Current knowledge about the in utero and peripartum management of fetal goiter associated with maternal Graves' disease

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A B S T R A C T

Maternal Graves' disease is the most common cause of fetal goiter. Fetal goiter can cause complications attributable either to the physical effects of the goiter itself or to thyroid dysfunction, which can be life-threatening and cause neurological impairment. Determining whether a goiter is caused by fetal hyperthyroidism or hypothyroidism is the main clinical problem, and in utero evaluations and management are essential. Ultrasonography combined with color Doppler and magnetic resonance imaging are helpful for the initial diagnosis and monitoring, but these imaging techniques have a limited ability to discriminate between fetal hyperthyroidism and hypothyroidism. To determine the fetal thyroid status, fetal blood sampling using cordocentesis is reliable but hazardous, and the indications must be considered carefully. Amniocentesis is an easier and safer alternative, but the correlations between the amniotic fluid and fetal serum thyroid hormone levels remain unclear. If a fetal goiter is accompanied by hypothyroidism, administering thyroid hormone intra-amniotically may be effective and relatively safe. However, the wide variety of approaches to treatment exemplifies the lack of guidelines, and no systematic studies have been conducted to date. Therefore, intrauterine treatment should be reserved for selected patients at a high risk of complications. Moreover, when intrauterine treatment fails and a fetal goiter can cause airway obstruction, intrapartum management, such as ex utero intrapartum treatment, may be required; however, reports describing the use of this procedure for fetal goiter are limited. This review summarizes the current knowledge about fetal goiter associated with maternal Graves' disease and evaluates the most significant new findings regarding its in utero and peripartum management.

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Introduction

Hyperthyroidism complicates approximately 0.1–0.4% of pregnancies, with 85–90% of cases due to Graves' disease (GD), an autoimmune disorder caused by an immunoglobulin G antibody that stimulates the thyroid-stimulating hormone (TSH) receptor [1]. If not properly managed, it can result in severe maternal, fetal, and neonatal morbidity and mortality. Maternal complications include abortion, pre-eclampsia, preterm labor, placental abruption, congestive heart failure, and thyroid storm [2].

The fetus of a pregnant woman with GD is at risk of thyroid dysfunction from the transplacental transfer of the TSH receptor antibody. A pregnant woman with GD is usually treated with antithyroid drugs (ATDs), but ATDs can pass through the placenta, and high doses can cause fetal hypothyroidism [3].

Fetal goiter is an abnormal enlargement of the fetal thyroid gland, and it indicates thyroid dysfunction [4]. Untreated fetal goiters are often associated with perinatal and postnatal complications caused by the goiters themselves and the attendant thyroid dysfunction. Prenatal management can prevent these adverse outcomes, but systematic verifications of these interventions are limited, and the risk-to-benefit ratio is controversial. This review summarizes the current knowledge about fetal goiter associated with maternal GD and evaluates the most significant new findings regarding its in utero and peripartum management.

Fetal goiter associated with maternal Graves' disease

Fetal goiter is found in 19% of the fetuses carried by mothers with GD [5]. Fetal goiter associated with maternal GD can result from either fetal hyperthyroidism or hypothyroidism. Fetal goiter is a very rare phenomenon; indeed, the incidence of goitrous hypothyroidism is approximately one per 40,000 live births, and goiter is found in only 10%–15% of all cases of congenital hypothyroidism [6,7]. The incidence of goitrous hyperthyroidism is unknown.

After 20 weeks of gestation, the fetal TSH receptors become responsive to TSH. Maternal thyroid-stimulating antibodies (TSAbs) cross the placenta and can overstimulate the fetal thyroid, causing hyperthyroidism and goiter [8]. Fetal goitrous hypothyroidism may occur in the presence of thyroid-blocking antibodies (TBAbs) or when high-dose ATDs are administered to the mother. As fetal hypothyroidism caused by TBAbs is extremely rare [8], fetal hypothyroidism accompanied by maternal GD is commonly caused by the excessive placental transfer of maternal ATDs [3]. Before the onset of fetal thyroid function during midgestation, the fetus relies on the transplacental passage of maternal thyroid hormone [8]; therefore, there is no need to consider any direct effects of ATDs. After midgestation, the maternal thyroxine (T_4) supply remains extremely important to the fetus, but the transfer of maternal T_4 may not be able to fully compensate for the blockage of fetal thyroid hormone synthesis by maternal ATDs. Consequently, the thyroid lobes enlarge, which is likely caused by the hyperstimulation of the tissue by the increased levels of fetal TSH in response to fetal thyroid insufficiency. Fetal goiter can cause complications that are attributable either to the goiter itself, for example, the mechanical effects of the neck mass, or to the hormonal abnormalities. In utero, a very large goiter may cause esophageal compression with secondary polyhydramnios or tracheal compression, both of which are compounded by dystocia caused by neck hyperextension [9]. At birth, tracheal compression caused by the enlarged thyroid gland can lead to respiratory distress and death [9].

