Conservative *in utero* treatment of fetal dyshormonogenetic goiter with levothyroxine, a systematic literature review

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Abstract. Fetal goitrous hypothyroidism is a rare condition associated with important obstetrical, neonatal complications, and neurodevelopmental impairments. Prenatal treatment remains controversial, and the risk to benefit ratio must be accurately assessed and considered for individualized management. The objective of this review was to evaluate the feasibility, safety, and effectiveness of the conservative *in utero* treatment of fetal goitrous hypothyroidism. In total, 25 reports that met our inclusion criteria were selected and the management of 38 cases was analyzed. Prenatal diagnosis consisted mainly of ultrasonographic findings. Fetal thyroid status was assessed by cordocentesis. Prenatal treatment varied widely in terms of levothyroxine (LT4) route of administration, dosage, number of injections, and frequency. Although different regimens and routes of administration were proposed, they seem to have similar results regarding fetal goiter reduction and thyroid status at birth. At birth, most babies had hypothyroidism, but the long-term follow-up indicated a normal psycho-neuromotor development. Our data confirm the feasibility of conservative treatment with LT4 for fetal goitrous hypothyroidism. Further studies are needed to determine the optimal management of this disorder.

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Introduction

Fetal dyshormonogenetic goiter is a rare disease characterized by increased fetal thyroid gland size due to inherited defects in genes that control thyroid hormone synthesis and transportation. The incidence varies between 1:30,000 and 1:50,000 live births in the European and North American regions, and it accounts for up to 15% of congenital hypothyroidism cases (1,2). It affects predominantly female fetuses (male:female ratio, 1:2) and has no racial or ethnic predilection, but it is encountered more often in consanguineous couples (3). Other causes of fetal goitrous hypothyroidism include maternal treatment for hyperthyroidism and endemic iodine deficiency (4).

The enlarged fetal goiter leads to mechanical and functional effects. Thus, tracheal and esophageal compression can cause breathing difficulties, disturbance of fetal movements, leading to asphyxia, and death at birth. Polyhydramnios is associated with an increased risk of preterm birth. In the end, hypothyroidism is related to impaired fetal growth and neuromotor development, which can induce cognitive and mental deficits (5,6).

Prenatal diagnosis of fetal dyshormonogenetic goiter involves the evaluation of fetal thyroid gland by ultrasonography or magnetic resonance imaging (MRI), and the detection of thyroid hormone changes in fetal blood or amniotic fluid by cordocentesis or amniocentesis, respectively. The ultrasound evaluates the size, echogenicity, and symmetry of fetal thyroid, its relationship with the surrounding organs, the amniotic fluid volume, bone maturation, and fetal heart rate. A thyroid gland with a width and circumference exceeding 95th centile affirms the morphological diagnosis of goiter (7). Also, the absence of the central thyroid vascularization, at color Doppler assessment, suggests a hypothyroid goiter (7). Fetal magnetic resonance is complementary to the ultrasonography and helps with the differential diagnosis and characterization of fetal thyroid functionality (8).

Cordocentesis is the gold standard for assessing the levels of thyroid hormone in fetal bloodstream (9). Because this procedure requires experienced specialists and is associated with a rate of complications as high as 9% (10), amniocentesis

can be an alternative, allowing the evaluation of the fetal hormone levels in the amniotic fluid (11), in combination with other markers.

The treatment of fetal goiter is conservative. It involves the administration of levothyroxine (LT4) into the amniotic fluid, umbilical vein, or intramuscularly. However, standard methods for management and treatment evaluation are still not well defined. These include the dose and frequency of the LT4 administration (12). Multiple protocols are defined, with different doses of LT4, but the exact pharmacokinetics of amniotic uptake remains unclear (13,14). Current evidence shows the efficacy of ~70% after intra-amniotic therapy (15).

