Clinical Study

Maternal compound W serial measurements for the management of fetal hypothyroidism

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Abstract

Objective: The diagnosis of fetal hypothyroidism is based present on measurements of TSH and free thyroxine (FT4) in fetal blood samples obtained by cordocentesis. The measurement of maternal serum and urinary concentrations of compound W, immunologically similar to but chromatographically distinct from diiodothyronine sulfate (T2S), has been advocated as a new possible marker for fetal hypothyroidism.

Design: In this paper, we measured serum compound W levels in 84 pregnant women, 20 with and 64 without thyroid disorders before and during specific treatment. Compound W was also assessed in fetal blood obtained by cordocentesis from 49 normal fetuses and 4 fetuses with suspected hypothyroidism due to transplacental passage of propylthiouracil (PTU). Compound W levels were measured by T2S RIA in maternal and fetal serum. To assess the possible usefulness of 3,5,3\textsuperscript{-}triiodothyroacetic acid (TRIAC) for therapy of fetal hypothyroidism we evaluated the transplacental passage of TRIAC by administering the drug to four pregnant women before therapeutic abortion.

Results: In normal pregnancies, both maternal and fetal compound W levels increased progressively during gestation with a significant direct correlation \((P<0.001\), in both mothers and fetuses). Moreover, a significant positive correlation was observed between fetal compound W and fetal FT4 values \((P<0.005)\), whereas no correlation was observed between maternal serum compound W and maternal FT4 in either euthyroid or hyperthyroid women, suggesting the fetal origin of compound W. The hypothyroid fetuses of PTU-treated mothers showed low compound W levels, and maternal compound W values were in the low normal range and did not show the typical increase during progression of gestation. A significant increase of maternal compound W was observed when the PTU dose was reduced. TRIAC was documented to cross the placental barrier and the treatment of a hyperthyroid pregnant woman on PTU caused the high fetal TSH levels and goiter to normalize.

Conclusions: Serial measurements of 3,3\textsuperscript{-}T2S crosreactive materials (compound W and 3,3\textsuperscript{-}diiodothyroacetic acid sulfate) in maternal blood and the administration of TRIAC to the mother may represent a useful and safe alternative to invasive techniques for the diagnosis and therapy of fetal hypothyroidism.

Introduction

Contrary to what occurs in thyroid hormone metabolism of the adult, the sulfation pathway in the fetus plays an important role, as the levels of sulfated iodothyronines are much higher in the fetus than in the adult (1), including pregnant women (2). The reduced clearance secondary to relatively low type I 5\textsuperscript{-}monodeiodinase activity in fetal tissue and the high fetal production rate account for these high levels (3). However, the sulfated iodothyronines thyroxine (T4) and triiodothyronine (T3) cannot be used as parameters of fetal thyroid function based on maternal sampling as the levels are too low in maternal serum and no correlation has been found between fetal and maternal concentrations (4). Interestingly, in recent studies a new iodothyronine sulfate analog, named compound W, has been described (5). Compound W, which is immunologically similar to diiodothyronine sulfate (T2S), but does not co-chromatograph with synthetic T2S by HPLC, has been reported to be present in maternal serum (5) and maternal urine (6) and to increase during pregnancy.
in parallel with the progressive maturation of fetal thyroid function (7). These observations and the finding of disappearance of this material after parturition strongly suggest the fetal origin of compound W. The chemical structure of compound W is not yet clear, but the possibility that it is produced by the fetus suggests that compound W could be considered a potential marker of fetal thyroid function. The measurement of fetal thyroid hormones in amniotic fluid is not a reliable method of detecting fetal hypothyroidism because the hormone levels reflect maternal as well as fetal thyroid function (8–11). Thus, the diagnosis of fetal hypothyroidism depends on thyrotropin (TSH) and free T4 (FT4) measurements in fetal blood samples obtained by cordocentesis. However, this technique is associated with a 1% fetal loss and the risk is compounded for hyperthyroidism-complicated pregnancy when more than one cordocentesis may be necessary to evaluate fetal well-being (12).

