal thyroid hormone levels and no TSH receptor or thyroid peroxidase antibodies. An umbilical cord blood sample was drawn in GW 23. The analysis indicated fetal hypothyroidism with TSH >100 mU/l

(reference value 6.8 ± 2.9 , mean $\pm$ SD), fT₄ 3.8 pmol/l (reference value 16.5 ± 5.3 , mean $\pm$ SD). Intra-amniotic injections of thyroxine were given in conjunction with ultrasound every 7–10 days, in total nine times during GW 24–33. A dose of 10 µg thyroxine/kg of estimated fetal weight per day was administered on six occasions, and 5 µg/kg/day the last three times. Upon injections of thyroxine further growth of the goiter was reduced. Elevated amniotic TSH levels fell from 13 to 2.5 mU/l (reference range 0.04–0.51). Throughout pregnancy, fetal heart rate and skeletal maturation were within normal limits. In week 34, chorioamnionitis was suspected and the child was delivered by cesarean section. Cord

blood revealed TSH 596 mU/l (reference value 8.0 ± 5.12 , mean $\pm$ SD), fT_4 4.4 pmol/l (reference value 19.3 ± 4.3 , mean $\pm$ SD) and total T_3 1.18 nmol/l (reference value 0.5 ± 0.3 , mean $\pm$ SD); the newborn was put on thyroxine supplementation. Psychomotor development of the child, now 3 years old, has been uneventful. The reported experience of treating dys-hormonogenetic fetal goiter is limited but growing, creating a need for guidelines on administration of intra-amniotic thyroxine and monitoring treatment.

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Introduction

Development of a fetal goiter reflects inadequate thyroid hormone production. A large goiter can cause premature labor due to polyhydramnios (impaired fetal swallowing of amniotic fluid), and cause complications at birth by tracheal compression or extension of the fetal head during the process of labor.

The thyroid gland, when sensing insufficient hormone production, responds with growth and development of goiter [1, 2]. This can occur in the presence of low iodine availability, genetic defects in hormonogenesis, inhibition of hormone synthesis by thyrostatic drugs (the most common explanation of fetal goiters today) and also, as reported in historical cases, when hormone synthesis is inhibited by excess iodide exposure [3, 4]. Thyroid growth is not critically dependent upon the TSH receptor signaling pathway, as illustrated in an experimental mouse model where deletion of the TSH receptor did not impair development of a normal sized gland [5]. Direct stimulation of the thyroid by TSH receptor antibodies can give rise to fetal thyrotoxicosis and a small/moderate goiter; a subsequent exposure to thyrostatic drugs can promote a considerable goiter [6].

The current incidence of congenital hypothyroidism is estimated to 1 in every 2,500–3,000 live births [7]. The consequences range from normality to sequelae in growth and psychomotor development [8, 9]. Approximately 15–20% of all cases are due to dys-hormonogenesis, caused by mutations in genes critical for thyroid hormone production, e.g. the sodium/iodide transporter, thyroid peroxidase, thyroid oxidase 2, thyroglobulin, and dehalogenase. About 80% of congenital hypothyroidism is not accompanied by goiter but due to thyroid dysgenesis. In this group, the genetic explanations largely remains to be identified, only a few percent have been found to be caused by mutations in thyroid transcription factors [10].

Congenital hypothyroidism of hypothalamic/pituitary origin is very rare.

Here, we give a detailed report of a case of dys-hormonogenetic fetal goiter and discuss the management and effects of treatment.