Data collection methods

Literature search was conducted in MEDLINE, EMBASE and Cochrane databases using the following keywords, including synonyms, and all the possible combinations of them: fetal, goiter, hypothyroidism, LT4, triiodothyronine (T3), intra-amniotic, intramuscularly and umbilical vein. Our search was conducted up to March 1, 2020, using the following inclusion criteria: diagnosed fetal goitrous hypothyroidism in singleton pregnancies; maternal euthyroid status confirmed; LT4 or T3 administration intra-amniotic, intramuscularly, or into the fetal vessels. The exclusion criteria were fetal hyperthyroidism, lack of evaluation of fetal or maternal thyroid function, multiple pregnancies, and confirmed maternal thyroid pathology. The search identified 44 reports, from which we select for inclusion in the review, 25 reports with 38 case reports of fetal goitrous hypothyroidism in singleton pregnancies from euthyroid mothers.

Results

The results of the literature search are summarized in Tables SI and SII. Table SI presents clinical diagnosis and conservative treatment of fetal goitrous hypothyroidism, whereas Table SII summarized the clinical outcomes and the follow-up of the infants diagnosed with fetal goiter *in utero*.

We identified 38 cases of fetal goitrous hypothyroidism meeting our inclusion criteria. The median gestational age at diagnosis was 25 weeks (range, 18-34 weeks). In all cases, an increased fetal goiter size was identified. At diagnosis, where the dimensions were available (76%), the transverse diameter of the thyroid had a median of 2.33 MoM for gestational age (range, 1.58-4.44), accompanied by polyhydramnios in 42.1% (16 of 38 cases). Two cases (5.2%) were diagnosed with cardiomegaly and one case (2.6%) with pleural effusion. Twenty-four cases (63%) of fetal goitrous hypothyroidism were evaluated by cordocentesis. In the other 15 cases (37%), the fetal thyroid function was assessed by amniocentesis alone or in combination with cordocentesis. The thyroid stimulating hormone (TSH) values from the fetal umbilical vein had a median of 127 mUI/l (range, 24-1500 mUI/l) (Tables I and SI).

Various rates in fetal goiter size reduction were dependent on the timing, frequency, and dosing of thyroid drugs. However, we found that in 8 of 10 cases where the thyroid measurements were available in dynamics, the goiter size increases after diagnosis. The doses used were between 20 and 800 μg for LT4 and 60-150 μg for T3. The LT4 was the preferred drug in almost all fetuses; only two cases received a combined LT4 with T3 treatment (12). The frequency of administration varied from 3 days to 4 weeks, but in most cases, a weekly protocol was used (16 cases, 42.1%). Five cases received only a single dose of LT4 treatment (13.1%). The intra-amniotic injection was the preferred route for drug administration. There was one case where the LT4 administration was intra-amniotic and into the umbilical vein. None of the cases reported intramuscular administration of the drug. In one case, the mother received oral LT4 (100 μg/day), followed by weekly intra-amniotic injections of LT4 (Tables I and SI).

Regarding mode of delivery, 14 cases (36.8%) were delivered vaginally and 10 cases (26.3%) by cesarean section. For the rest of the cases, the data was either absent or unclear. There was one stillbirth at 31 weeks of gestation (shortly after LT4 administration) (16). Three cases were delivered between 31 and 33 gestational weeks. For the rest, the median age of delivery was 38 gestational weeks. The median birth weight of newborns was 3070 g (range, 1890-3960 g), and the male to female ratio was 17:8.

A postnatal follow-up was available for 21 cases (55%). The infant's goiter size was increased in 16 cases, while 4 cases had a clinically normal appearance of the thyroid gland (Table I). The hypothyroid state persisted in the postpartum period for most of the neonates. The highest TSH value measured was 596 mU/l, and all required oral LT4 substitution (median 35 μg/day). Genetic studies identified four cases with heterozygous mutations of the Tg gene and one case with two heterozygous mutations of the TPO gene. For available data, the mean follow-up was 22 months (range 1-72 months), without significant neuro-psychomotor impairment (Tables I and SII).

