



Foetal goitrous hypothyroidism — easy to recognise, difficult to treat. Is combined intra-amniotic and intravenous L-thyroxine therapy an option?

Płodowa niedoczynność tarczycy z wolem — łatwo rozpoznać, trudno leczyć. Czy podawanie doowodniowe i dożylnie L-tyroksyny jest jedną z opcji terapeutycznych?

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Abstract

Introduction: Foetal hypothyroidism negatively impacts somatic and neurological child development and can be the cause of serious obstetric and perinatal complications. We present a rare case of a large foetal dysmorphogenetic goitre, causing foetal neck hyperextension, oesophageal compression, and cardiac high-output failure.

Material and methods: A foetal goitre complicated by cardiomegaly and polyhydramnios was diagnosed at 23 weeks of gestation (WG) on a routine ultrasonographic (US) assessment in a healthy nullipara. Foetal blood sampling was performed and a severe foetal hypothyroidism was diagnosed. Treatment was undertaken with an intra-amniotic followed by combined intra-amniotic and intravenous injections of L-thyroxine (L-T4). A total of 11 doses of L-T4 were administered between 24–37 WG to the foetus.

Results: A complete regression of foetal goitre, cardiomegaly, and polyhydramnios was observed. At 38 WG the patient delivered vaginally a male infant with mild hypothyroidism and no signs of goitre or cardiomegaly on postnatal US. Neurological development of the one year old baby is normal.

Conclusions: The effective diminishing of serum TSH concentration and goitre size was reached after combined intra-amniotic and intravenous L-T4 injections were given. L-T4 requirement in the foetus is equal to or above 15 µg/kg daily and should be given in weekly intervals due to its rapid metabolism by the foetus and by placental type 3 deiodinase. Intra-amniotic L-T4 administration may be ineffective when a large goitre indisposes amniotic fluid swallowing by the foetus, so then the combined L-T4 injections into the umbilical vein and intra-amniotically in experienced hands seems to be a reasonable and effective option. (*Endokrynol Pol* 2018; 69 (4): 442–446)

Key words: foetal goitre, dysmorphogenesis, L-thyroxine in utero treatment

Streszczenie

Wstęp: Przedstawiamy rzadki przypadek wola dysmorphogenetycznego u płodu leczonego l-tyroksyną *in utero*. Niedoczynność tarczycy w okresie życia płodowego zaburza rozwój somatyczny i intelektualny dziecka. Obecność wola powodującego odgięciowe ułożenie głowy, ucisk przełyku oraz niewydolność serca w mechanizmie krążenia hiperkinetycznego może sama w sobie być przyczyną groźnych powikłań położniczych i okołoporodowych.

Materiał i metody: U zdrowej pierwiastki w trakcie rutynowego badania ultrasonograficznego przeprowadzonego w 23 tygodniu ciąży stwierdzono wole płodowe, kardiomegalię i wielowodzie. Wykonano kordocentezę stwierdzając ciężką płodową niedoczynność tarczycy. Podjęto leczenie l-tyroksyną (L-T4) podawaną początkowo doowodniowo a następnie metodą jednoczesnych iniekcji doowodniowych i do żyły pępowinowej. W okresie od 24–37 tygodnia ciąży podano łącznie 11 dawk L-T4.

Wyniki: Uzyskano całkowitą regresję wola i kardiomegalii, a w 38 tygodniu ciąży nastąpił poród fizjologiczny. U noworodka stwierdzono niedoczynność tarczycy o niewielkim nasileniu, natomiast w badaniu ultrasonograficznym nie obserwowano cech wola, ani niewydolności serca.

Wnioski: Istotne zmniejszenie stężenia TSH w krwi pępowinowej i rozmiarów wola uzyskano dopiero po jednoczesnym podawaniu L-T4 doowodniowo i do żyły pępowinowej. Wydaje się, że zapotrzebowanie płodu na L-T4 wynosi powyżej 15 µg/kg/d. Lek powinien być podawany co tydzień z powodu jego szybkiego metabolizowania przez płód i deiodynazę łożyskową typu 3. Stosowanie L-T4 wyłącznie doowodniowo może być nieskuteczne w przypadku dużego wola utrudniającego polykanie płynu owodniowego: w takich przypadkach dodatkowe podawanie leku do żyły pępowinowej przez doświadczony zespół wydaje się skuteczną i bezpieczną opcją terapeutyczną. (*Endokrynol Pol* 2018; 69 (4): 442–446)

Słowa kluczowe: wole dysmorphogenetyczne, leczenie L-tyroksyną *in utero*



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Introduction

Foetal goitre is a rare condition usually caused by maternal reasons: transplacental passage of thyroid stimulating antibodies (TSAb) in maternal Graves' disease or treatment with excessive amounts of antithyroid drugs (ATD) or iodine. It is reported in up to 19–25% of cases of maternal Graves' disease and is always accompanied by foetal thyroid dysfunction; hyper- or hypothyroidism [1]. Foetal US monitoring is therefore recommended in pregnancies with high maternal TSAb or ATD treatment [2, 3]. Primary foetal conditions accompanied by goitre are autosomal recessive mutations in proteins involved in thyroid hormone synthesis, among which thyroperoxidase and thyroglobulin gene defects occur the most often.

