Management of Graves’ disease during pregnancy: the key role of foetal thyroid gland monitoring

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ABSTRACT

Background. Foetuses from mothers with Graves’ disease may experience hypothyroidism or hyperthyroidism due to transplacental transfer of antithyroid drugs (ATD) or anti-thyrotropin receptor antibodies, respectively. Little is known about the foetal consequences. Early diagnosis is essential to successful management. We investigated a new approach of the foetal diagnosis of thyroid dysfunction and validated the usefulness of foetal thyroid ultrasonograms.

Methods. 72 mothers with past or present Graves’ disease and their foetuses were monitored monthly from 22 weeks of gestation. Foetal thyroid size and Doppler signals and foetal bone maturation were determined on ultrasonograms, and thyroid function was evaluated at birth. Thyroid function and ATD dosage were monitored in the mothers.

Results. The 31 foetuses whose mothers were anti-thyrotropin receptor antibodies negative and took no ATDs during late pregnancy had normal test results. Of the 41 other foetuses, 30 had normal test results at 32 weeks; 29 were euthyroid at birth and 1 had moderate hypothyroidism on cord blood tests. In the remaining 11 foetuses, goiter was visualized by ultrasonography at 32 weeks, and foetal thyroid dysfunction was diagnosed and treated; there was one death, in a late referral, and 10 good outcomes with normal or slightly altered thyroid function at birth. The sensitivity and specificity of foetal thyroid ultrasound at 32 weeks for the diagnosis of clinically relevant foetal thyroid dysfunction were 92% and 100%, respectively.

Conclusion. In pregnant women with past or current Graves’ disease, ultrasonography of the foetal thyroid gland by an experienced ultrasonographer is an excellent diagnostic tool. This tool, in conjunction with close teamwork among internists, endocrinologists and obstetricians, echographists and paediatrician, can ensure normal foetal thyroid function.

Keywords (MeSH)
Prenatal treatment, Foetal medicine, Graves' disease, Ultrasonography, Pregnancy
INTRODUCTION

Graves' disease is present in about 0.2% of pregnancies. Neonatal hyperthyroidism has been extensively studied, although clinical hyperthyroidism seems to occur in only 1% of neonates born to mothers with Graves' disease (1, 2, 3, 4, 5). The relative abundance of information available on neonates contrasts sharply with the paucity of data on the foetal effects of maternal Graves' disease. Evidence indicates a need for moving diagnostic efforts from the neonatal to the foetal period, to prevent foetal death or permanent neurological impairment (6, 7, 8, 9). Foetal thyroid dysfunction precedes neonatal hyperthyroidism (2, 3, 9, 10, 11). The foetal thyroid gland starts secreting thyroid hormones around week 12 of development, and foetal thyroid-stimulating hormone (TSH) receptors become responsive to TSH and to TSH-receptor antibodies around week 20 (10). Whereas maternal thyroxine usually crosses the placenta in only minimal (but crucial for foetal development) amounts and TSH not at all, maternal TSH-receptor antibodies freely cross the placenta and can cause overstimulation of the foetal thyroid gland during the second half of pregnancy (11). As antithyroid drugs (ATDs) cross the placenta, administration of ATDs to the mother improves the foetal and neonatal prognosis (8, 9, 12, 13, 14, 15, 16, 17). However, ATDs administration to the mother can also jeopardize foetal development by inducing foetal hypothyroidism.

Few data on foetal abnormalities and outcomes are available to internists, endocrinologists and obstetrician for devising guidelines on the management of pregnant women with Graves’ disease (18). Published guidelines deal both with managing Graves’ disease in the woman and with predicting the risk of neonatal thyrotoxicosis. The objective of the present study was to assess foetal ultrasonography as a non-invasive tool for detecting foetal thyroid dysfunction, determining the appropriate treatment, and monitoring treatment.
effects during pregnancy in patients with active or treated Graves’ disease. The pregnant women were included and monitored prospectively by a multidisciplinary hospital team.