Fetal thyroid function may be impaired by the transplacental passage of anti-thyroid drugs (13) and fetal hypothyroidism carries the risk of neurological damage despite early neonatal treatment (14). A recent report suggests that 3,5,3'-triiodothyroacetic acid (TRIAC) given to propylthiouracil (PTU)-treated hyperthyroid mothers might be useful in the treatment of fetal goiter (15). TRIAC is a thyroid hormone analog that results from the oxidative deamination and decarboxylation of the alanine side-chain of T3 and is present in low concentration in normal subjects (16). TRIAC binds to thyroid hormone receptors with an affinity higher than that of T3 (17) but with shorter duration of nuclear occupancy (18) and will reduce TSH concentrations with less pronounced thyromimetic effects at the peripheral tissue level (19). The present study was undertaken in order to investigate both the utility of compound W as a maternal serum marker of fetal hypothyroidism, and the application of TRIAC for treatment of fetal hypothyroidism.

Materials and methods

Subjects

Samples from 64 normal pregnant women and 49 normal fetuses were obtained at gestational ages ranging from 14 to 40 weeks. Fetal blood was collected by cordocentesis carried out for rapid karyotyping and diagnosis of infection or hematological disorders or during elective cesarian section. The normal fetuses included in this study were judged healthy by measurements of blood oxygenation and acid-base balance status conducted at the time of fetal sampling. Definitive confirmation of their healthy status was achieved by clinical examination at birth and during at least 2 months of follow-up. Twenty pregnant women with thyroid disorders were monitored monthly with obstetric ultrasonography, evaluation of thyroid function and measurement of serum compound W levels. Among them, eight patients were hypothyroid; two others with non-toxic nodular goiter were started or continued on T4 therapy in substitutive or TSH-suppressive doses. Ten patients were hyperthyroid and treated with PTU. Fetal blood samples were collected by cordocentesis carried out for suspected fetal hypothyroidism in four of these women and all four fetuses were found to be hypothyroid. One other hyperthyroid patient was treated with combined PTU and TRIAC (orally at the dose of 2.1–2.8 mg/day). The study protocol was approved by the Ethical Committee of our Institutions, and informed consent was obtained from each woman.

Cordocentesis

Fetal blood was sampled via cordocentesis using a 22 gauge heparinized needle guided by ultrasonography and under aseptic conditions. The reliability of fetal sampling was assessed by analysis of red cell volume with a Coulter counter and Kleihauer smears were prepared to confirm the fetal source of blood (8, 20).

Transplacental passage of TRIAC

Six pregnant women (20–25 weeks of gestation) electing therapeutic abortion for severe fetal malformations gave their informed consent to the study. TRIAC (3.5 mg orally) was administered to four women, whereas T3 (200 µg orally) was given to the other two; 46–76 min after TRIAC or T3 administration, fetal blood samples were obtained by cordocentesis carried out before the abortive operations. Serum concentrations of the analog were quantified using a fluoroimmunoassay method for free T3 (FT3) measurement which shows 100% crossreactivity with TRIAC. Placental function was documented to be normal in all women based on fetal heart rate, umbilical-artery blood flow and blood gas levels (21).

TSH and free thyroid hormone measurements

Circulating levels of TSH, FT4 and FT3 were measured by ultrasensitive immunofluorometric assay and fluoroimmunoassay, using Delfia techniques (Pharmacia, Milan, Italy). The crossreactivity of TRIAC in the FT3 assay was 100%.

T2S RIA

The T2S RIA procedure employed in this study was described previously (5). In brief, serum samples were extracted with 3 volumes 63% (final) ethanol before assay. Final values of T2S or compound W (expressed as T2S-equivalence) were not corrected for recovery. 3,3'-T2S and 125I-3,3'-T2S were prepared by the method of Eelkman-Rooda and co-workers (21). T2S was further purified and quantitatively recovered by reverse phase
HPLC with a preparative column. The RIA employed an anti-3,3'-T2S antibody obtained from rabbits immunized with 3-T2S BSA conjugate. The lower limit of detection of the assay was 5 ng/dl. The results are expressed as T2S-equivalent in ng/dl.