Fetal hyperthyroidism can cause fetal growth restriction (FGR) which is accompanied by accelerated bone maturation, goiter development, and craniosynostosis. Thyrotoxicosis, comprising tachycardia, cardiac failure, and hydrops, can occur, which may cause premature birth, intrauterine or perinatal death, or serious neurological sequelae [10]. Fetal hypothyroidism is associated with retarded skeletal development, mental retardation, hearing defects, poor visuomotor abilities, delayed speech and language development, and poor attention and memory skills [11]. Despite immediate postnatal evaluations and thyroid hormone replacement, some neurological abnormalities may persist. The degree of neurological impairment has been associated with the severity of the hypothyroidism and the age at diagnosis. The treatment of fetal hypothyroidism without a goiter remains controversial, because it is difficult to diagnose, and it is unclear whether the condition affects a child's prognosis [3,9]. Since the presence of a goiter clearly indicates serious fetal thyroid dysfunction, prenatal identification and treatment of goiter are recommended [12].

Diagnosis of fetal goiter and thyroid status

The early detection of fetal goiter and appropriate evaluation of fetal thyroid dysfunction are crucial to prevent adverse outcomes in fetuses and neonates.

Fetal ultrasonography

As the fetal thyroid gland can be accurately assessed using serial ultrasonography (US) at 20–36 weeks of gestation, a fetal goiter can be diagnosed using US during the second or third trimester. On US, a fetal goiter appears as a homogeneous, symmetrical, and hyperechogenic mass in the anterior neck region, and it is defined as a fetal goiter when the thyroid gland's width and circumference exceed the 95th percentile for the gestational age [4]. When a goiter is detected, it is important to document its size and vascularity, and more importantly, the size of the trachea and the presence of fetal swallowing should be noted.

In fetuses with goiters, determining whether the cause is fetal hypothyroidism or hyperthyroidism is the main clinical challenge [3]. On US, goiter vascularization, the fetal heart rate, bone maturation, and fetal movement differ appreciably according to the presence of fetal hyperthyroidism or hypothyroidism. For example, using the Doppler technique, an increased blood flow throughout the gland is linked to fetal hyperthyroidism, whereas an increased blood flow at the periphery of the gland has been associated with fetal hypothyroidism [12]. Huel et al. proposed an ultrasound scoring system, based on the color Doppler pattern (peripheral/central vascularization), fetal heart rate (tachycardia/normal heart rate), bone maturation (early/late), and fetal movements (intense/normal), to predict fetal thyroid function in cases of fetal goiter [5]. Although the researchers correctly distinguished 36 cases of fetal hypothyroidism from hyperthyroidism using this scoring system, some inconsistency remains, and its practical applicability is poor.

Fetal magnetic resonance imaging

Fetal magnetic resonance imaging (MRI) complements US examinations by helping to differentiate goiters from cervical tumors, delineate a goiter's full extent [13], and to assess the levels by which a goiter obstructs the trachea and esophagus in the presence of massive polyhydramnios [14]. Fetal MRI also helps differentiate the status of the thyroid by analyzing the T1 and T2 signals. A fetal thyroid gland can be identified as a hyperintense structure in the neck on T1-weighted images, which can differentiate goiters from other neck masses more readily than US [15]. Moreover, the intensity of the thyroid T2 signals varies with the functional status, because it correlates with the iodine concentration; hence, a thyroid gland with a high iodine

concentration has a low signal intensity, and a gland with a low iodine concentration has a high signal intensity [16]. As a normal thyroid gland's signal intensity is as low as that of muscle on T2-weighted images, the presence of a signal that is higher than that associated with muscle signifies a hypofunctioning thyroid gland [16]. Table 1 summarizes our review of previous reports that describe MRI findings from fetal goiters between 2000 and 2018 [13,15,17–27]. Without a maternal thyroid gland abnormality, fetal hypothyroidism is characterized by a fetal thyroid gland that shows a hyperintense signal on T2-weighted images. In contrast, in the presence of maternal GD, there might be no relationship between the signal intensity and fetal thyroid abnormalities on T2-weighted images. Therefore, MRI may not correspond to expectations regarding the discrimination of fetal hyperthyroidism and hypothyroidism in the presence of maternal GD.