PATIENTS AND METHODS

We prospectively included 72 pregnant women (72 foetuses) managed between 1999 and 2002 at the Robert Debré Teaching Hospital in Paris, France, and not included in our previous study (17). The inclusion criterion was a past or current history of Graves' disease diagnosed by an endocrinologist based on clinical and laboratory test evidence of hyperthyroidism with goiter, Graves' ophthalmopathy or dermopathy, and at least one positive test for TSH-receptor antibodies (19, 20). Patients were not selected on thyroid function, disease activity, or history of thyroidectomy or ATD therapy. They were included as soon as possible during their pregnancy, without exclusion criteria. A single-centre design was chosen because all foetal sonograms are done by the same person (EV) at the Robert Debré Teaching Hospital.

In each woman, thyroid function tests and radioreceptor assay for TSH receptor antibodies (TRAK assays) were done monthly from study inclusion to delivery. The treatment and in particular the ATD therapy, was adjusted by the endocrinologist, for FT4 to be maintained at the upper limit of the normal range of pregnant women (our own data on 102 such women). Therefore FT4 levels did not differ significantly between the two groups of pregnant women (see below) nor between women with and without history of thyroidectomy. Once a month starting at 22 weeks gestation (WG), foetal heart rate (FHR) was recorded and a foetal ultrasound scan was done for measurements of thyroid gland size (diameter and circumference) (figure 1a), determination of foetal growth parameters, and evaluation of foetal bone maturation. A Hitachi EVB 525 variable-focus ultrasound machine with a 3.5 MhZ sector transducer was used for all foetal sonograms.
Foetal goitre was defined as a thyroid circumference equal or superior to the 95th percentile for gestational age, according to the normative data established by Ranzini et al. (21) and to our own unpublished normogram established by EV in 250 patients, which is consistent with Ranzini’s curves (data not shown). When foetal goitre was found, colour flow Doppler of the thyroid was performed as previously described with a velocity of 13 cm/s (17,22): a Doppler signal throughout the gland was considered suggestive of foetal hyperthyroidism and a Doppler signal confined to the periphery of the gland of foetal hypothyroidism (figure 1b, 1c) (17, 22).

Bone maturation was evaluated on the sonogram obtained at 32 WG. Normally, the distal femoral ossification center is undetectable before 28 WG, dot-like around 32 WG, smaller than 3 mm before 33 WG, and consistently visible after 35 WG. Accelerated bone maturation was defined as presence of the distal femoral ossification centre before 31 WG and delayed bone maturation as absence of the centre after 33 WG (23).

Foetal tachycardia was defined as a FHR continuously greater than 160 beats per minute (24).

TSH, free triiodothyronine (FT3), and free thyroxine (FT4) were measured using a chemiluminescence immunoassay with the ACS-180SE system (Bayer Diagnostics, Westwood CA, USA). The values were interpreted according to gestational age or postnatal age (25). TSH-receptor antibodies (TRAK) were measured by radioimmunological assay with second-generation antibodies (RIA-2 Dynotest TRAK human, B.R.A.H.M.S Diagnostica GmbH, Berlin, Germany) (19). A positive result (TRAK+) was defined as an antibody titre greater than 2 U/L. The results are reported as multiples of the upper limit of normal (ULN). TRAK assay results and ATD treatment were used to divide the mothers into two groups. The high-risk group, in which the foetuses were considered at risk for thyroid dysfunction, comprised the mothers with at least one positive TRAK assay (TRAK+) (20) and/or ATD
treatment in the third trimester of pregnancy. The low-risk group was composed of mothers with consistently negative TRAK assays (TRAK-) and no ATD treatment, indicating a low risk for foetal thyroid dysfunction (26). The thyroid function did not differ between the two groups of mothers showing the adequate ATD and/or thyroxine treatment in those treated (see below).

