Fetal goitre is a very rare disease that can be secondary to thyroid dysfunction, generally hypothyroidism. Before Down syndrome cause, congenital hypothyroidism (CH) is the most frequent congenital cause of intellectual disability(1). The incidence of fetal goitre associated with hypothyroidism is 1/30,000 to 1/50,000 live births; this becomes more frequent in pregnant women with Graves’ disease or other thyroid dysfunctions(2). Fetal goitre represents an enlargement of the fetal thyroid gland, it may be preventable. This pathology has a predilection for females, with the fetal incidence being 2:1 for females than males(3).

Fetal goitre indicates a thyroid dysfunction, and it can be associated with all types of different thyroid hormone levels: hypothyroidism, hyperthyroidism and even euthyroidism(4,5).

The fetal goitre is a sign of maternal hyperthyroidism when there is a placental passage of TSI (thyroid stimulating immunoglobulins) from the mother with Graves’ disease to the fetus, or a sign of hypothyroidism due to the antithyroid medication given to the pregnant woman(6,7).

While the fetal thyroid develops between the 7th and the 12th weeks of gestation, it reaches its final site in the neck and it does not function autonomously until around the 18-20th weeks. Until that gestational age, having a balanced status of the maternal thyroid hormones is important for the neuromotor and intellectual physiological development of the fetus(8).

These findings may justify that an endocrinological evaluation of the thyroid gland may be highly recommended preconceptionally and during pregnancy, especially in endemic areas. Any pathologies discovered de novo could be diagnosed and treated. Alternatively, the treatment doses can be adjusted for the preexisting pathologies to prevent consecutive fetal thyroid pathology development.

**Diagnostic**

The first case of antenatal diagnosis of fetal goitre was reported back in 1980, and this was also the first case of fetal hypothyroidism treated in utero with thyroxine, which helped reduce the goitre volume after its administration considerably(9).
Fetal goitre is diagnosed by prenatal ultrasound or, in special cases, combined with fetal magnetic resonance imaging (MRI).

Fetal thyroid size can be measured by transvaginal ultrasonography from 14 weeks, and by transabdominal ultrasonography from 18 weeks of gestation\(^{10}\).

Many anatomical studies have reported normal length values: first trimester – 3.47 ± 0.54 mm; second trimester – 7.48 ± 1.74 mm; third trimester – 13.66 ± 2.05 mm; at 40 weeks – 21.34 ± 3 mm\(^{11,12}\).

There are few ultrasound reference curves for fetal thyroid measurements, including fetal thyroid length in a single plane, with measurements of circumference, total transverse diameter or thyroid area and volume\(^{13-19}\). Barbosa et al. have published very good reference ranges for thyroid measurement\(^{20}\).

Fetal thyroid examination is not systematically recommended during prenatal screening evaluation. Fetal goitre appears as a hyperechogenic, symmetric mass in the neck region, anteriorly, with a length diameter above the 90-95th percentile for gestational age\(^{16}\).

Attempts have been made to establish the standard diagnostic criteria by using ultrasonography starting with week 20, but protocols have not yet been developed for this investigation.

Huel et al. have recommended the analysis of the following four parameters for the diagnosis of hypo- or fetal thyroid hyperfunction: vascular pattern of the goitre, fetal heartbeat, bone maturation of the fetus, fetal movement (Table 1)\(^{21}\).

Bone maturation was evaluated at 32 weeks using ultrasound. Advanced bone maturation was defined by the presence of the distal ossification centre before 31 weeks and delayed bone maturation as the absence of the distal femoral ossification centre after 33 weeks.

Fetal tachycardia was defined as a fetal heart rate frequency higher than 160 bpm\(^{21}\).

Also, a useful score scale for the diagnosis fetal hypo- or hyperthyroidism was imagined (Table 2).

Thus, having a total score above 2 suggests the presence of hyperthyroidism, while a score below 2 indicates fetal hypothyroidism.

Fetal MRI is complementary to ultrasonography; it can help in the differential diagnosis and for obtaining a detailed fetal thyroid functionality\(^{22}\).

After the imaging investigations, the second step involves performing laboratory investigations. It was initially thought that fetal thyroid pathologies could be diagnosed based on the level of thyroid hormones in the amniotic fluid. However, it has been shown that fetal blood collected from the umbilical cord has a much higher sensitivity\(^{17}\), given that the level of thyroxine in the amniotic fluid is both from fetal and maternal sources. On the other hand, TSH in the amniotic fluid seems to only reflect the fetal level’s, given that it cannot cross the fetal-placental barrier. Cordocentesis is considered the gold standard for diagnosis, although the complication rate is significantly higher, and the technique is significantly more laborious than amniocentesis\(^{23,24}\).

The etiology of fetal hypothyroidism is diverse; in about 85% of cases, it is caused by thyroid dysgenesis (agenesis, hypoplasia or ectopy). The other 15% of cases of primary congenital hypothyroidism are due to defective hormone synthesis (thyroid dyshormonogenesis) caused by different mutations involving SLC26A4, DUOX2, DUOX2, DEHAL1, sodium/iodine transporter, thyroid peroxidase (TPO) and thyroglobulin (TG)\(^{25-27}\).