Case Report

A routine ultrasound examination performed at a maternity clinic in the second trimester of pregnancy, gestational week (GW) 18, in a 28-year-old healthy woman revealed an abnormal expansion in the neck of a female fetus. The woman was referred to the Fetal Medicine Unit at the University Hospital, a tertiary level center, and repeat ultrasound examinations demonstrated a symmetrically enlarged thyroid gland with a homogeneous pattern (fig. 1), and with high blood flow in the periphery as shown by color Doppler sonography. The amniotic fluid was mildly increased. The woman had no history of thyroid disease and had not been exposed to any goitrogens. She had a normal diet and used iodized salt as is common in Sweden. The urinary output of iodine was not determined. Maternal blood tests showed normal thyroid hormone values (TSH 0.45 mU/l, fT_4 11.6 pmol/l, and fT_3 2.5 pmol/l) and absence of TSH receptor (examined with an automatic immune analyzer, Cobas E601; Roche Diagnostics, Basel, Switzerland) and thyroid peroxidase antibodies; thyroglobulin antibodies were not determined. The fetal goiter persisted, dys-hormonogenesis was suspected and an umbilical cord blood sample was drawn during GW 23. Analysis showed fetal hypothyroidism with TSH >100 mU/l (the sample was not further diluted; reference value 6.8 ± 2.9 , mean $\pm$ SD [11]) and fT_4 3.8 pmol/l (reference value 16.5 ± 5.3 , mean $\pm$ SD [11]). Treatment with intra-amniotic injections of thyroxine was initiated and given in conjunction with ultrasound every 7–10 days with a dose 10 μ g thyroxine/kg of estimated fetal weight per day on six occasions. The dose was then reduced to 5 μ g thyroxine/kg/day because of rising amniotic fT_4 values and given three times. At each injection, amniotic fluid was withdrawn for hormone analysis, which was carried out at the Laboratory of Clinical Chemistry, Uppsala University Hospital. Reference ranges for amniotic TSH (0.04–0.51 mU/l) and fT_4 (1.29–9.93 pmol/l) are based on the study by Baumann and Gronowski 2007 [12]. The ultrasound equipment used was Voluson E8, Expert (General Electric Co./GE Healthcare).

The response to the treatment is detailed in table 1. Upon the injections, the Doppler flow and further growth of the fetal thyroid were reduced but not normalized (fig. 2). Throughout pregnancy, the fetal heart rate and skeletal maturation were within normal limits. Amniotic fT_4 values increased and TSH levels decreased after the start of treatment (fig. 3). In GW 34, chorioamnionitis was suspected and the child was delivered by cesarean section. Cord blood revealed TSH 596 mU/l (reference value 8.0 ± 5.12 , mean $\pm$ SD [11]), fT_4 4.4 pmol/l (reference value 19.3 ± 4.3 , mean $\pm$ SD [11]) and total T_3 1.18 nmol/l (reference value 0.5 ± 0.3 , mean $\pm$ SD [11]). The newborn was put on thyroxine supplementation. At 3 months a slight hypotonia was suspected, at 6 months the tonus was normal. The psychomotor development of the child, now 3 years of age, has been uneventful.

The mother has given her permission to publish the case history and the ultrasonographic pictures.

Fig. 1. **a** Sagittal (left) and 3D views of the neck at GW 22, showing a large goiter (arrow). **b** Transverse view with and without power Doppler of the neck at GW 22, hypervascularity in the large goiter is apparent (left).

Discussion

In the present case, fetal goiter was found at a routine examination of a woman with no history of thyroid disease. The goiter was thought to reflect dyshormonogenesis [10], as low thyroid hormone output had developed without any exposure to goitrogens. No genetic analysis was performed. To our knowledge, detection of a fetal goiter as early as in GW 18 has not previously been reported. The work-up revealed fetal hypothyroidism and to avoid serious sequelae in growth and psychomotor de-

velopment, treatment with intra-amniotic injections of thyroxine was initiated GW 23. Doses were based on experience described in the literature [13] and adjusted according to laboratory findings.

Intra-amniotic thyroxine reaches the fetus by gastrointestinal uptake after swallowing of the amniotic fluid, and through intramembranous absorption from the umbilical cord or fetal placenta surface. In an experimental study of pregnant sheep given intra-amniotic injections of radiolabeled T_3 and T_4 , about 90% of the injected hormones were taken up by the ovine fetus within 1 day [14]. There are no

Table 1. Characteristics of a female fetus with goiter and its response to intra-amniotic injections of thyroxine during GW 24–33