In neonates with a gestational age at birth of 36 weeks or more, normal ranges for cord blood values were defined as follows: FT4, 10.4-16.4 pmol/L, and TSH, 2.6 to 11.8 mU/L (25). Hypothyroidism was defined as an FT4 level under the 2.5th percentile and aTSH value greater than the 97.5th percentile. Hyperthyroidism was defined as an FT4 value greater than the 97.5th percentile and a TSH value under the 2.5th percentile. FT3 levels in cord blood are normally very low and consequently unhelpful for diagnosing hypothyroidism, although they can assist in the diagnosis of hyperthyroidism. We therefore used only cord blood FT4 and TSH for diagnosing foetal thyroid dysfunction.

Decisions to perform foetal blood sampling (FBS) were based on the treatment in the mother, Doppler signal pattern, and TRAK positivity; maternal consent was required before the procedure. FBS was not performed when the results of other tests discriminated between hypothyroidism and hyperthyroidism or when the pregnancy was sufficiently advanced to allow induction of labour within a reasonable period (27).

Once the type of foetal thyroid dysfunction was determined, the treatment consisted of an ATD dosage increase when the diagnosis was foetal hyperthyroidism (with maternal levothyroxine therapy if needed) and of ATDs withdrawal or dosage reduction when the diagnosis was foetal hypothyroidism, as permitted by the maternal endocrine status. When early-onset foetal hypothyroidism was diagnosed, intra-uterine intra-amniotic levothyroxine
was administered by amniocentesis, as previously described (17). Of note this approach has been used sparingly and should only be discussed in team used to this type of prenatal care.

At delivery, cord blood was retrieved for thyroid function tests, the newborn was examined by a paediatric endocrinologist, and ultrasonography of the thyroid gland was performed (28).

This study was approved by the Paris-Saint Louis Ethics Committee for Biomedical Studies in Humans, on 2 November 1998, and was conducted in compliance with French law. Written informed consent was obtained from the pregnant women.

RESULTS

Description of the cohort of women with Graves' disease (n=72)

Mean age in the overall population was 33 years (range, 26-43 years). Gestational age at inclusion was 17 WG (range 10-28 WG). Of the 72 women, 41 were in the high-risk group and 31 in the low-risk group. Details are given in table 1. Overall, 45 women received no treatment or only levothyroxine (LT4) and 27 received ATD therapy (with or without LT4). Of the 41 high-risk women, 33 had at least one positive TRAK assay during the pregnancy and 8 took ATD therapy during the last trimester but had consistently negative TRAK tests; these 8 patients were treated because of recent onset or exacerbation of Graves' disease, in keeping with the widely recognized need for giving ATD therapy for 18 months and not more(20). Of the 26 women with a history of total (n=3) or subtotal (n=23) thyroidectomy, 9 (34%) had at least one positive TRAK test during their pregnancy
Foetal thyroid function and its relation to maternal thyroid function:

In the low-risk group (n=31), foetal sonograms showed no evidence of goitre. Cord blood thyroid function tests were normal at delivery in all 31 neonates. Thyroid dysfunction did not develop in any of these neonates during the first postnatal month (Figure 2).

In the high-risk group (n=41), 11 of the 41 foetuses had ultrasonogram evidence of goitre at 32 WG and, consequently, were evaluated for thyroid dysfunction (Figure 2). The results showed hypothyroidism in 7 foetuses and hyperthyroidism in 4 foetuses at 32 WG (Table 2). Foetal hypothyroidism was usually associated with low maternal TRAK titres and/or high ATD dosages (≥150 mg/day of propylthiouracil, ≥15 mg/day of methimazole, or ≥100 mg/day of benzylthiouracil), and/or delayed foetal bone maturation. The Doppler signal was positive throughout the foetal thyroid gland in two cases and at the periphery of the gland in four cases; it was not detected in one case and was not documented in one case. Delayed bone maturation was noted in two of these seven foetuses. Foetal blood was obtained in four cases for thyroid function tests, which confirmed the diagnosis of foetal hypothyroidism. The ATD dosage was reduced in all seven cases, and levothyroxine was injected into the amniotic fluid in three foetuses after confirmation of hypothyroidism by foetal blood sampling. In one case (Case 4 Table 2), FBS was not performed because the low TRAK level led us to postulate that the foetus had hypothyroidism. This prompted us to decrease the ATD dose. This appeared subsequently to be right because followed by a decrease in the thyroid size two weeks later. Indeed following treatment, sonograms done at 2-week intervals consistently showed a decrease in the size of the thyroid gland; in two cases, the size returned to normal.

