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CASE REPORT

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Intra-amniotic levothyroxine infusions in a case of fetal goiter due to novel *Thyroglobulin* gene variants

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Abstract

Indications and administration of intra-amniotic infusions of L-thyroxine in the context of non-immune fetal hypothyroidism with goiter lack of standardization. Systematic follow-up of clinical features related to thyroid hormonal homeostasis may be useful to evaluate their efficiency and develop standardized management guidelines.

KEYWORDS

dyshormonogenesis, fetus, goiter, hypothyroidism, intra-amniotic infusions

1 | INTRODUCTION

Non-immune hypothyroidism with fetal goiter is a rare cause of congenital hypothyroidism. Major disparities exist in the prenatal management and follow-up of this affection. We present a case of fetal hypothyroid goiter successfully treated by intra-amniotic infusions of levothyroxine and discuss the clinical follow-up, before and after the treatment.

Fetal goiter (FG) affects 1 out of 50,000 newborns and becomes increasingly reported due to higher sensitivity of the imaging technics.[1] FG is a clinical feature defined as a thyroid volume exceeding +2DS when measured using transabdominal echography or magnetic resonance imaging.[2] Primary clinical assessment focus on the evaluation of thyroid functional tests (TFTs) and auto-immunity in the fetus and the mother, respectively, using cordocentesis and venous puncture.[3] Detailed echography investigates the comorbidities that may be associated with FG (eg, polyhydramnios, fetal head hyperextension, tracheal compression, intrauterine fetal death).[4-6] Congenital hypothyroidism (CH) with FG has various etiologies including dyshormonogenesis.[7,8] Practically, CH differs from congenital myxedema that corresponds to a nosological entity defined by the status of CH associated with a spectrum of typical clinical characteristics (eg, weakness, poor weight gain, brittle hair, thickened facial features, macroglossia, thickened and dry skin, coma). CH may lead to long-term complications (eg, neurocognitive and motor-skills deficits)[9-11] questioning the role of an early substitution therapy.

Therapeutic management of non-immune hypothyroidism with FG remains a challenge as the placenta limits the exchanges of thyroid hormones (TH) between the mother and the fetus, barring the possibility of maternal levothyroxine oral substitution.[12-14] IAIs remains the gold standard treatment in

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fetuses with hypothyroid goiter associated with clinical complications (ie, polyhydramnios, cardiac failure, lung atrophy), but requires systematic monitoring of TFTs (see Discussion section). Currently, no consensus exists regarding the treatment and clinical follow-up of the fetus during IAIs, pressing for standardization of the technique.[3,15,16]

We present a case of non-immune hypothyroidism with FG secondary to compound heterozygous variants in the thyroglobulin (*TG*) gene. IAIs of levothyroxine were initiated to reduce the size of the goiter and improve the clinical outcome. Clinical parameters were assessed during pregnancy (echography) and after delivery (eg, bone age, jaundice, hearing test, posterior fontanel opening).

2 | CASE REPORT/CASE PRESENTATION

A 32-year-old Caucasian primiparous woman living in an area of Western Europe with mid iodine insufficiency was referred to our clinic for FG at 23 gestational weeks (GW) +6.[17] There was no familial history of thyroid disease. Detailed fetal echography revealed a goiter (thyroid circumference 73 mm, [mean ± SD, 46 ± 5.9][2]) without other associated abnormalities. The neck was slightly hyperextended and moderate polyhydramnios was present with an amniotic fluid index (AFI) measured at 25 cm (shown in Figure 1).

Concertation between the medical team and the parents was done and decision to investigate the thyroid status in the mother and the fetus was taken. Results of maternal blood sampling and cordocentesis are shown in Table 1. The mother had normal TFTs and negative autoantibodies (value [reference, unit], anti-thyroperoxidase 9.1 [0–34, U/ml], anti-TSH receptor <0.3 [0–1.8, UI/L]).[18] Cordocentesis revealed fetal hypothyroidism and negative autoantibodies (value [references, unit], anti-thyroperoxidase <0.5 [0–34, U/ml], anti-TSH receptor <0.3 [0–1.8, U/L], anti-TG 37.8 [0–115, U/L]). We confirmed the diagnosis of FG in the context of non-immune congenital hypothyroidism. Therapeutic options were discussed between pediatricians and obstetricians: (1) absence of treatment and clinical follow-up, (2) maternal oral treatment by levothyroxine (despite limited materno-fetal transfer), and (3) IAIs of levothyroxine in case of pejorative outcome in fetus (increase of FG and AFI, cardiac failure, risk of malposition).