Amniotic fluid sampling

Amniocentesis to evaluate the TSH levels in the amniotic fluid may be useful to check fetal thyroid metabolism, and it is less technically demanding and safer than cordocentesis. Previous reports indicate that the amniotic fluid TSH levels reflect fetal rather than maternal thyroid function, because TSH does not cross the placenta [28]. Moreover, reference ranges have been established for thyroid hormone levels in the amniotic fluid [29]. These data may support the use of amniotic fluid analysis to diagnose fetal hypothyroidism; however, the value of amniotic fluid analysis alone in the presence of fetal thyroid dysfunction is controversial. Discrepancies between the intra-amniotic and neonatal blood TSH levels have been described, and the relative maternal and fetal contributions to the hormone levels in the amniotic fluid are unclear [28]. Indirect quantification based on the thyroid hormone levels in the amniotic fluid does not accurately reflect the function of the fetal thyroid gland, and it only enables the assessment of dynamic changes. Hence, the TSH levels in the amniotic fluid may have some diagnostic value for fetuses with severe hypothyroidism, especially when cordocentesis is not available.

Fetal blood sampling

Cordocentesis, which is the gold standard diagnostic method [9], enables direct measurements of the fetal thyroid hormone levels and accurate determinations of the fetal thyroid status

because normal reference values for fetal thyroid function have been established [8,30]. However, the minor and major complications associated with this invasive procedure should be stressed; these include fetal bleeding, infections, bradycardia, premature rupture of membranes, and death, which occur in 0.5−9.0% of patients [28]. Cordocentesis may not be required for all patients, and it should only be undertaken in specialist centers. The European Society for Paediatric Endocrinology consensus guidelines on the screening, diagnosis, and management of congenital hypothyroidism recommend using cordocentesis rather than amniocentesis to assess fetal thyroid function [31].

Intrauterine treatment of fetal goiter

Regardless of whether hyperthyroidism or hypothyroidism is present, the treatment of a large fetal goiter is essential, because tracheal obstruction could cause neonatal death and fetal neck hyperextension could cause mechanical issues during delivery.

Treatment of fetal goiter caused by hyperthyroidism

A fetus that has hyperthyroidism benefits directly from the administration of ATDs to the mother, because ATDs cross the placenta and act on the fetal thyroid gland. A mother with hyperthyroidism who receives ATDs will usually require an increased ATD dose. If a euthyroid mother who is not receiving medication is carrying a fetus with a goiter, it is usually possible to treat the mother with ATDs. Although propylthiouracil (PTU) and methimazole (MMI) control hyperthyroidism similarly, PTU is a first-line drug for the treatment of fetal hyperthyroidism, and its use as the initial treatment is preferred, because MMI causes a series of malformations when it is used during the first trimester [32]. The resolution of fetal tachycardia has been used to indicate the successful intrauterine medical treatment of fetal hyperthyroidism. Nonetheless, ATDs may expose a fetus to the risk of hypothyroidism; therefore, ATDs should be administered at low doses that maintain the fetal heart rate at 140 beats/min [8]. If the mother develops hypothyroidism during this treatment, levothyroxine (L-T_4) is added, because very little T_4 is transferred across the placenta.

A hyperthyroid fetus that required urgent treatment and was administered potassium iodide in combination with ATDs has been described with favorable results [19]. Potassium iodide acutely

Table 1
Intrauterine magnetic resonance imaging for fetuses with goiters, 2000–2018.