The thyroid function did not differ between the low-risk and high-risk groups of mothers. In the low risk group, mean (± SD) FT4 and FT3 levels (pmol/l) were respectively during the
third trimester $12.4 \pm 1.3$ and $4.1 \pm 0.3$ not different from the high risk group with FT4 and FT3 of $13.9 \pm 2.5$ and $4.8 \pm 1.1$. Even the maternal FT4 and FT3 of the three women with foetuses with the more severe hypothyroidism (see table 2) did not differ from those of the others women of the high risk group (Mean of the third trimester: FT4: 12.2 and FT3: 4.1 for case 1 , FT4: 11.2 and FT3: 3.9 for case 5 , FT4: 15.3 and FT3: 5.2 for case 7 (Table 2)). However at the precise time of FBS and ultrasonography, FT4 and FT3 were as follows in those three women: FT4: 8.6 and FT3: 3.2 for case 1 , FT4: 9.7 and FT3: 3.9 for case 5 , FT4: 16.1 and FT3: 5 for case 7 (Table 2).

At birth, cord blood tests showed normal FT4 levels in six babies and a borderline low FT4 in one (Table 2). Within the first postnatal week, hyperthyroidism requiring ATD therapy developed in three of these seven neonates (Table 2, upper part). The mothers of these seven foetuses had normal thyroid function.

Foetal hyperthyroidism ($n=4$) was usually associated with high maternal TRAK titres and/or accelerated foetal bone maturation. The Doppler signal was positive throughout the foetal thyroid gland in all four cases. Advanced bone maturation was noted in two foetuses. In two cases, after a multidisciplinary evaluation, foetal blood tests were performed and confirmed the diagnosis, showing a very high T4 value (51.7 pmol/L) and a minimally elevated one (14.8 pmol/L but a high T3 (7.5 pmol/L) value in this case) and both cases with a low (<0.05 mU/L) TSH (Table 2 and its legend). The ATD dosage was increased in all four mothers. The size of the foetal thyroid gland decreased within the next two weeks; it returned to normal in one foetus. However, one foetus died in utero at 35.5 WG from congestive heart failure with cardiomyopathy. This was a late-referred case with very high TRAK values and a pre-existing foetal goitre as shown by a positive central Doppler flash at 22 WG. ATD therapy was increased up to 60 mg of methimazole per day, to no effect. FBS confirmed the diagnosis
of severe hyperthyroidism, and the foetal blood TRAK titre was massively elevated (320 N). Of the three surviving foetuses, one had normal cord blood thyroid function tests at birth with no subsequent hyperthyroidism, one had normal FT4 with low TSH at birth, and one had cord blood values indicating mild low FT4 with normal TSH, which resolved spontaneously without treatment after clearance of the maternal ATD (Table 2). Within the first postnatal week, hyperthyroidism requiring ATD therapy developed in two of these three neonates (Table 2, lower part). Of the four mothers, two had hyperthyroidism and two had normal thyroid function.

The remaining 30 foetuses in the high-risk group had no goitre and consequently were not considered at risk for thyroid dysfunction (Figure 2). All had normal thyroid values in cord blood at delivery except one neonate who had moderate hypothyroidism (FT4=9.6 pmol/L and TSH=20.6 mU/L) that resolved spontaneously without treatment. Retrospectively, this case could have been detected, as a peripheral colour Doppler signal was noted at 38 WG, when thyroid gland size parameters were at the upper limit of normal.

Based on the values of the thyroid cord blood testing at delivery and the therapeutic interventions in the treated foetuses the sensitivity and specificity of foetal thyroid ultrasound at 32 WG in screening for clinically relevant (leading to therapeutic action) foetal thyroid dysfunction were 92% and 100%, respectively (Table 3). This clearly indicates a major role for foetal thyroid ultrasonography in diagnosing foetal thyroid dysfunction.