Dyshormonogenesis occurs in 1 per 30,000 newborns, accounting for 10–15% of congenital hypothyroidism. Foetal thyroid dysfunction, especially hypothyroidism, negatively impacts somatic and neurological development of the child. The goitre causing foetal neck hyperextension, oesophageal compression, cardiac high-output failure derived from arterio-venous shunting within the goitre can itself be the cause of serious obstetric and perinatal complications. If maternal disease is the reason for foetal goitre, then modification of maternal treatment (ATD dose diminishing or therapy withdrawal) is the fundamental approach. In cases of a large foetal goitre in healthy pregnant woman, intra-amniotic L-T4 injections can be performed by an experienced team [4].

In this article, we present a case of foetal goitrous hypothyroidism that was successfully treated in utero by combined intra-amniotic and intravenous injections of L-T4.

Case report

The foetal goitre was diagnosed at week 23 of gestation (WG) in a healthy 20-year-old nullipara on a routine US assessment. The goitre had a typical bilobular shape, intense central vascularisation, 3.5 cm diameter, and 4.17 cm² area on the transverse scan (> 97 centile according to our nomograms [5]) and caused hyperextension of the foetal head (Fig. 1). There was also mild cardiomegaly (Ha/Ca 0.38) and polyhydramnios; foetal stomach was not visible. Severe foetal hypothyroidism was diagnosed by cordocentesis. Foetal blood TSH concentration was 1500 μ IU/mL (n. $6.8 \pm 2.93 \mu$ IU/mL), fT3 — 0.87 pmol/L (n. 0.2–0.5 pmol/L), fT4 — 2.0 pmol/L (n. 16.5 ± 5.3 pmol/L) [6, 7], thyroglobulin 1500 ng/mL (n. 0.55 ng/mL), and pro-BNP 1247 ng/mL (n. 0.125 ng/mL). Evaluation of the maternal thyroid status showed normal TSH 2.357 μ IU/mL (n. 0.05–3.44 μ IU/L) and fT4 13.59 pmol/L (n. 10.46–16.67 pmol/L) [8], negative

antiperoxidase (a-TPO) < 37 IU/mL (n. 0.60 IU/mL), antithyroglobulin (aTg) < 25 IU/mL (n. 0–60 IU/mL), and anti-TSH receptor antibodies 0.42 IU/L (n. < 1.8 IU/L), no signs of excessive iodine excretion in urine, and normal thyroid US scan. Intra-amniotic treatment with L-T4 was started from 24 WG: the first dose was 500 μ g, followed by two doses of 250 μ g given in weekly intervals. Three weeks later the foetal goitre and foetal heart enlargement were still observed, suggesting that swallowing of the amniotic fluid by the foetus is very poor due to persisted oesophageal compression. Then we decided to administer a combined L-T4 treatment with injections given into the umbilical vein (20 μ g IV as the rapid treatment) and intra-amniotically (230 μ g intra-amniotically as a long-lasting treatment).

At 29 weeks, foetal cardiomegaly still increased significantly (Ha/Ca 0.46) and the goitre was still present. Due to the premature uterine contractions and cervix shortage to 10 mm, the patient was hospitalised and steroids and tocolytics were given. Also, digoxin was administered to the mother to improve foetal heart function. Foetal therapy with L-T4 was continued, and gradually a decrease of foetal thyroid size and amniotic fluid amount was observed. A total of 11 doses of L-T4 were administered between 24 and 37 WG to the foetus: seven only intra-amniotic and four combined — intra-amniotic and intravenous (Tab. I).

A complete regression of foetal goitre and cardiomegaly until delivery was observed. At 38 WG the patient delivered vaginally a male infant with 3080 g of weight, 52 cm of length, 10 Apgar scores, with no signs of goitre and cardiomegaly on US. A mild hypothyroidism was observed in the child after birth — TSH 22.77 μ IU/L (n. 1.79–9.69), fT3 1.79 pg/mL (n. 1.87.6 pg/L), and fT4 16.40 pmol/L (n. 22.5–39.9 pmol/L). L-thyroxine therapy with the dose of 15 μ g/kg was started immediately after delivery. Early neural development of neonate was normal. The boy is one year old now and his development is normal.