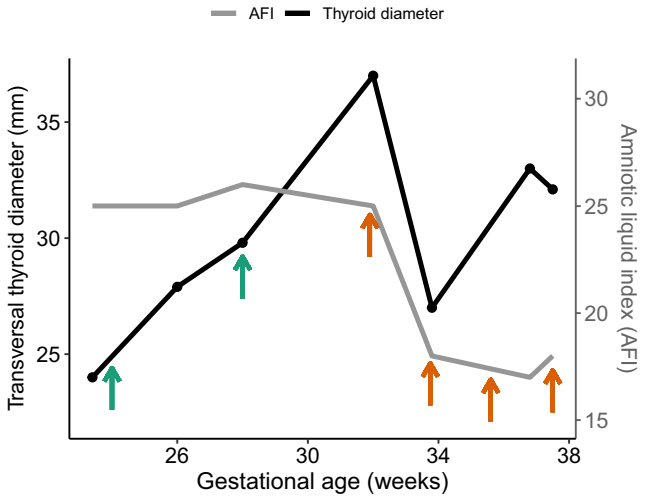

FIGURE 1 Evolution of thyroid diameter and amniotic fluid index from diagnosis to delivery. Green vertical arrows correspond to the initiation of maternal oral substitution by Levothyroxine (1st = 50 µg/day, 2nd = 75 µg/day), orange arrows correspond to intra-amniotic infusions of Levothyroxine (400 µg/injection)

As the fetus health situation remained stable, oral substitution was started in the mother by 50 µg/day of levothyroxine (1 µg/kg.day) and later increased to 75 µg/day (1.5 µg/kg.day). Thyroid circumference and AFI were assessed weekly (shown in Figure 1). At 32 GW +2, as the goiter became clinically patent (ie, progressive increase of AFI, head hyperextension), the decision was taken to remove 400 ml of amniotic fluid and process to an IAI of 400 µg of levothyroxine (190 µg/kg of estimated fetal weight). A series of three more injections (400 µg per IAI) was performed at 33 GW +6, 35 GW +4, and 37 GW +5. After the first injection, we observed a subsequent decrease in the size of the FG and a normalization of AFI until birth (shown in Figure 1). Distal femoral epiphysis bony nucleus appeared at 33 GW, confirming a normal bone maturation.[19] There were no complications related to IAIs. Microarray (*Affymetrix Cytoscan 750K*) on amniocentesis revealed a normal female karyotype and the absence of genomic unbalanced abnormalities.

Vaginal delivery happened spontaneously at 39 GW and was uneventful. Birth weight of the newborn was 3390 g (P50) and height was 54 centimeters (P90-97). Clinical assessment revealed a tonic newborn with a soft goiter confirmed by echography (1.6 ml, >P95[20]), moderate hypothyroidism on cord blood (shown in Table 1), and normal bone maturation (by extrapolating a score established on the points of Beclard).[21] Re-assessment of the thyroid status at 24 h of life showed severe hypothyroidism (shown in Table 1). The patient was started on 50 µg/day (17 µg/kg.day) of levothyroxine at 36 h of life. Thyroid dyshormonogenesis gene panel assessment (Illumina NovaSeq 6000) revealed a new form of compound heterozygous variants in the *TG* gene (TG: [c.229G>A, p. Gly77Ser]; [c.7813C>T, p. Arg2605*]). Results were confirmed with Sanger sequencing. Genetic investigations showed that both parents carried a mutation in a heterozygous state. Neurocognitive and psychomotor development at 12-months were normal though the patient did not undergo specific psychometric testing. The child grew on the P25 for weight, P50 for height, and P75 for head circumference. The infant