Reference	Maternal thyroid disease	Antithyroid drugs	Maternal thyroid status	GA at MRI (weeks)	Signal intensity		Fetal thyroid status	Comments
					T1-weighted image High	T2-weighted image Iso		
Miyata, et al. [17]	GD	Yes	Hyper	36	N/A	High	Hypo	
Harreld, et al. [18]	GD	Yes	N/A	34	High	Low	N/A	
Matsumoto, et al. [19]	GD	Yes	Euthyroid	34	N/A	High	Hyper	
Kanai, et al. [20]	GD	Yes	Euthyroid	36	High	Low	Hypo	
Oguma, et al. [21]	GD	Yes	Hyper	32	High	Low	Hypo	
Overcash, et al. [22]	Hypo	No	Hypo	29	N/A	High	N/A	
Matsumoto, et al. [23]	No	No	Euthyroid	29	High	N/A	Hypo	
Kondoh, et al. [15]	No	No	N/A	32	High	High	Hypo	
Ohira, et al. [24]	No	No	Hypo	28	N/A	High	Hypo	Maternal TSBAb
Miyamoto, et al. [25]	No	No	Euthyroid	37	High	High	Hypo	Maternal iodine excess
Inoue, et al. [26]	No	No	Euthyroid	29	High	High	Hypo	
Neto, et al. [27]	No	No	Euthyroid	34	N/A	High	N/A	

GA: gestational age; MRI: magnetic resonance imaging; GD: Graves' disease; N/A: not available; Hypo: hypothyroidism; Hyper: hyperthyroidism; Iso: isointense; TSBAb: thyroid stimulation-blocking antibody.

Table 2

. Previous cases of fetal goiter in maternal Graves' disease treated with intraamniotic thyroxine administration.

Reference	Maternal ATD and dose (mg/day)	GA at diagnosis of fetal goiter (WGA)	Fetal blood thyroid function at treatment completion			ATDs reduction	Intraamniotic LT$_4$ administration				Goiter reduction	Complication	GA at birth (WGA) and delivery mode	Birth weight (g)	Birth asphyxia	Respiratory distress	Neonatal blood thyroid function at birth			Developmental delay
			TSH (mIU/L)	Free T$_4$ (pmol/L)	Total T$_4$ (nmol/L)		GA at initiation (WGA)	Dose (μg/dose)	Frequency	Interval (week)							TSH (mIU/L)	Free T$_4$ (pmol/L)	Total T$_4$ (nmol/L)	
Weiner, et al. [34]	PTU, 400	30	N/A	N/A	N/A	Yes	34	200	1	–	Yes	No	36, CS	2891	No	Yes (TTN)	17.9	N/A	100	N/A
Davidson, et al. [9]	PTU, 450	28	25	N/A	41	Yes	35	250	3	1	Yes	No	38, VD	2960	No	No	15.8	N/A	81	No
Noia, et al. [36]	PTU, 200	26	17	N/A	62	N/A	36	250	1	–	Yes	No	Term, VD	3639	No	No	2.8	24.4	188	No
Van Loon, et al. [37]	PTU, 600	33	>50	3.5	N/A	Yes	33	250	4	1	Yes	No	39, VD	3090	No	No	15	8.8	N/A	No
Hadi, et al. [38]	PTU, 600	31	32	N/A	45	Yes	33	250	3	1	Yes	No	37, VD	2980	No	Yes	15	N/A	116	No
Hadi, et al. [38]	PTU, 300	27	25	N/A	37	Yes	29	230	4	1	Yes	Preterm birth	33, VD	2210	No	No	17	N/A	103	No
Nicolini, et al. [39]	PTU, 300	24	1640	1	N/A	Yes	25	600	5	1–6	Yes	No	38, VD	1830	No	No	96.5	N/A	145	No
Bruner, et al. [40]	PTU, 100	28	378	3.2	<16	Yes	29	250–500	5	1	Yes	Preterm birth	35, VD	2413	No	No	Normal	Normal	Normal	No
Bruner, et al. [40]	PTU, 150	31	324	N/A	<16	Yes	32	250	1	–	Yes	Preterm birth	32, CS	1723	No	No	N/A	N/A	N/A	No
Maragliano, et al. [41]	PTU, 250	31	15,74	6	N/A	Yes	34	250–500	2	2	Yes	No	39, CS	2650	No	No	<0.1	11.8	N/A	No
Okumura, et al. [42]	PTU, 300	25	98.65	11.6	N/A	Yes	32	250	2	3	Yes	No	39, VD	2630	No	No	Normal	Normal	Normal	No
Yanai, et al. [43]	PTU, 200	29	38	9.8	N/A	Yes	29	200	3	1	Yes	No	36, VD	3000	No	No	Normal	Normal	Normal	No
Nath, et al. [44]	PTU, 100	23	23.61	N/A	N/A	Yes	30	500	2	2	Yes	No	36, CS	N/A	No	No	Normal	Normal	Normal	No
Miyata, et al. [17]	PTU, 300	36	99	3.7	N/A	No	37	300	2	1	Yes	No	38, CS	3042	No	No	33	18	N/A	No
Lassen, et al. [45]	MMI, 30	31	29.9	10.7	N/A	Yes	32	70 μg/kg/EFW	4	1	Yes	No	36, CS	2880	No	Yes (RDS)	8.3	14.2	N/A	No
Corral, et al. [6]	PTU, 300	24	480	1.8	18.5	Yes	34	500	4	1	Yes	No	37, CS	3500	No	No	26	18	149	Yes
Koyuncu, et al. [46]	PTU, 200	30	69.9	5.9	N/A	No	30	250	1	–	No	Preterm birth	30, CS	1200	Yes	Yes (RDS)	39.2	10.7	N/A	No
Bliddal, et al. [47]	PTU, 200	23	>200	3.4	N/A	Yes	23	50–100	6	1	Yes	No	40, VD	4100	No	No	5.4	N/A	N/A	No
Bliddal, et al. [47]	MMI, 20	21	34.5	13.8	N/A	Yes	25	55–150	2	1	Yes	No	40, CS	3630	No	No	0.7	40.4	N/A	No
Munoz, et al. [48]	PTU, 600	23	N/A	N/A	N/A	No	29	200–400	2	4	Yes	Preterm birth FGR	35, CS	1880	No	No	N/A	N/A	N/A	No
Kim, et al. [49]	Radioactive	30	390	6.7	N/A	–	30	200–400	2	1–4	Yes	No	38, VD	2495	No	No	11.8	17.9	N/A	No
Kobayashi, et al. [50]	PTU, 150	32	97.8	6.1	N/A	Yes	35	300	2	1	Yes	No	37, CS	3224	No	No	42.5	17.9	N/A	No