DISCUSSION

Foetuses and neonates born to mothers with Graves' disease are at risk for thyroid dysfunction if the mother tests positive for TSH-receptor antibodies (TRAK+) and/or takes ATD therapy during the pregnancy. The first major finding from our study is that foetal
function was normal before and after birth in the offspring from the 31 low-risk women. These women had negative TRAK tests throughout pregnancy and took no ATDs during the last trimester of pregnancy, indicating resolution of the Graves’ disease; some of these women were taking LT4, usually because of a history of thyroidectomy. In contradiction with the European Thyroid Association guidelines, this result highlights the importance of TRAK determination in pregnant women with Graves’ disease (18) and shows that no special care is required when TRAK tests are negative. Furthermore, 9 (34%) of the 26 patients with a history of thyroidectomy were TRAK+, indicating that TRAK assays should be done in this patient subgroup, at least at the beginning of the pregnancy. This later point is in line with the European Thyroid Association recommendations (18).

Propylthiouracil was the most widely used ATD among the women who took ATD therapy during pregnancy. This drug is currently preferred over methimazole based on its lower teratogenic potential, even if its limited transplacental passage has been shown to be similar to that of methimazole in in vitro assay using the isolated perfused placenta lobule (29). Indeed methimazole given during organogenesis has been reported to cause aplasia cutis and tracheo-oesophageal fistula as well as a characteristic embryopathy (30, 31).

The second important finding from our study is that 11 (27%) of the 41 foetuses from high-risk mothers had a goitre by foetal ultrasonography. Normograms for foetal thyroid size were published by Ranzini et al in 2001 (21) and validated in our setting in 250 euthyroid pregnant women (our own unpublished data), thus allowing a precise diagnosis of foetal goitre. Monthly foetal thyroid ultrasonograms ensured the detection of all cases of foetal goitre and therefore of all cases of clinically significant (requiring therapeutic modifications) thyroid dysfunction, with 100% specificity. Indeed it has been published that, at birth, several offspring’s of mothers with Graves’ disease treated by ATD had transient elevated TSH levels, and no goitre (32,33). However no neonatal thyroid ultrasound was performed and
therefore the presence of a subtle thyroid enlargement can not be ruled out fully (32,33). Moreover, this technic can be acquired by ultrasonographists therefore allowing its widespread use. Nachum et al. (34) recently reported data from 18 women managed over a period of ten years. In these patients, foetal blood sampling was extensively practiced even in the absence of foetal goitre and occasionally revealed foetal thyroid dysfunction. This discrepancy with our results can be explained by the fact that foetal sonograms were less standardized in the study by Nachum et al. Our data establish that fetal blood sampling is unnecessary in the absence of a foetal goitre. Similarly, Kilpatrick (35) stated that isolated high TRAK titres are not sufficient to recommend routine FBS. In a series of 20 women including 5 with goitre in the foetus, Cohen et al. (36) also obtained convincing evidence that ultrasonography is an effective non-invasive screening tool for detecting foetal goitre. However, they did not assess maternal TRAK titres, so that the interpretation of foetal goitre in their study is difficult.