Discussion

Ultrasound identification of an enlarged homogeneous mass in the anterior neck compartment, with peripheral vascularization on color Doppler, associated with polyhydramnios or delayed bone maturation, can lead the diagnosis to fetal goitrous hypothyroidism. However, the final diagnosis is offered by cordocentesis, which allows a correct assessment of thyroid hormone levels in fetal blood.

The earliest diagnosis cited in literature was at 18 weeks by Ribault *et al* (15). Although magnetic resonance imaging (MRI) may allow a better description of the anatomical rapport with the neighboring structures and the differential with other cervicothoracic tumors, the practicality of this investigation is not clear. Two reports described the MRI use for evaluation of fetal airway patency (17,18).

Cordocentesis is the gold standard for the evaluation of fetal hormonal status, allowing the measurement of the fetal thyroid hormone levels in fetal blood (9). Amniocentesis can also be used in selected cases or when cordocentesis is not available. However, a certain degree of discrepancy was observed between the thyroid hormone levels when those methods are compared (19-21).

The gestational age for LT4 or T3 treatment initiation should be determined clinically by balancing the risks associated with a 'watchful-waiting' strategy. Usually, as soon as the diagnosis was confirmed, the treatment with LT4 was

Table I. Clinical diagnosis and conservative treatment of fetal goitrous hypothyroidism with LT4.

Author/Ref.	Diagnosis method	Route	Dose (μg/ml)	Dosing interval	Postpartum thyroid size
Sagot *et al* (20)	Amnio/ cordo	ia	300	Single dose	3.9 cm
Abuhamad *et al* (28)	Cordo	ia	10 μg/kg	Weekly	Normal
Grüner *et al* (12)	Cordo	ia	250-500	Weekly	8.3 ml
Perrotin *et al* (10)	Amnio	ia	150-435	2 weeks	2.1 cm
Agrawal *et al* (23)	Cordo	ia	60-120/150-300	Weekly	Enlarged
Morine *et al* (29)	Cordo	ia	250	Single dose	Small goiter
Caron *et al* (30) case 1	Cordo	ia	200	4 weeks	3.2 cm
Caron *et al* (30) case 2	Cordo	ia	500	4 weeks	Not palpable
Mirsaeid Ghazi *et al* (31)	Amnio	ia	500	Weekly	3.5 ml
Simsek *et al* (32)	Cordo	ia	500	Weekly	No data
Hanono *et al* (33)	Cordo	ia	250-500	Weekly	Enlarged
Mayor-Lynn *et al* (34)	Amnio	ia	70-100 μg/kg	Weekly	Slightly enlarged
Francois *et al* (19)	Amnio/cordo	ia	35-200	Weekly	3 cm
Ribault *et al* (15) case 1	Cordo	ia	300-400	weekly	
Ribault *et al* (15) case 2	Cordo	ia	200	2 weeks	
Ribault *et al* (15) case 3	Cordo	ia	500	4 weeks	
Ribault *et al* (15) case 4	Amnio	ia	150	weekly	
Ribault *et al* (15) case 5	Amnio	ia	200-400	1-2 weeks	
Ribault *et al* (15) case 6	Amnio	ia	400	2 weeks	
Ribault *et al* (15) case 7	Amnio	ia	400	2 weeks	
Ribault *et al* (15) case 8	Cordo	ia	200	2 weeks	
Ribault *et al* (15) case 9	Cordo	ia	400-800	1-2 weeks	
Ribault *et al* (15) case 10	Amnio	ia	100-200	4 weeks	
Ribault *et al* (15) case 11	Cordo	ia	300	Single dose	
Ribault *et al* (15) case 12		ia	250	Single dose	
Stoppa-Vaucher *et al* (24)	Cordo	ia	100/200	Daily/2 weeks	7.2 ml
Stewart *et al* (21)	Cordo/amnio	ia	120-300	1-2 weeks	Minimally enlarged
Saini *et al* (35)	Cordo	ia	no data	Weekly	Slightly enlarged
Corbacioglu *et al* (36) case 1	Cordo	ia	500	3 weeks	Small goiter
Corbacioglu *et al* (36) case 2	Cordo	ia	500	2 weeks	Normal
Khamisi *et al* (37)	Cordo	ia	5-10 μg/kg	7-10 days	No data
Mastrolia *et al* (18)	Amnio	ia	150	Single dose	Enlarged
Taff *et al* (38)	Cordo	ia	400-800	Weekly	
Aubry *et al* (39)	Cordo	ia	400	2 weeks	Not palpable
Vasudevan *et al* (16)	Amnio	ia	150/120	3 days	no data
Figueiredo *et al* (17)	Amnio	ia	300-400	10 days	Enlarged
Dębska *et al* (40)	Amnio/cordo	ia/uv	230-500/20	No data	Without goiter
Bashari *et al* (41)	No data	ia	200-400	No data	No data