ATD: antithyroid drug; GA: gestational age; WGA: weeks of gestation; TSH: thyroid-stimulating hormone; T$_4$: thyroxine; LT$_4$: levothyroxine; PTU: propylthiouracil; MMI: methimazol; N/A: not available; EFW: estimated fetal weight; FGR: fetal growth restriction; CS: cesarean delivery; VD: vaginal delivery; TTN: transient tachypnea of the newborn; RDS: respiratory distress syndrome. Reference ranges of fetal thyroid function according to Thorpe-Beeston et al. are: TSH: 2–12 mIU/L; Free T$_4$: 5.1–27 pmol/L; T$_4$: 15–125 nmol/L [24]. Reference ranges of neonatal thyroid function according to Fisher are: TSH: 1–39 mIU/L; free T$_4$: 28–68 pmol/L; T$_4$: 142–277 nmol/L [10].

inhibits hormonal secretions within hours of its administration to hyperthyroid patients, and there are few side-effects. However, additional fetal monitoring is advised, because administering iodine to mothers may cause fetal and neonatal hypothyroidism and goiters [32]. Beta-adrenergic blocking agents, including propranolol, can be used in severe cases. As most symptoms of fetal thyrotoxicosis, including tachycardia, are mediated by increased adrenergic responses, beta-blockers can ameliorate these symptoms within a few hours of their administration; however, their use requires caution because of their adverse effects, including FGR, prolongation of labor, neonatal bradycardia, hypotension, hypoglycemia, and prolonged jaundice [32].