TABLE 1 Thyroid function in the mother and the fetus

Dosage, units	Cord blood (prenatal) 23 +6 GW [mean ± SD][a]	Maternal blood 23 GW [range]	Cord blood (postnatal) 39 GW [range]	Newborn veinous blood (24 h of life) [range]
TSH, mU/L	>100 [2.7 ± 2.4]	1.81 [0.27–4.2]	12.72 [0.3–4.2]	>100 [0.3–4.2]
FT4, pmol/L	5 [17.5 ± 8.8]	11.3 [17.5 ± 8.8]	11.7 [12–22]	11 [10.8–36.3]
FT3, pmol/L	NA	4.3 [3.1–6.8]	1.5 [3.3–11.4]	NA
TG, ng/ml	NA	1.8 [1–40]	NA	0.5 [1–40]
T4T, nmol/L	NA	NA	102 [66–181]	NA
T3T, pmol/L	NA	NA	0.6 [1.3–3.1]	NA

Abbreviations: FT3 = free-T3; FT4 = free-T4; GW = Gestational weeks; NA = Not available; T3T = total-T3T4T = total-T4; TG = thyroglobulin.
[a]Normograms using Hume et al. 2004[18].

remained dependent on thyroid hormonal substitution with a progressive decrease in posology reaching 37.5 µg/day (5 µg/kg.day).

3 | DISCUSSION/CONCLUSION

Diagnosis of FG provides a unique opportunity to treat severe forms of congenital hypothyroidism during the prenatal period. Our case highlights the potential role of IAIs of levothyroxine in decreasing the size of the FG and supplying the fetus with TH, allowing the prevention of short and long-term complications (eg, obstetrical, neuro-developmental) in our patient. We also focused on the effects of IAIs of levothyroxine aside from the thyroid gland by assessing clinical features associated with TH homeostasis (eg, bone maturation, jaundice).

Prenatal management of FG associated with hypothyroidism remains a challenge as the fetus relies equally on materno-fetal transfer (MFT) and self-production of TH from 20 GW.[13,22] Three factors, namely thyroid receptor transporters, desionidase D3 and transthyretin-T4 transporter,[13] physiologically limit the transport of maternal TH across the placental barrier. This system regulates maternal influx of TH allowing adequate neuropsychological development of the fetus and avoiding fetus loss in case of maternal hyperthyroidism, although complications have been already reported in this situation.[23,24] In the context of congenital hypothyroidism, mechanisms such as an increase of MFT by transthyretin-T4 transporter and type-II desionidase in the brain of the fetus reduce the impact of TH deprivation on fetus development.[12,25,26] However, those protection mechanisms fail to compensate for the lack of TH production in the fetus, as previously described in the literature and supported by a low level of TH in the cordocentesis of our patient (shown in Table 1).[12,15] Confirming the idea of transplacental TH limitation, substitution by maternal oral intake of levothyroxine did not decrease the size of the goiter in our patient (shown in Figure 1), suggesting this method as inadequate for fetus with congenital hypothyroidism and FG (shown in Table 1).

Huge disparities exist in the assessment, follow-up, and treatment of FG (eg, method, posology, and intervals between doses),[3,15,27] making early management of FG challenging. Currently, European Society for Paediatric Endocrinology (ESPE) guidelines define IAIs of levothyroxine as the gold standard treatment for hypothyroidism with complicated FG (ie, with polyhydramnios, airway obstruction, and/or lung hypoplasia). Careful assessment of the benefit-risk balance is essential as cordocentesis and IAIs remain associated with complications in a minority of cases (ie, premature labor, infection).[6,28] In some rare cases, alternative routes for levothyroxine administration to the fetus have been used (ie, intravenous or intramuscular).[3,16,27,29]

We evaluated the impact of IAIs on the fetus using different clinical parameters (eg, thyroid size, AFI, and bone age) as (1) amniotic fluid TH levels do not correlate with fetal thyroid status, (2) normalization of the thyroid hormone status at birth was only reported in a few cases and (3) there are currently no recommendations for the assessment of the response to treatment.