Amnio, amniocentesis; Cordo, cordocentesis; ia, intraamniotic; uv, umbilical vein; LT4, levothyroxine.

initiated (22). There were exceptions when the treatment was initiated within 3 weeks from the diagnosis, due to lack of drug availability (23).

The protocol of administration of LT4 and T3 is not clearly defined. Intra-amniotic administration of LT4 was the preferred method of treatment, with doses ranging between 150 and 800 μg, with a dosing interval between 3 days and 4 weeks, depending on the rate of decrease in fetal goiter size. LT4 was administered in half of the cases weekly, and in a quarter fortnightly. Others described two different protocols of combined LT4 and T3 intra-amniotic administration (16,23). Stoppa-Vaucher *et al* used an oral LT4 treatment of the euthyroid mother, before initiating the intra-amniotic administration of the drug, because of a rapid increase of the fetal goiter's size and the amniotic fluid volume (24).

Intra-amniotic LT4 or T3 injections reversed the hypothyroidism and reduced the fetal goiter's size, minimizing maternal and fetal complications at birth. From the cases reported to date in literature, it appears that most of the patients did not experience major adverse events at birth. The most common

adverse outcome was preterm delivery (9.7%). There was only one stillbirth reported, with an unclear cause, shortly after LT4 administration (16).

The route of delivery requires careful assessment. If the fetal goiter size does not prevent cardinal movements at birth, does not produce airway obstruction, and there is no other obstetrical contra-indication, a vaginal birth should be attempted. However, should feto-maternal complications be expected, a cesarean section would allow an intrapartum EXIT procedure or endoscopic tracheal intubation (25-27). Also, the long-term outcomes of the infants were favorable, with normal psycho-neuromotor development up to 18 years (15).

In conclusion, fetal goitrous hypothyroidism is a rare disorder that requires a multidisciplinary approach for minimizing the maternal-fetal complications. The decision to initiate *in utero* treatment and the protocol for thyroid drug administration will consider the clinical context and operator skills available. Treatment monitoring is warranted, by serial ultrasound and cordocentesis, with careful evaluation of the risk-benefit. Postpartum thyroid status of the infant and assessment of the neuro-psychomotor development is compulsory, with the initiation of LT4 substitution immediately postpartum. We need further studies for the development of a standardized treatment protocol of goitrous hypothyroidism in fetuses from euthyroid mothers.

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Availability of data and materials

All data generated or analyzed during this study are included in this published article and its supplementary files.

Authors' contributions

DN and IAT designed the study. DN, IAT and DBN contributed to the data extraction and quality assessment. IAT, DBN and DLS were responsible for the analysis and discussion of the data. DN, IAT and AEV wrote the manuscript. DLS and AEV participated in the review process and made substantive intellectual contributions to the published study. All authors read and approved the final version of the manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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