Treatment of fetal goitrous hypothyroidism

The treatment of fetal goitrous hypothyroidism requires optimization of the maternal thyroid status, which includes reducing or discontinuing treatment with ATDs [3], followed by conservative management involving neonatal administration of L-T_4 [9,14]. In contrast to fetal hyperthyroidism, fetal hypothyroidism cannot be treated by administering L-T_4 to the mother because the placental transfer of maternal T_4 is minimal [9]. Hence, fetal hypothyroidism can only be treated by directly administering thyroid hormone to the fetal blood vessels or muscles, or to the amniotic fluid. Injecting the fetus itself is associated with the risk of injury and may require several puncture attempts. Injecting L-T_4 intra-amniotically represents a safer and simpler management option compared with other methods, and it has a long treatment interval [33]; the fetus swallows and ingests the L-T_4, and the fetal thyroid function normalizes as a consequence of the higher serum L-T_4 levels and reduced TSH levels, which may be beneficial to the developing fetal brain [9]. The simultaneous decrease in the size of the goiter should reduce the obstetric risks at delivery [33]. To our knowledge, the first case of intra-amniotic L-T_4 injections associated with maternal ATD overtreatment was reported in 1980 [34]. Since then, several intra-amniotic L-T_4 injections have been performed; however, most data that describe the prenatal treatment of fetuses with goitrous hypothyroidism are from anecdotal case reports. The findings from one retrospective cohort study of 12 patients with fetal goitrous hypothyroidism support the benefits associated with reducing goiter sizes [35]; however, only two of the patients in this study had normal serum T_4 levels at birth. The findings from a recent systematic review showed that six of 22 neonates (27%) had hypothyroidism after prenatal maternal ATD dose reductions and intra-amniotic L-T_4 injections [3]. Hence, this effective treatment does not always prevent hypothyroidism after birth.

Unanswered questions remain that include when treatment should begin, L-T_4 dosing, and the interval and frequency of administration. As few pharmacokinetic data portray the fetal uptake and absorption of L-T_4 from the amniotic fluid, different treatment regimens have been described. Table 2 summarizes 22 case reports that describe intra-amniotic L-T_4 injections for fetal goitrous hypothyroidism in maternal GD [6,9,17,34,36–50]. The median (interquartile range) dose, frequency, interval, and gestational age at the initiation of therapy were 250 (128–350) μg, 3 (2–4) times, 1 (1–2) weeks, and 32 (29–34) weeks of gestation, respectively. The critical gestational age at which therapy must be initiated should be determined clinically by balancing the risk of not treating the condition against the risk of prematurity at that gestational age. While some clinicians believe that the hormonal deficiency should be corrected quickly to prevent negative effects on the fetal brain and have initiated treatment at as early as 20 weeks of gestation, other clinicians have initiated treatment at as late as 37 weeks of gestation [9,33]. Regarding the fetal outcomes, intra-amniotic L-T_4 injections

reversed the laboratory evidence that indicated hypothyroidism, resolved the fetal goiters, and prevented asphyxia and respiratory distress in all except one of the patients. Moreover, all except one of the patients grew and developed normally after birth, but the follow-up period was no more than 4 years. Whether prenatal L-T_4 treatment improves neurodevelopmental outcomes remains a matter of debate. In this series, most of the patients did not experience any adverse events, but two babies were born prematurely and chorioamnionitis occurred in one patient. Another publication describes preterm labor, FGR, chorioamnionitis, and fetal death following intra-amniotic L-T_4 injections [14]. Moreover, a T_4 overdose may cause fetal thyrotoxicosis.

As a possible alternative, intra-amniotic L-tri-iodothyronine (L-T_3) injections given either alone or in combination with L-T_4, have been administered successfully [33,51]. As the effects of L-T_3 on the fetus begin within 4–8 h of its administration, intra-amniotic L-T_3 injections may reduce the size of the goitrous mass faster and at a lower dose than L-T_4 injections. On the other hand, more frequent intra-amniotic L-T_3 injections may be required to maintain a consistent effect because the half-lives of L-T_3 and L-T_4 are 1–2 days and 6–7 days, respectively [33]. The optimal dosing regimen for L-T_3 remains unclear.

Limited literature reviews have evaluated the different administration routes for L-T_4, including umbilical cord injections or fetal intramuscular injections [6,52]. These methods should be considered for a patient whose ability to swallow is critically impaired, because the goitrous mass is causing extreme pressure on the esophagus. The wide variety of approaches to treatment exemplifies the lack of guidelines, and no systematic studies have been undertaken to date.

Peripartum management of fetal goiter

The major problem regarding fetuses with goiters is how to manage their delivery when intrauterine treatment fails; however, there has been no generally accepted strategy for the management of childbirth. As the peripartum prognosis is mainly related to the risk of dystocia at delivery as a consequence of cervical deflection in such cases, cesarean delivery is highly recommended [48]. In all cases, the pediatric team must be informed of the goiter diagnosis to optimize the prevention of potential serious perinatal mechanical complications.