In our propositus, IAIs allowed a decrease in the volume of FG. Additionally, no delay in bone maturation was observed during the prenatal follow-up, the latter being known as an indirect sign of hypothyroidism severity and a pejorative factor for long-term neurocognitive performance when delayed at birth.[9,11,21] Similar effects of IAIs were described in a retrospective cohort of 12 cases of FG though bone age was only assessed in half of the patients.[15] Neurocognitive outcome in children with fetal goiter and hypothyroidism which were treated with IAIs of levothyroxine was reported as normal in all cases.[30] The Table 2 summarizes the therapeutic management, laboratory results, short- and long-term outcomes of 21 cases reports of non-immune hypothyroidism fetal goiter during the last ten years.[6,31-45] Finally, IAIs likely

TABLE 2 Cases of non-immune hypothyroidism fetal goiter, therapeutic management, laboratory results, short and long-term outcomes

Patient no	References	GW[a] (week)	TSH[b] (mU/L)	fT4[b] (pmol/l)	Complications (of the goiter)	Diagnosis method
1	Marín et al[31]	22	24	0.6	None	AC; CC
2	Stewart et al[32]	31	42	2.3	Retroflexed neck	AC; CC
3	Saini et al[33]	29	100	2.6	No	CC
4	Esmer et al[34]	29	24	14.1	Polyhydramnios	CC
5	Blumenfeld et al[35]	27	None	None	Retroflexed neck; trachea compression; polyhydramnios	None
6	Blumenfeld et al[35]	22	None	None	Trachea compression	None
7	Khamisi et al[36]	24	100	3.8	No	CC
8	Mastrolia et al[37]	36	NA	NA	Polyhydramnios	AC
9	Taff et al[38]	24	Hypothyroid	Hypothyroid	No	CC
10	Aubry et al[39]	25	35	6.5	No	CC
11	Vasudevan et al[6]	29	NA	NA	Polyhydramnios	AC
12	Ferianec et al[40]	27	150	5.5	None	AC; CC
13	Figueiredo et al[41]	32	NA	NA	No	AC
14	Dębska et al[42]	24	1500	2	Polyhydramnios; retroflexed neck	AC; CC
15	Tanase-Nakao et al[43]	33	253	3.7	Polyhydramnios	CC
16	Stoupa et al[44]	25	150	3.3	None	CC
17	Delay et al[45]	NA	61	9.9	NA	NA
18	Delay et al[45]	NA	100	6.6	NA	NA
19	Delay et al[45]	NA	500	2.3	NA	NA
20	Delay et al[45]	31	None	None	NA	None
21	Our case	32	100	5	Polyhydramnios; retroflexed neck	CC

Abbreviations: NA = not available; fT4 = free-T4; AC = amniocentesis; CC = cordocentesis; yo = years old; IA = intra-amniotic.

[a]Gestional Week of 1[rst] IAI.

[b]At cordocentisis.

[c]On cordblood or before 72 h of life.

prevented the hearing loss in a fetus with iodine-induced hypothyroidism, highlighting the impact of prenatal TH substitution on complications.[46,47]

Prenatal echography represents a unique opportunity to diagnose and treat congenital hypothyroidism with FG before birth. In this specific context, IAIs demonstrate a global metabolic effect on the fetus and may prevent obstetrical and neurocognitive complications related to this condition. Prenatal and postnatal evaluation of bone maturation in those patients may be an indirect indicator of the global TH homeostasis and a predictor of psychomotor delay in the first year of life.[21] However, these parameters were assessed in less than 50% of reported cases treated by IAIs of levothyroxine.[15] Systematization of their evaluation, before and after birth, may give additional information to standardize levothyroxine IAI procedures in patients with FG and hypothyroidism. Further studies are needed to investigate bone maturation and clinical evolution of fetus treated or not by levothyroxine IAIs.

Limitations of this case report rely on the measurement of the thyroid by two different operators and the absence TFTs biological follow-up in the fetus by cordocentesis during the treatment.

4 | STATEMENT OF ETHICS

Parents were informed and gave their written informed consent for publishing the case report.

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Published with written consent of the patient.