One particular case where the antepartum diagnosis cannot be made is when there is a congenital resistance to TSH, an autosomal recessive inheritance of TSH resistance caused by inactivating mutations in the TSHR\(^{28}\). The clinical and paraclinical aspects of these pathologies are extremely varied and are generally associated with normal or low glandular volume, ranging from asymptomatic forms with elevated TSH to forms with a lack of thyroid gland\(^{21,29}\).

It is also vital to monitor fetuses with Down syndrome, who frequently have low levels of T4 and high levels of TSH, thus associating various forms in terms of severity of primary congenital hypothyroidism. In this way, some of the neurological and psychomotor disorders of newborns with trisomy 21 can be explained by these disorders in the thyroid hormone levels. Their adverse effects on fetal development could be interrupted by the

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Criteria for the ultrasound evaluation of fetal thyroid(^{21})</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Criteria</strong></td>
<td><strong>Hypothyroidism</strong></td>
</tr>
<tr>
<td>Peripheral vascular pattern (color Doppler)</td>
<td>68.8%</td>
</tr>
<tr>
<td>Central vascularization (color Doppler)</td>
<td>0%</td>
</tr>
<tr>
<td>Fetal tachycardia</td>
<td>57.1%</td>
</tr>
<tr>
<td>Delayed bone maturation</td>
<td>46.9%</td>
</tr>
<tr>
<td>Advanced bone maturation</td>
<td>0%</td>
</tr>
<tr>
<td>Increase in fetal movement</td>
<td>43.8%</td>
</tr>
</tbody>
</table>
administration of thyroxine in pregnant women with fetuses with specific changes in Down syndrome\(^{(30,31)}\).

**Complications**

Fetal goitre can lead to numerous complications *in utero* or perinatally, such as fetal growth restriction, polyhydramnios, pleural effusion, preterm delivery, neonatal asphyxia or fetal death, labor dystocia, craniosynostosis, but also the most frequent neurodevelopmental deficits\(^{(32,33)}\). Moreover, fetal thyrotoxicosis can lead to tachycardia, cardiac failure or hydrops, and to premature birth or fetal death\(^{(34)}\).

The goitre mass can lead to different complications, such as airway compression, polyhydramnios due to compression of the cervical mass on the esophagus, vicious obstetrical presentations due to cervical hyperextension, and numerous childbirth impediments that can lead to neonatal asphyxia and even death.

In addition, due to the cervical mass, neonatal intubation and ventilation are often performed with difficulty\(^{(35)}\).

Maternal complications include placental abruption, preterm labor, preeclampsia, congestive heart failure and thyroid storm\(^{(36)}\).

**Treatment**

Deciding on the prenatal treatment represents another challenge because the trade-offs of initiating intrauterine treatment must be balanced with the trade-offs of the “watchful waiting” strategy. The reduction in the thyroid goitre (as observed on ultrasound imaging) is not equivalent to normalising fetal thyroid hormone concentrations. This decision to treat or not is affected by the substance being administered as treatment, generally indicating LT4 or a combination of LT4 and T3, dose, method of administration and frequency. Often, despite treatment, infants are born with hypothyroidism, but with normal neuromotor and psychoemotional development.

In terms of methods of administration, intraamniotic, intramuscular or fetal administration are currently practised. Intraamniotic L-thyroxine hormones administration was proven to be the most effective, although in 9.7% of cases this method led to preterm delivery or chorioamniotitis\(^{(37-39)}\). Its efficiency is explained by the deficiency in the transplacental transport of the thyroid hormone.

Doses can vary between 150 and 800 µg, and they are being adjusted depending on the response to the treatment, every few days or a few weeks to a month. The length of time between the last dose of treatment and birth seems to influence the evolution of this pathology in extrauterine life\(^{(1)}\).

In cases of fetal hyperthyroidism, a decrease in the dose of maternal antithyroid medication is recommended. Regarding the way of birth, if the goitre is not a voluminous one, it is recommended to give birth vaginally. In the rest of cases, or in those that require an *in utero* intervention for airway clearance, giving birth by caesarean section is more suitable\(^{(40-43)}\).

There are no guidelines or general recommendations for optimal treatment regimen. However, there are currently a wide variety of approaches to treatment.

In conclusion, the diagnosis and treatment of fetal hypothyroidism goitre are challenging, especially when maternal thyroid function is normal.

**Conflicts of interests:** The authors declare no conflict of interests.

---

### Table 2

<table>
<thead>
<tr>
<th>Ultrasoundography criteria</th>
<th>Scale</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Vascularization</strong></td>
<td></td>
</tr>
<tr>
<td>Peripheral or absent</td>
<td>0</td>
</tr>
<tr>
<td>Central</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fetal heart rate</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>1</td>
</tr>
<tr>
<td><strong>Bone maturation</strong></td>
<td></td>
</tr>
<tr>
<td>Delayed</td>
<td>-1</td>
</tr>
<tr>
<td>Normal</td>
<td>0</td>
</tr>
<tr>
<td>Accelerated</td>
<td>1</td>
</tr>
<tr>
<td><strong>Fetal movements</strong></td>
<td></td>
</tr>
<tr>
<td>Normal</td>
<td>1</td>
</tr>
<tr>
<td>Increased</td>
<td>0</td>
</tr>
</tbody>
</table>

---

Interdisciplinary
References