In foetuses with goitre, the main clinical problem was to determine whether the cause was maternal treatment, adequate to have normal maternal thyroid function but inadequate and excessive for the foetus and therefore responsible for foetal hypothyroidism or foetal thyroid stimulation by maternal Graves’ disease IgGs responsible for foetal hyperthyroidism. It is generally agreed that foetal FT4 levels correlate with maternal FT4 levels and that foetal euthyroidism can be achieved by maintaining maternal FT4 in the upper normal to mildly thyrotoxic range during antithyroid drug treatment. This fact is underlined by the present results as maternal FT4 levels in the three cases with extremely severe hypothyroidism were in the normal range in case 7 (table 2) and in the lower normal range in the two others (case 1 and 5 of table 2). Therefore in these two last cases maternal FT4 level may have also help us in the diagnosis of the foetal hypothyroidism.
Nevertheless we mainly used a combination of the following maternal criteria (TRAK titre and ATD use and dosage) and foetal criteria (thyroid Doppler signal, FHR, and bone maturation) to distinguish between foetal hypothyroidism and hyperthyroidism. Foetal blood sampling was only discussed after patient’s agreement, and if there was a foetal goitre with no possibility to distinguish hypothyroidism and hyperthyroidism using maternal and foetal criteria. Foetal hyperthyroidism was diagnosed based on high maternal TRAK titres, accelerated foetal bone maturation, and a FHR greater than 160 bpm; this last sign was uncommon as it occurs late in the natural history of foetal hyperthyroidism. The limited usefulness of FHR for diagnosing foetal hyperthyroidism has been underlined also by Nachum et al (34). Doppler examination of the foetal thyroid gland proved useful only when the flash was confined to the periphery of the gland, a pattern suggestive of foetal hypothyroidism. The prenatal response to treatment, results of thyroid function tests on foetal blood when obtained, and cord blood at birth indicated that our criteria were effective in differentiating hypothyroidism and hyperthyroidism in all 11 foetuses with goitre.

Foetal blood was sampled from six of the 11 foetuses with goitre, and the results consistently confirmed the suspected diagnosis. Abortion, foetal bradycardia, and infection have been reported after FBS in 1% of cases (27). Consequently, FBS should be reserved for those cases in which intra-amniotic thyroxine injection is considered or the thyroid status is in doubt in a foetus whose mother has positive TRAK assays and takes ATD therapy.

Routine cord blood assays of FT4 and TSH at delivery allowed us to validate our prenatal strategy but did not help to predict subsequent neonatal thyroid dysfunction as already published (37). Indeed the remaining 30 foetuses in the high-risk group had no foetal goitre and it has to be noticed that the major evidence of the absence of foetal thyroid dysfunction is based on the results of the cord blood at birth. Normal thyroid function in utero
was not definitively demonstrated as FBS appeared to us unnecessary and therefore unethical in this group of patients.

From our data we suggest the following strategy for the care of these pregnancies that differ from that of the European Thyroid Association. It should now be validated in others data set taking into account our sample size:

- TSH-receptor antibodies should be assayed routinely when foetal thyroid function is on. For practical reasons, we believe that it can be done at the beginning of pregnancy in women with a current or past history Graves’ disease; indeed it can be performed with others screening procedures offered to pregnant women at 12-13 GA for example and the negativity of the results will avoid unnecessary further work-up.

- during pregnancy in women who are taking ATD therapy and/or who have positive tests for TSH-receptor antibodies, a foetal ultrasonogram should be done monthly after 20 WG to screen for goitre and/or other evidence of foetal thyroid dysfunction.

- during pregnancy in a woman with negative tests for TSH-receptor antibodies and no ATD treatment, the usual ultrasonograms recommended during pregnancy at 22 WG and 32 WG, in France, should be done.

- of note most of the foetal thyroid dysfunction (10 out of 11) arose in women with no history of thyroidectomy in our high risk group whereas only one case was observed in the offsprings of the 26 women who underwent thyroidectomy. Therefore the former group should be the target of careful prenatal follow-up.

In conclusion, our study shows that prenatal screening ultrasonography is a powerful tool for detecting foetal thyroid dysfunction in case of maternal Graves’ disease. Ultrasonogram monitoring of foetuses from mothers with Graves’ disease was extremely sensitive and specific for detecting intrauterine thyroid dysfunction and therefore allowed appropriate foetal management. In that it was a prospective and systematic study of fetal thyroid size, it is a new
approach which is not comparable to previous studies. This tool, in conjunction with close teamwork among internists, endocrinologists and obstetricians, echographists and pediatrician, can ensure normal foetal thyroid function. Whether this systematic monitoring makes a difference in terms of ultimate psychomotor development of the children compared to more targeted investigations remains to be demonstrated.
References

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Figure 1: Foetal thyroid and ultrasonography

Figure 1a:

Foetal thyroid gland with normal circumference and increased diameter. Note the central echo-free disc corresponding to the trachea and carotid arteries visualised by colour Doppler.