	Gestational week										
	23	24	25	26	27	28	29	30	32	33	34 ^a (partus)
Thyroid circumference, mm	59	65	70	66	84	90	88	92	92	85	
Fetal weight, g		646	837	894	1,154	1,194	1,501	1,778	2,118	2,474	2,850
Heart rate	140		143	149	150				130	150	
Thyroxine dose, µg		45	60	50	103	70	120	60	74	120	
TSH amnion, mIU/l	12.4	13.5	12.6	13.9		8.2	5.8	3.7	2.8	2.5	
fT ₄ amnion, pmol/l	3.7	4.2	19.9	57		22	22	17.6	6.4	14.2	
TSH cord, mIU/l	>100				237						596
fT ₄ cord, pmol/l	3.8				11.7						4.4
Total T ₃ cord, nmol/l											1.18

^a Birth in GW 34 by cesarean section.

turnover studies of intra-amniotic thyroxine injected in humans, but in a study of 18 pregnant women with pre-eclamptic toxemia, where single doses of 500 µg of thyroxine were injected into the amniotic fluid to accelerate fetal pulmonary maturity, the amniotic total T₄ values increased more than 20-fold at 48 h, from 1.05 to 24.0 µg/dl (12.9–309 nmol/l, reference range 1.8–2.9 µg/dl) [12]. Subsequently, at delivery 5–6 days after the administration, the total T₄ values practically showed basal values [15]. This report together with the findings of an average amniotic fluid volume of 780 ml in late gestation [16] and that fetal swallowing averages 210–760 ml/day [17] suggest that injected amniotic thyroxine has a turnover of 1–2 days.

Amniotic fluid TSH and fT₄ levels provide useful information as the levels reflect fetal thyroid status and are independent of the thyroid status of the mother [18]. How fetal TSH reaches the amniotic fluid is not known. The fetal kidney is likely to excrete intact TSH as protein reabsorption in the proximal tubules of the kidney is not fully developed at birth [19]. Thyroid hormones could also pass through the pars placentaris of the amnion from the chorion plate and placenta. The exchange of thyroid hormones between fetal blood and amniotic fluid will be influenced by several factors, i.e. the amount of intra-amniotic thyroxine given, the severity of the underlying dys-hormonogenesis, and the duration of fetal hypothyroidism. An additional phenomenon that could influence the levels of TSH in a hypothyroid fetus is hypertrophy of pituitary thyrotrophs, see below.

Treatment of dys-hormonogenetic goiter has been reported since the 1980s. In all, little more than 30 cases have been published; see Ribault et al. [20], who, in 2009, reported 12 cases and gave references for another 18 oth-

Fig. 2. Thyroid circumference of the fetus examined throughout the end of pregnancy. The first intra-amniotic injection of thyroxine was given during GW 24. Nomogram (mean ± 95%) values derived from Gietka-Czernel et al. [21] are given with the thin solid and the dashed lines.

er cases. The doses of thyroxine and the intervals between injections have varied considerably, e.g. from 1 to 7 injections in doses ranging from 70 to 800 µg per injection, or 3–23 µg/kg estimated fetal weight per injection, and intervals between 1 and 4 weeks. Most studies have reported changes in goiter size, some have presented fetal blood levels by cordocentesis and/or amniotic TSH and fT₄ values. No consensus regarding management has emerged.

We decided to start treatment with a dose of 10 µg thyroxine/kg estimated fetal body weight and monitored goiter size, TSH and fT₄ in amniotic fluid. The second cordocentesis at GW 26 showed that cord blood fT₄ had increased from 3.8 pmol/l GW 23 to 11.7 pmol/l after

Fig. 3. **a** Amniotic fT₄ (pmol/l) during treatment, normal range fT₄ 1.29–9.93 pmol/l [10]. First injection of thyroxine was given GW 24. **b** Amniotic TSH (mU/l) during treatment, normal reference range TSH 0.04–0.51 mU/l [10]. First injection of thyroxine was given at GW 24.

2-weekly injections of thyroxine and 1 week without injection, i.e. the dose chosen was sufficient to bring cord blood fT₄ values into the normal fetal range (5.1–27 pmol/l), but cord blood TSH was still elevated (237 mU/l). The goiter growth seemed lessened. The amniotic TSH values showed a downward trend but did not reach the normal reference range. The dose of thyroxine was reduced to 5 µg/kg/day in the three injections as nadir fT₄ values rose above the normal reference range. At birth, which occurred 9 days after the last intra-amniotic injection, cord blood TSH was 596 mU/l (8.0 ± 5.12, mean ± SD) [11], fT₄ 4.4 pmol/l (19.3 ± 4.3) and total T₃ 1.18 nmol/l (0.5 ± 0.3). The high TSH value could to some

extent have been influenced by the surge phenomenon. Conceivably, the fT₄ blood levels had been higher during the preceding 9 days after the last injection of thyroxine, as the total T₃ level at birth indicated a close to adequate supplementation with thyroxine.

