Intra-amniotic levothyroxine infusions in a case of fetal goiter due to novel Thyrogblobulin 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, intraterine 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.\textsuperscript{3,15,16}

We present a case of non-immune hypothyroidism with FG secondary to compound heterozygous variants in the thyroglobulin (\textit{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 iodine insufficiency was referred to our clinic for FG at 23 gestational weeks (GW) +6.\textsuperscript{17} There was no familial history of thyroid disease. Detailed fetal echography revealed a goiter (thyroid circumference 73 mm, \{mean \pm SD, 46 \pm 5.9\}\textsuperscript{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]).\textsuperscript{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).

As the fetus health situation remained stable, oral substitution was started in the mother by 50 \(\mu\)g/day of levothyroxine (1 \(\mu\)g/kg.day) and later increased to 75 \(\mu\)g/day (1.5 \(\mu\)g/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 \(\mu\)g of levothyroxine (190 \(\mu\)g/kg of estimated fetal weight). A series of three more injections (400 \(\mu\)g 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 bone nucleus appeared at 33 GW, confirming a normal bone maturation.\textsuperscript{19} There were no complications related to IAIs. Microarray (\textit{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\textsuperscript{20}), moderate hypothyroidism on cord blood (shown in Table 1), and normal bone maturation (by extrapolating a score established on the points of Beclard).\textsuperscript{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 \(\mu\)g/day (17 \(\mu\)g/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 \textit{TG} gene (\{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

![AFI Thyroid diameter](image-url)

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 \(\mu\)g/day, 2nd = 75 \(\mu\)g/day), orange arrows correspond to intra-amniotic infusions of Levothyroxine (400 \(\mu\)g/injection)
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, desiodnase 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 desiodnase 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 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 venous 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-T3; T4T = total-T4; TG = thyroglobulin.

*aNormograms using Hume et al. 200418.
prevented the hearing loss in a fetus with iodine-induced hypothyroidism, highlighting the impact of prenatal TH substitution on complications.\textsuperscript{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.\textsuperscript{21} However, these parameters were assessed in less than 50\% of reported cases treated by IAIs of levothyroxine.\textsuperscript{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 of TFTs biological follow-up in the fetus by cordocentesis during the treatment.

### TABLE 2

| Patient no | References | GW\textsuperscript{a} (week) | TSH\textsuperscript{b} (mU/L) | fT4\textsuperscript{b} (pmol/l) | Complications (of the goiter) | Diagnosis method |
|------------|------------|-----------------------------|-------------------------------|-------------------------------|--------------------------|-----------------|
| 1          | Marín et al\textsuperscript{31} | 22                          | 24                            | 0.6                           | None                     | AC; CC          |
| 2          | Stewart et al\textsuperscript{32} | 31                          | 42                            | 2.3                           | Retroflexed neck         | AC; CC          |
| 3          | Saini et al\textsuperscript{33}  | 29                          | 100                           | 2.6                           | No                       | CC              |
| 4          | Esmer et al\textsuperscript{34}  | 29                          | 24                            | 14.1                          | Polyhydramnios            | CC              |
| 5          | Blumenfeld et al\textsuperscript{35} | 27                          | None                          | None                          | Retroflexed neck; trachea compression; polyhydramnios | None          |
| 6          | Blumenfeld et al\textsuperscript{15} | 22                          | None                          | None                          | Trachea compression       | None            |
| 7          | Khamisi et al\textsuperscript{36} | 24                          | 100                           | 3.8                           | No                       | CC              |
| 8          | Mastrolia et al\textsuperscript{37} | 36                          | NA                            | NA                            | Polyhydramnios            | AC              |
| 9          | Taff et al\textsuperscript{38}    | 24                          | Hypothyroid                   | Hypothyroid                   | No                       | CC              |
| 10         | Aubry et al\textsuperscript{39}   | 25                          | 35                            | 6.5                           | No                       | CC              |
| 11         | Vasudevan et al\textsuperscript{6} | 29                          | NA                            | NA                            | Polyhydramnios            | AC              |
| 12         | Ferianec et al\textsuperscript{40} | 27                          | 150                           | 5.5                           | None                     | AC; CC          |
| 13         | Figueiredo et al\textsuperscript{41} | 32                          | NA                            | NA                            | No                       | AC              |
| 14         | Dębska et al\textsuperscript{42}  | 24                          | 1500                          | 2                             | Polyhydramnios; retroflexed neck | AC; CC         |
| 15         | Tanase-Nakao et al\textsuperscript{43} | 33                          | 253                           | 3.7                           | Polyhydramnios            | CC              |
| 16         | Stoupa et al\textsuperscript{44}  | 25                          | 150                           | 3.3                           | None                     | CC              |
| 17         | Delay et al\textsuperscript{45}   | NA                          | 61                            | 9.9                           | None                     | NA              |
| 18         | Delay et al\textsuperscript{45}   | NA                          | 100                           | 6.6                           | NA                       | NA              |
| 19         | Delay et al\textsuperscript{45}   | NA                          | 500                           | 2.3                           | NA                       | NA              |
| 20         | Delay et al\textsuperscript{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.
\textsuperscript{a}Gestational Week of 1st IAI.
\textsuperscript{b}At cordocentesis.
\textsuperscript{c}On cordblood or before 72 h of life.

### STATEMENT OF ETHICS

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

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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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