Figure 1b

Foetal goitre and hypothyroidism; peripheral flash on the colour Doppler

Figure 1c

Foetal goitre and hyperthyroidism; central flash on the colour Doppler

The measure of the foetal thyroid size has been validated and can be used in routine prenatal care. The colour Doppler is still an experimental method to be validated in more cases.
Figure 2: Ultrasonography for foetal thyroid monitoring according to maternal status and cord blood thyroid function test results

Hypot: Hypothyroidism

Eut: Euthyroidism

Hypert: Hyperthyroidism

(1): In one mother FT4 (20.2pmol/l) was at the upper limit of normal with a suppressed TSH (<0.05mUI/l), despite high maternal dose of PTU.

(2): FT4: mean of FT4 in all these newborns with one standard deviation; TSH: mean of TSH in all of these new-borns with one standard deviation)
Table 1: Treatment during pregnancy and status in TSH-receptor antibodies in the pregnant women

ATD: antithyroid drug therapy

LT4: levothyroxine

ATD + LT4: antithyroid drug therapy + levothyroxine

None: no treatment

TRAK +: positive test for TSH-receptor antibodies at least once during the pregnancy

TRAK -: negative test for TSH-receptor antibodies throughout pregnancy

41 high risk women, 33 from the TRAK+ column and 8 from the TRAK- column treated with ATDs (in bold type)

*: all but 3 were TRAK + after 20 weeks of gestation. The 3 remaining patients were TRAK + in the first trimester and TRAK – subsequently.
Table 2: Foetuses at 32 WG: 7 with hypothyroidism (upper part of the table), 4 with hyperthyroidism (lower part of the table).

TRAK: ULN (number times the upper limit of normal), Treat/day: daily treatment; Doppler + periph: peripheral signal; Doppler + total: signal throughout the thyroid gland; Foetal blood sampling: FT4 is expressed in pmol/l, TSH in mUI/l (14 pmol/l is the upper limit of our normal data (the fetus with a FT4 of 14.8 pmol/l had a FT3 of 7.5 pmol/l for a upper limit of normal of 1.9 pmol/l (25)); IALT4: intra-amniotic L-thyroxine injection; FHR: foetal heart rate; Bone: bone maturation; Cord blood: thyroid function tests on cord blood: FT4 is expressed in pmol/l, TSH in mUI/l; normal ranges for cord blood values were defined as follows: FT4, 10.4-16.4 pmol/L, and TSH, 2.6 to 11.8 mU/L (25).
Table 3: Foetal thyroid ultrasonogram in screening or foetal thyroid dysfunction

Sensitivity=92%, Specificity=100%, Positive predictive value=100%; Negative predictive value=98%. These values were calculated with our criteria at 32 WG in screening for clinically relevant (leading to therapeutic action) foetal thyroid dysfunction and based on the values of the thyroid cord blood testing at delivery and the therapeutic interventions in the treated foetuses.

TP: true positive
FP: false positive
TN: true negative
FN: false negative

(1): measured in cord blood at delivery
Figure 1a:
Ultrasonographic thyroid monitoring and thyroid function in 72 foetuses

MOTHERS

41 TRAK+ and/or ATS+

31 TRAK- ATS-

FOETUSES

30: NO GOITRE

11: GOITRE

16 mothers treated with PTU (1)

7 HYPOT.

4 HYPERT.

TREATMENT

CORD BLOOD

1 MODERATE HYPOT. (fT4: 9.6pmol/l, TSH: 20.2mUI/l)

29 EUT (fT4: 14+/−1.65 pmol/l, TSH: 9.4+/−6.5mUI/l)(2)

1 HYPOT.

6 EUT.

1 HYPOT.

1 HYPERT.

2 EUT.

1 HYPOT.

31: ALL EUT.

(fT4: 13.3+/−2.8pmol/l TSH: 7.3+/−4.4mUI/l)(2)

Figure 2
# Table 1

<table>
<thead>
<tr>
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<th>TRAK +</th>
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<tr>
<td>ATD</td>
<td>16</td>
<td>8</td>
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