Discussion

In the presented case no maternal cause of foetal goitrous hypothyroidism was found, so the most probable diagnosis was dyshormonogenesis. Thyroglobulin gene defect could be excluded because of the enormously high serum thyroglobulin concentration obtained during cordocentesis. We decided to perform cordocentesis to evaluate foetal thyroid status because previous reports documented the lack of reliability of TSH concentration measurement in amniotic fluid [9–11].

Initial therapy with L-T4 given intra-amniotically was unsatisfactory probably because of oesophageal compression and difficulties in amniotic fluid

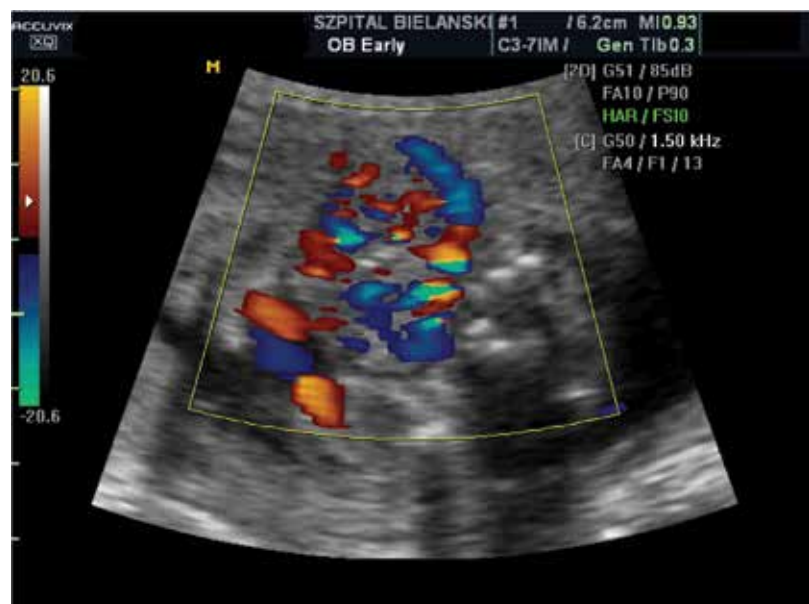


Figure 1. A. Foetal goitre, head hyperextension, and polyhydramnios at week 23 of gestation on longitudinal ultrasound scan; B. Foetal goitre at week 23 of gestation on transverse ultrasound scan; C. Foetal goitre with increased central blood flow at week 23 of gestation on colour Doppler examination

Rycina 1. A. Wole, odgięciowe ułożenie głowy i wielowodzie, przekrój podłużny w 23 tygodniu ciąży na ultrasonografii płodu; B. Wole, przekrój poprzeczny; C. Wole z intensywnym przepływem centralnym w badaniu kolorowego Dopplera, przekrój poprzeczny

Table I. Treatment of foetal goitrous hypothyroidism with intra-amniotic and intravenous L-thyroxine injections: changes in foetal thyroid status and goitre size

Tabela I. Leczenie płodowej niedoczynności tarczycy z wolem L-tyroksyną podawaną doowodniowo i do żyły pępowinowej: zmiany w stężeniach TSH, fT4, fT3 ocenianych w krwi pępowinowej i wielkości wola

Gestational age (weeks)	L-thyroxine	Foetal thyroid dimensions [cm]*	Foetal thyroid status		
			TSH [μ IU/mL]†	fT4 [pmol/L]†	fT3 [pmol/L]‡
23	500 μ g IA	D: 3.5 (1.04–1.74) C: 7.55 (3.02–4.73)	1500 (6.8 \pm 2.93)	2.0 (16.5 \pm 5.3)	1.34 (0.2–0.5)
25	250 IA	D: 4.2 (1.13–1.89) C: 12.8 (3.27–5.12)	528 (6.8 \pm 2.93)	4.66 (16.5 \pm 5.3)	0.87 (0.4–0.8)
27	230 μ g IA 20 μ g IV	D: 3.9 (1.21–2.02) C: 9.99 (3.49–5.47)	342 (6.8 \pm 2.93)	6.56 (16.5 \pm 5.3)	1.17 (0.4–0.9)
28	230 μ g IA 20 μ g IV	D: 4.5 (1.25–2.08) C: 11.7 (3.60–5.64)	404 (7.0 \pm 3.73)	6.34 (18.6 \pm 5.5)	1.08 (0.4–1.0)
29	230 μ g IA 20 μ g IV	D: 4.0 (1.28–2.14) C: 11.7 (3.71–5.80)	124 (7.0 \pm 3.73)	8.63 (18.6 \pm 5.5)	1.23 (0.5–1.1)
31	230 μ g IA 20 μ g IV	D: 2.5 (1.35–2.26) C: 7.3 (3.89–6.1)	61.8 (8.0 \pm 5.12)	9.80 (19.3 \pm 4.3)	1.30 (0.4–1.2)
32	250 IA	D: 3.0 (1.38–2.31) C: 9.0 (3.99–6.25)			
33	250 IA	D: 3.3 (1.42–2.36) C: 9.2 (4.08–6.38)			
34	500 μ g IA	D: 3.4 (1.44–2.41)			
35	250 IA	D: 2.7 (1.47–2.46)	4.44 (7.6 \pm 5.88)	20.4 (19.2 \pm 5.2)	1.00 (0.5–2.0)
36	500 μ g IA	D: 2.8 (1.49–2.5) C: 9.16 (4.32–6.76)			