Totale i.a L-T4.	No of injection	TSH at birth mIU/L	fT4 at birth (pmol/l)	Peripartal complication	Bone age (at birth)	Neuro developpement
10–20 µg/kg/day	8	64	3.8	Suspicion of chorioamniotis	NA	Normal at 2 yo
10 µg/kg/week	5	Normal	Normal	None	NA	Normal at 6 months
NA	5	NA	NA	None	NA	NA
1000 µg	2	24	11.6	None	NA	Normal
No treatment	No	237	12.8	None	NA	NA
No treatment	No	84.6	16.7	None	NA	NA
5–10 µg/kg/day	9	596	4.4	Suspicion of chorioamniotis, premature birth	NA	Normal at 3 yo
150 µg	1	241	6.4	Premature birth	NA	NA
7200 µg	15	NA	NA	None	NA	NA
2400 µg	6	142	6.4	None	NA	Normal at 1 yo
120 µg T3, 140 µg T4	2	NA	NA	Fœtus death	NA	NA
1400 µg	5	150	5.4	None	Normal	NA
800 µg	2	715	2.6	Respiratory distress	NA	Normal at 6 yo
2610 µg	11	23	16.4	None	NA	Normal at 1 yo
600 µg	2	60	11.8	Respiratory distress	NA	Normal at 7 yo
2000 µg	6	68	5.6	NA	Delayed	Normal at 15 yo
400 µg	1	111	12.9	NA	NA	NA
600 µg	1	143	13.5	NA	NA	NA
400 µg	1	557	4.2	NA	NA	NA
No treatment	None	Normal	Normal	None	NA	NA
1600 µg	4	100	11	None	Normal	Normal at 1 yo

CONFLICT OF INTEREST

The authors report no conflict of interest.

AUTHOR CONTRIBUTIONS

Olivier Pollé centralized the conception, the design of the article, initially wrote the draft and revised it. Philippe Lysy participated and supervised the conception, the design of the article, the draft redaction and the draft revision. Pierre Bernard participated in the conception, the design of the article and the draft revision. Alexander Gheldof participated in the draft revision.

DATA AVAILABILITY STATEMENT

The data used to support the findings of this study are available from the corresponding author upon request.

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REFERENCES

1. Fisher DA, Klein AH. Thyroid development and disorders of thyroid function in the newborn. *N Engl J Med*. 1981;304:702-712.
2. Ranzini AC, Ananth CV, Smulian JC, Kung M, Limbachia A, Vintzileos AM. Ultrasonography of the fetal thyroid. *J Ultrasound Med*. 2001;20:613-617.
3. Léger J, Olivieri A, Donaldson M, et al. European society for paediatric endocrinology consensus guidelines on screening, diagnosis, and management of congenital hypothyroidism. *Horm Res Paediatr*. 2014;81(2):80-103.
4. Kornacki J, Mrozinski B, Skrzypczak J. A rare case of recurrent fetal goiter. *Fetal Diagn Ther*. 2012;31(1):69-72.
5. Davidson KM, Richards DS, Schatz DA, Fisher DA. Successful in utero treatment of fetal goiter and hypothyroidism. *N Engl J Med*. 1991;324(8):543-546.
6. Vasudevan P, Powell C, Nicholas AK, et al. Intrauterine death following intraamniotic triiodothyronine and thyroxine therapy for fetal goitrous hypothyroidism associated with polyhydramnios and caused