Identification of compound W

T2S immunoreactivity was studied in maternal and fetal serum. Greater than 0.5 ml was extracted with 2 volumes 95% ethanol and subsequently lyophilized. The dried extracts were dissolved in 1–2 ml H2O and purified using an LH-20 column as previously described. One milliliter of the solubilized extract was applied to a small LH-20 column (bed volume, 1.2 ml) equilibrated in 0.1 mol/l HCl. After rinsing the column with 4 ml 0.1 mol/l HCl, the ensuing seven H2O eluant fractions were collected and lyophilized. The dried fractions were dissolved in 500 ml 0.025 mol/l NaOH, 200 ml aliquots were applied to an HPLC Bondapak C18 column (Waters, Millipore Corporation, Millford, MD, USA), and eluates were developed isocratically with a mixture of acetonitrile and 0.02 mol/l ammonium acetate, pH 4.0 (22:78 v/v) at a flow rate of 2 ml/min. One-milliliter eluent fractions was collected, and 50 ml of these aliquots were subjected to T2S RIA. Radioactive or non-radioactive T2S-supplemented serum extracts from non-pregnant women were used to identify the T2S and compound W peaks.

One milliliter of 63% ethanol serum extract was mixed with 1 ml 1.0 mol/l HCl, followed by heating at 80°C for 1 h to hydrolyze sulfated iodothyronines, as described by Mol & Visser (22). After the addition of 1 ml 1 mol/l NaOH, the concentration of 3,3'-diiodothyronine (T2) was measured in duplicate 300 ml aliquots of the resulting mixture by specific RIA (23). On hot acid digestion of serum extracts, less than 10% of T2S immunoreactivity was recovered as 3,3'-T2.

Identification of 3,3'-diiodothyroacetic acid sulfate (DIACS)

In serum extracts from the TRIAC-treated pregnant women, a new T2S-crossreactive peak, in addition to the compound W peak, was identified by HPLC with a Bondapak C18 column eluted isocratically with acetonitrile and 0.02 mol/l ammonium acetate, pH 4.0 (22:78 v/v) (5). This new peak of activity eluted 35 min was later than the peak of compound W. This peak was not found in pregnant women who were not treated with TRIAC. 125I-3,3'-DIACS, which was synthesized from 3-monoiodothyroacetic acid (a gift from Dr Hans J Cahnmann, Bethesda, MD, USA), was found to co-chromatograph with the T2S-crossreactive peak. The extent of crossreactivity of 3,3'-DIACS and T2S is not known due to a lack of stable and pure 3,3'-DIACS for use in the T2S RIA. The HPLC identification of 3,3'-DIACS in fetal serum was not made due to inadequate sample volumes.

Statistical analysis

Data are expressed as mean ± s.d. Student’s unpaired t-test was used to assess differences among the various groups. Differences were considered statistically significant at P < 0.05. Simple linear regression analysis was used to test the correlation during different gestational ages.

Results

Compound W concentrations in fetal and maternal sera

Serum compound W concentrations in 49 normal fetuses and in 64 normal pregnant women increased progressively throughout gestation as shown in Table 1 and Fig. 1.

Table 1 Ranges and mean of fetal and maternal compound W (ng/dl) at various gestational ages in normal pregnancies.

<table>
<thead>
<tr>
<th></th>
<th>14–20 weeks</th>
<th>21–26 weeks</th>
<th>27–36 weeks</th>
<th>37–40 weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fetuses</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. samples</td>
<td>7</td>
<td>24</td>
<td>13</td>
<td>5</td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>70 ± 56</td>
<td>98 ± 34</td>
<td>138 ± 48</td>
<td>158 ± 27</td>
</tr>
<tr>
<td>Mothers</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. samples</td>
<td>10</td>
<td>28</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Range</td>
<td>27–138</td>
<td>23–159</td>
<td>53–164</td>
<td>84–194</td>
</tr>
<tr>
<td>Mean ± s.d.</td>
<td>54 ± 31</td>
<td>67 ± 29</td>
<td>90 ± 32</td>
<td>108 ± 50</td>
</tr>
</tbody>
</table>

Figure 2 shows the significant positive correlations between fetal compound W and fetal FT4 (n = 29, P < 0.003), and maternal compound W (n = 42, P < 0.0001). No significant correlations were observed between maternal compound W and fetal FT4 or compound W and fetal TSH. Moreover, no significant correlation was seen between maternal compound W and maternal FT4.