Reference values (in parentheses) according to: *Gietka-Czernel et al.⁵, †Hume et al.⁶, and ‡Thorpe-Beeston et al.⁷ IA — intra-amniotic injection, IV — into umbilical vein injection, D — diameter, C — circumference on a transverse ultrasonographic scan

swallowing. The effective diminishing of serum TSH concentration and goitre size was reached only after the combined intra-amniotic and intravenous L-T4 injections were given. The concept of administering L-T4 into the umbilical vein was reasonable because cyclical cordocentesis in an attempt to examine foetal TSH and free thyroid hormones was part of the monitoring of the foetal thyroid status. No adverse effects of the treatment were recorded. To the best of our knowledge, this is the first such therapy successfully undertaken in a foetal dyshormonogenetic goitre.

There are no available recommendations concerning the treatment of foetal dyshormonogenetic goitre because of the rarity of the disease. The still unanswered questions are the amount of L-T4 dose, the route and frequency of its administration, and eventually whether L-T4 alone or L-T4 combined with L-tri-iodothyronine (L-T3) should be advocated.

In the retrospective study of 12 cases of foetal goitrous hypothyroidism, the therapy with intra-amniotic L-T4 was conducted from 24 to 36 WG, the doses varied from 200 to 800 μ g per injection (3–23 μ g/kg of estimated foetal weight) and were given 1–6 times at 1–4 week intervals. As a result, all children at birth had elevated serum TSH

from 39 to 450 mU/L, only two of them had normal serum T4, and the majority presented with goitre [9]. Of note, at 2.5–18 years of age all of them presented normal growth and normal neurological and cognitive function.

Another report described therapy with intra-amniotic L-T4 injections given seven times weekly between 29 and 37 WG in a dose of 10 μ g/kg of estimated foetal weight per day. The child had normal serum TSH, fT4, and thyroid size at birth [12]. Such an approach appeared insufficient in another case: intra-amniotic L-T4 treatment was started from 26 WG and after the initial five weekly doses had to be augmented from 10 μ g/kg to 15 μ g/kg of estimated foetal weight per day because of goitre persistence [13]. Other authors successful administered three intra-amniotic doses of 500 μ g of L-T4 in weekly intervals [14].

The different route of L-T4 administration was undertaken by Börgel et al.: after the initial intra-amniotic L-T4 injection of 250 μ g the next two doses of 200 and 100 μ g were given into the umbilical vein. Two weeks later a hypothyroid child was born with small goitre and cord blood TSH 200 μ IU/mL. Interestingly, this patient and his older brother were diagnosed to have the same mutation in the thyroid peroxidase gene, but

the prenatally treated patient had higher IQ values than his older brother, who was treated only postnatally [15]. Of note is the experience with intra-amniotic and intramuscular L-T4 therapy given to goitrous hypothyroid foetus caused by maternal ATD overtreatment. The first intra-amniotic L-T4 dose of 500 µg was administered at 34 WG followed one week later with 100 µg intramuscular and 400 µg intra-amniotic because of the goitre increase. Although the authors observed that rapid goitre diminishing was obtained only after intramuscular L-T4 injection was given, the child was hypothyroid at birth [16]. Therapy with two thyroid hormones given intra-amniotically was also described: three doses of 60 and 120 µg of L-T3 and two doses of 150 and 300 µg of L-T4 were administered at weekly intervals between 31 and 35 WG. The course of treatment was uneventful but a mild hypothyroidism was observed in the child at birth [17].

Conclusions

In utero thyroid hormone treatment should be considered in carefully selected fetuses with goitrous hypothyroidism. Our experience and limited literature review of the prenatal treatment of the foetal dys-hormonogenetic goitre allows us to hypothesise that L-thyroxine requirement in foetus is probably greater than in neonates and is equal or above 15 µg/kg daily. It should be given in weekly intervals because of its rapid metabolism by the foetus and by placental type 3 deiodinase. Intra-amniotic L-T4 administration may be ineffective when a large goitre indisposes amniotic fluid swallowing by the foetus. The combined L-T4 injections into the umbilical vein and intra-amniotically may seem a reasonable and effective option if performed by experienced operators. Ultrasonography with periodic assessment of TSH and thyroid hormones in the umbilical vein is an excellent method of diagnosing foetal goitre and monitoring the effectiveness of treatment.

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