by a thyroglobulin mutation. *Endocrinol Diabetes Metab Case Rep*. 2017;2017.
7. Abduljabbar MA, Afifi AM. Congenital hypothyroidism. *J Pediatr Endocrinol Metab*. 2012;25(1–2):13-29.
8. Targovnik HM, Scheps KG, Rivolta CM. Defects in protein folding in congenital hypothyroidism. *Mol Cell Endocrinol*. 2020;501:110638.
9. Dimitropoulos A, Molinari L, Etter K, et al. Children with congenital hypothyroidism: long-term intellectual outcome after early high-dose treatment. *Pediatr Res*. 2009;65(2):242-248.
10. Rovet JF. Children with congenital hypothyroidism and their siblings: do they really differ? *Pediatrics*. 2005;115(1):e52-e57.
11. Rovet JF, Ehrlich R. Psychoeducational outcome in children with early-treated congenital hypothyroidism. *Pediatrics*. 2000;105(3):515-522.
12. Vulsma T, Gons MH, de Vijlder JJM. Maternal-fetal transfer of thyroxine in congenital hypothyroidism due to a total organification defect or thyroid agenesis. *N Engl J Med*. 1989;321(1):13-16.
13. Patel J, Landers K, Li H, Mortimer RH, Richard K. Delivery of maternal thyroid hormones to the fetus. *Trends Endocrinol Metab*. 2011;22(5):164-170.
14. Landers K, Richard K. Traversing barriers – How thyroid hormones pass placental, blood-brain and blood-cerebrospinal fluid barriers. *Mol Cell Endocrinol*. 2017;458:22-28.
15. Ribault V, Castanet M, Bertrand AM, et al. Experience with intraamniotic thyroxine treatment in nonimmune fetal goitrous hypothyroidism in 12 cases. *J Clin Endocrinol Metab*. 2009;94(10):3731-3739.
16. Polak M, Van Vliet G. Therapeutic approach of fetal thyroid disorders. *Horm Res Paediatr*. 2010;74:1-5.
17. Vandevijvere S, Ruttens A, Wilmet A, et al. Urinary sodium and iodine concentrations among Belgian adults: results from the first National Health Examination Survey. *Eur J Clin Nutr*. 2021;75(4):689-696.
18. Hume R, Simpson J, Delahunty C, et al. Human fetal and cord serum thyroid hormones: Developmental trends and interrelationships. *J Clin Endocrinol Metab*. 2004;89(8):4097-4103.
19. Delle Donne H, Faúndes A, Tristão EG, De Sousa MH, Urbanetz AA. Sonographic identification and measurement of the epiphyseal ossification centers as markers of fetal gestational age. *J Clin Ultrasound*. 2005;33(8):394-400.
20. Mikołajczak A, Borszewska-Kornacka MK, Bokiniec R. Sonographic reference ranges for the thyroid gland in euthyroid term newborns. *Am J Perinatol*. 2015;32(13):1257-1262.
21. Wasniewska M, De Luca F, Cassio A, et al. In congenital hypothyroidism bone maturation at birth may be a predictive factor of psychomotor development during the first Year of life irrespective of other variables related to treatment. *Eur J Endocrinol*. 2003;149(1):1-6.
22. Obregon M, Calvo R, Escobar Del Rey F, Morreale De Escobar G. Ontogenesis of thyroid function and interactions with maternal function. *Endocr Dev*. 2007;10:86-98.
23. Haddow JE, Palomaki GE, Allan WC, et al. Maternal thyroid deficiency during pregnancy and subsequent neuropsychological development of the child. *N Engl J Med*. 1999;341(8):549-555.
24. Anselmo J, Cao D, Karrison T, Weiss RE, Refetoff S. Fetal loss associated with excess thyroid hormone exposure. *J Am Med Assoc*. 2004;292(6):691-695.
25. Szinnai G. State of the art of diagnosis and treatment of paediatric thyroid diseases. In: Szinnai G, ed. *Paediatric Thyroidology*. Basel: Karger Medical and Scientific Publishers; 2018:257-328.
26. Calvo R, Obregon MJ, Ruiz de Ona C, Escobar del Rey F, Morreale de Escobar G. Congenital hypothyroidism, as studied in rats. Crucial role of maternal thyroxine but not of 3,5,3'-triiodothyronine in the protection of the fetal brain. *J Clin Invest*. 1990;86(3):889-899.
27. Corral E, Reascos M, Preiss Y, Rompel SM, Sepulveda W. Treatment of fetal goitrous hypothyroidism: value of direct intramuscular L-thyroxine therapy. *Prenat Diagn*. 2010;30(9):899-901.