Figure 3 shows the correlation of fetal and maternal serum compound W values and maternal urine
compound W (n = 27, P < 0.05 and n = 39, P < 0.001 respectively).

Compound W concentrations in pregnant women with thyroid disorders were within the normal range for gestational age, both before and during specific treatment (Fig. 4). In fact, in eight hypothyroid mothers treated with L-T4, serum compound W increased progressively during gestation and levels were in the normal range for gestational age (Fig. 4). Similar data were found in two women treated with TSH-suppressive doses of L-T4 for non-toxic goiter (Fig. 4). The range of compound W levels in ten hyperthyroid mothers was similar to values in the euthyroid women both before and during PTU treatment (Figs 1 and 4).

Figure 5 shows the trend of compound W during gestation, assessed by serial measurements in three normal pregnant women (followed for suspected hyperthyroidism) (Fig. 5A), in six hypothyroid women treated with substitutive doses of L-T4 (Fig. 5B) and in four hyperthyroid women treated with PTU (Fig. 5C). In the last four patients, compound W, though in the normal range, did not increase during the progression of gestation. Clinical and biochemical features of these women precluded reducing the therapy dose to less than 100 mg/day of PTU. At 14 weeks of gestation, one patient discontinued PTU therapy for unknown reasons. As shown in Fig. 5C (open triangle), compound W levels increased remarkably and declined when PTU therapy was reestablished. Unfortunately, these hyperthyroid women did not give consent to cordocentesis and
no information on fetal thyroid function could be obtained.

Transplacental passage of TRIAC

Forty-six to 76 min after TRIAC administration, FT3 concentrations were extremely elevated in both the maternal and fetal circulation (Table 2). In fact, the maximum FT3 level recorded in 70 normal fetuses at that gestational age was 3.1 pmol/l, indicating a clear transplacental passage of the analog. In all fetuses, TSH and FT4 levels were within the normal range with one exception, a patient (no. 3, Table 2) who was hypothyroid (TSH: 19.6 mU/l). In this fetus, the recorded FT3 levels were the highest observed (18.8 pmol/l). In contrast, no transplacental passage of T3 was observed during T3 administration, although FT3 levels in the mothers increased by 4- to 10-fold (Table 2). During both TRIAC and T3 administration, maternal TSH levels decreased, while FT4 did not vary significantly. No adverse reaction was observed in any woman.

Compound W concentrations in three hyperthyroid pregnant women treated with PTU

The first patient (Fig. 6A) started therapy with 100 mg of PTU/day and the dosage was increased to 300 mg/day because of the marked thyrotoxicosis; the dose was subsequently reduced to 100 mg/day and finally 50 mg/day until the end of pregnancy. At 28 weeks of gestation, a cordocentesis revealed fetal hypothyroidism (fetal TSH: 66.9 mU/l, FT4: 8.3 pmol/l) and the ultrasound scan

Figure 4 Compound W levels in pregnant women affected by thyroid disorders before and during specific treatment are in the normal range for gestational age.

Figure 5 Serial measurement of serum compound W in three pregnant women without thyroid disorders (A), in six hypothyroid pregnant women treated with substitutive doses of L-T4 (B) and in four hyperthyroid pregnant PTU-treated women (C). One patient (open triangles) discontinued PTU therapy at 14 weeks of gestation for unknown reasons; in that period compound W levels remarkably increased, but declined when PTU therapy was reestablished.
indicated an associated fetal goiter (fetal thyroid width: 28 mm vs 15.2–18.1 mm in controls) (24). The fetal compound W level at 32 weeks of gestation was clearly low (64 vs 94–260 ng/dl as range for the same period) (Table 1), whereas at term the value had increased to 150 ng/dl (range at 37–40 week of gestation: 124–200 ng/dl). Compound W in maternal serum was within the normal range for gestational age, but did not show the usual progressive increase expected at that period of pregnancy. Compound W levels increased only after 30 weeks of gestation when the PTU dose was reduced to 50 mg/day.