Our case has some similarities with that reported by Abuhamad et al. [13], where fetal goiter in a 31-year-old primigravida was detected at GW 23. Cordocentesis performed at 28 weeks showed hypothyroidism, TSH 127 mU/l, fT₄ 0.6 ng/dl (0.5–1.1). At GW 29, weekly intra-amniotic injections of thyroxine were started with a dose of 10 µg/kg/day. Seven injections were given, the last at 36 weeks 4 days of gestation. A second cordocentesis was performed the day after the sixth injection (270 µg thyroxine had been given) and showed normalization of the fetal blood levels of TSH 0.6 mU/l, but fT₄ 8.0 ng/dl (103 pmol/l), suggestive of overtreatment. Amniotic hormone values had been followed from GW 29 to 37. TSH fell from 3.3 to 0.3 mU/l. Surprisingly, no significant changes of amniotic fT₄ levels, which ranged between 0.6 and 1.2 ng/dl, were reported. No explanation as to why the amniotic fT₄ values did not change is given. Spontaneous delivery occurred at 37.2 weeks, and the first day of life TSH was 0.4 mU/l and fT₄ 25.7 pmol/l. It appears to us that in this case, the seven administered doses of thyroxine 10 µg/kg/day had led to minor overtreatment.

Both cases, ours and that cited above, illustrate that TSH in amniotic fluid is reduced upon intra-amniotic injections of thyroxine, but that the extent of change is difficult to predict, as is the outcome of fetal/newborn blood TSH in relation to amniotic TSH levels at birth. This is supported by the report of Ribault et al. [20] of 12 cases of fetal dyshormonogenic goiter treated with intra-amniotic thyroxine. Before treatment, amniotic TSH was investigated in 6 cases and ranged from 1 to 6 mU/l. The levels decreased upon treatment and reached normal range in 4 cases (<0.5 mU/l). All 12 cases had however hypothyroidism at birth as detected by elevated blood TSH values at 0–4 days postpartum. Thus, the relationship between amniotic TSH levels and fetal blood TSH at birth in fetal goiters given treatment during gestation seems complex [21].

When a case of congenital hypothyroidism is detected in a newborn, the current recommended practice is to provide thyroxine supplementation in doses of 10–15 µg/kg body weight [22]; cf. 1.6–1.7 µg/kg body weight recommended in adults with hypothyroidism. The high thyroxine dose brings neonatal fT₄ blood values into the upper normal range within 3 days, whereas TSH reaches the

normal range after an average of 3 weeks [23]. The fact that TSH values remain elevated, long after fT_4 values have reached the upper/above the upper normal limit, is generally thought to reflect an expanded and hyperplastic mass of thyrotrophs. In few cases, a degree of hypothalamic-pituitary thyroid hormone resistance has been suggested to also contribute to elevated TSH levels [24].

As ultrasound techniques are becoming more frequently used in monitoring pregnancies, fetal goiters will be detected in increasing numbers. Analysis of amniotic fluid TSH and fT_4 values seems to provide a possibility to diagnose dyshormonogenesis and form a basis for start of treatment in cases detected early in gestation. Later in the course, when an unwanted complication at cordocentesis is compatible with survival of a premature child, blood sampling can be performed in order to evaluate the situ-

ation. Throughout the course, data on growth, weight, heart rate, bone age, thyroid size and amniotic hormone values should be collected.

Fetal goiter and hypothyroidism have been associated with severe complications during pregnancy as well as sequelae in growth and psychomotor development. In order to improve the clinical handling of fetal goiters, we suggest that guidelines on dosing intra-amniotic injections of thyroxine and monitoring effects of treatment should be produced in a collaborative effort.

Disclosure Statement

All authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

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