28. Akolekar R, Beta J, Picciarelli G, Ogilvie C, D'Antonio F. Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. *Ultrasound Obstet Gynecol*. 2015;45(1):16-26.
29. Börgel K, Pohlenz J, Holzgreve W, Bramswig JH. Intrauterine therapy of goitrous hypothyroidism in a boy with a new compound heterozygous mutation (Y453D and C800R) in the thyroid peroxidase gene. A long-term follow-up. *Am J Obstet Gynecol*. 2005;193(3):857-858.
30. Stoppa-Vaucher S, Francoeur D, Grignon A, et al. Non-immune goiter and hypothyroidism in a 19-week fetus: a plea for conservative treatment. *J Pediatr*. 2010;156(6):1026-1029.
31. Marín RC, Bello-Muñoz JC, Martínez GV, Martínez SA, Moratonas EC, Roura LC. Use of 3-dimensional sonography for prenatal evaluation and follow-up of fetal goitrous hypothyroidism. *J Ultrasound Med*. 2010;29(9):1339-1343.
32. Stewart CJM, Constantatos S, Joolay Y, Muller L. In utero treatment of fetal goitrous hypothyroidism in a euthyroid mother: a case report. *J Clin Ultrasound*. 2012;40(9):603-606.
33. Saini A, Reddy MM, Panchani R, Varma T, Gupta N, Tripathi S. Two cases of fetal goiter. *Indian J Endocrinol Metab*. 2012;16(8):358-360.
34. Esmer AC, Gul A, Dagdeviren H, Bakirci IT, Sahin O. Intrauterine diagnosis and treatment of fetal goitrous hypothyroidismjog. *J Obstet Gynaecol Res*. 2013;39(3):720-723.
35. Blumenfeld YJ, Davis A, Milan K, et al. Conservatively managed fetal goiter: an alternative to in utero therapy. *Fetal Diagn Ther*. 2013;34(3):184-187.
36. Khamisi S, Lindgren P, Karlsson FA. A rare case of dyshormonogenetic fetal goiter responding to intra-amniotic thyroxine injections. *Eur Thyroid J*. 2014;3(1):51-56.
37. Mastrolia SA, Mandola A, Mazor M, et al. Antenatal diagnosis and treatment of hypothyroid fetal goiter in an euthyroid mother: a case report and review of literature. *J Matern Neonatal Med*. 2015;28(18):2214-2220.
38. Taff C. Prenatal diagnosis and treatment of fetal goiter. *J Diagnostic Med Sonogr*. 2016;32(1):40-43.
39. Aubry G, Pontvianne M, Chesnais M, Weingertner AS, Guerra F, Favre R. Prenatal diagnosis of fetal goitrous hypothyroidism in a euthyroid mother: a management challenge. *J Ultrasound Med*. 2017;36(11):2387-2394.
40. Ferianec V, Papcun P, Grochal F, Schenková K, Bártová M. Prenatal diagnosis and successful intrauterine treatment of severe congenital hypothyroidism associated with fetal goiter. *J Obstet Gynaecol Res*. 2017;43(1):232-237.
41. Figueiredo CM, Falcão I, Vilaverde J, et al. Prenatal diagnosis and management of a fetal goiter hypothyroidism due to dyshormonogenesis. *Case Rep Endocrinol*. 2018;2018:1-4.
42. Dębska M, Gietka-Czernel M, Kretowicz P, et al. Foetal goitrous hypothyroidism — Easy to recognise, difficult to treat. Is combined intra-amniotic and intravenous L-thyroxine therapy an option? *Endokrynol Pol*. 2018;69(4):442-446.

43. Tanase-Nakao K, Miyata I, Terauchi A, et al. Fetal goitrous hypothyroidism and polyhydramnios in a patient with compound heterozygous DUOXA2 Mutations. *Horm Res Paediatr*. 2018;90(2):132-137.
44. Stoupa A, Al Hage Chehade G, Kariyawasam D, et al. First case of fetal goitrous hypothyroidism due to SLC5A5/NIS mutations. *Eur J Endocrinol*. 2020;183(5):K1-K5.
45. Delay F, Dochez V, Biquard F, et al. Management of fetal goiters: 6-year retrospective observational study in three prenatal diagnosis and treatment centers of the Pays De Loire Perinatal Network. *J Matern Neonatal Med*. 2020;33(15):2561-2569.
46. Overcash RT, Marc-Aurele KL, Hull AD, Ramos GA. Maternal iodine exposure: a case of fetal goiter and neonatal hearing loss. *Pediatrics*. 2016;137(4):e20153722.
47. Hardley MT, Chon AH, Mestman J, Nguyen CT, Geffner ME, Chmait RH. Iodine-induced fetal hypothyroidism: diagnosis and treatment with intra-amniotic levothyroxine. *Horm Res Paediatr*. 2018;90(6):419-423.

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