For a patient in whom a fetal goiter may be causing airway obstruction, a cesarean delivery with ex utero intrapartum treatment (EXIT) should be considered. This procedure permits access to the fetal airway via intubation, laryngoscopy, or bronchoscopy, and, eventually, tracheostomy while the fetus remains under placental support, and can prevent respiratory insufficiency after birth, and it has significantly reduced the mortality of patients with large neck masses [53]. However, to the best of our knowledge, only eight cases involving EXIT for fetal goiter have been reported to date, although the detailed clinical course in each case was not described (Table 3) [54–61]. Meanwhile, EXIT is accompanied by difficulties associated with preserving an adequate blood flow through the umbilical cord, protecting the placenta, and avoiding uterine contractions to ensure that there is sufficient time to establish an airway. Although there have been few fetal complications directly related to EXIT, the partially delivered fetus should be directly monitored with pulse oximetry and continuous echocardiography to detect fetal bradycardia and decreased myocardial contractility [53]. Regarding maternal complications, an important concern is bleeding, which is usually associated with uterine atony, related to the administration of high-dose tocolytic drugs or excess time spent establishing the fetal airway during the procedure [62]. Therefore, careful coordination among a multidisciplinary team that includes

Table 3
. Reported cases in which the ex utero intrapartum treatment procedure was performed in fetus with goiter.

Reference	Maternal thyroid disease	Cause of fetal goiter	Intrauterine treatment	Gestational age at delivery (weeks)	EXIT procedure	Time to airway	Apgar score (1 min/5 min)	Maternal or neonatal complication	Neonatal outcome
Klee, et al. [54]	Graves' disease	Hypothyroidism	Intraamniotic T_4 injection	38	Endotracheal intubation	N/A	8 / 9	No	Alive
Fink, et al. [55]	Graves' disease	N/A	No	36	Endotracheal intubation	9 min	3 / 8	N/A	Alive
Harreld, et al. [56]	Graves' disease	Hypothyroidism	No	36	N/A	N/A	3 / 8	Stridor in the neonate	Alive
Sriram, et al. [57]	Unknown	Hypothyroidism	No	37	Endotracheal intubation	N/A	N/A / 8	No	Alive
Niiya, et al. [58]	Unknown	Hypothyroidism	No	35	Endotracheal intubation	6 min	N/A	No	Alive
Whited, et al. [59]	N/A	N/A	N/A	36	Endotracheal intubation	9 min	N/A	No	Alive
Scott, et al. [60]	N/A	N/A	N/A	34	N/A	N/A	N/A	No	Alive
Kornacki, et al. [61]	Unknown	Hypothyroidism	Intraamniotic T_4 injection	37	Endotracheal intubation	N/A	9 / 9	No	Alive

EXIT: ex utero intrapartum treatment; N/A: not available; T_4: thyroxine.

obstetricians (usually perinatologists), neonatologists, pediatric surgeons, otolaryngologists, and anesthesiologists is required to achieve successful outcomes from EXIT [53].

An innovative alternative to EXIT is fetal endoscopic tracheal intubation. The procedure involves fetal tracheoscopy and the subsequent insertion of an intrauterine orotracheal cannula under ultrasound guidance. This procedure ensures fetal tracheal permeability before delivery. However, to date, only two publications describe this new procedure that was performed on patients with large neck masses but not goiters [63,64].

Summary and recommendations

The potential morbidity and mortality associated with a fetal goiter warrants a complete evaluation of the fetal thyroid status. This can be achieved through a combination of imaging methods, such as ultrasound examinations, which include color Doppler imaging, and MRI, and cordocentesis or amniocentesis to measure the fetal thyroid hormone levels. However, the thyroid hormone levels in the amniotic fluid may not accurately reflect fetal thyroid function. Regarding the treatment of fetal goitrous hypothyroidism, administering thyroid hormone intra-amniotically shrinks goiters and results in good developmental outcomes. In addition, when intrauterine treatment fails and a fetal goiter causes airway obstruction, intrapartum management, including EXIT, is required; however, no guidelines are available currently. A large-scale, well-designed study is necessary for monitoring therapeutic efficacy and long-term prognosis. For now, intrauterine and intrapartum treatments should be reserved for selected patients who are at a high risk of complications, and they should only be conducted by physicians with experience in intrauterine and peripartum care and related procedures.

Disclosure statement

The author has no conflicts of interest to declare.

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