The second patient (Fig. 6B) was treated at 6 weeks of gestation with 300 mg/day of PTU. Because of the severity of hyperthyroidism, this dose was continued until 14 weeks, at which time it was possible to reduce the dose of PTU to 200 mg/day and then to 100 mg/day. At 19 weeks of gestation, a cordocentesis was carried out because of a coexisting hematological disorder (thalassemia minor in both parents). Thalassemia major was excluded, but the fetal TSH levels were elevated (35.8 mU/l). There was no fetal goiter. Fetal compound W was normal, though maternal compound W (36 ng/dl) was in the low normal range at 19 weeks (range at

| Patient no. | Time (min) | Mother | | | | Fetus | | | |
| --- | --- | | | | | | | | |
| TSH (mU/l) | FT4 (pmol/l) | FT3/TRIAC (pmol/l) | TSH (mU/l) | FT4 (pmol/l) | FT3/TRIAC (pmol/l) |
| 1 (TRIAC) | 76 | 0.9 | 10.0 | >75 | 4.7 | 9.7 | 5.2 |
| 2 (TRIAC) | 48 | 3.4 | 8.5 | >75 | 19.6 | 7.9 | 18.8 |
| 3 (TRIAC) | 60 | 0.9 | 10.2 | <75 | 3.3 | 13.6 | 8.0 |
| 4 (TRIAC) | 60 | 0.9 | 10.1 | >75 | 8.3 | 12.3 | 4.9 |
| 5 (T3) | 53 | 6.0 | 11.4 | 46.5 | 5.0 | 10.6 | 2.0 |
| 6 (T3) | 46 | 1.5 | 11.0 | 16.3 | 6.4 | 8.6 | 0.5 |

Table 2 Effects of administration of TRIAC (3.5 mg) or T3 (200 μg) to the mother on both maternal and fetal TSH and thyroid hormone levels.

Figure 6 Levels of fetal and maternal compound W and fetal TSH in three hyperthyroid mothers treated with PTU (A, B and C respectively).
14–20 weeks of gestation: 27–138 ng/ml). The patient dropped out of the study at 20 weeks of gestation for unknown reasons.

In the third case (Fig. 6C) the patient started therapy with PTU 200 mg /day and at 20 weeks of gestation the dose was reduced to 100 mg/day. At 30 weeks a cordocentesis revealed an elevated fetal TSH (56.2 mU/l). There was no goiter. The patient was clinically euthyroid, so it was possible to further decrease the dose of PTU (50 mg/day). Fetal compound W levels were normal and serial measurements in the mother revealed that maternal compound W increased only after the PTU dose was reduced to 50 mg/day.

**Compound W concentrations in one hyperthyroid pregnant woman treated with PTU and TRIAC**

Figure 7 summarizes data for the woman treated with combined PTU (200 mg/day at the 15th week and then 100 mg/day until term) and TRIAC (2.1–2.8 mg/day orally from the 26th week until term). This therapy was provided because of fetal goiter (fetal thyroid width: 32 mm vs 12.2–15.1 mm in euthyroid controls) (24) and mild fetal hypothyroidism, documented by mildly elevated serum TSH levels (10.0 mU/l) and low FT4 levels (3.1 pmol/l; reference range for 90 fetuses at 24–27 weeks of gestation: 8.6–19.5 pmol/l). Serial measurements of maternal compound W were within the normal range, but without the usual increase expected during the second trimester. At 26 weeks of gestation, when the first cordocentesis was carried out, fetal compound W levels were normal. After 15 days of TRIAC treatment, fetal TSH levels decreased and an ultrasound scan revealed shrinking of the fetal goiter (thyroid width: 20 mm vs 15.2–18.1) (24). Successive fetal and maternal compound W measurements increased progressively and markedly after 30 weeks reaching values of 250–300 ng/dl. These measurements reflect the combined crossreactivity of 3,3'-DIACS and fetal compound W. TRIAC was not associated with untoward maternal effects, and after spontaneous onset of labor at 39 weeks of gestation, the patient delivered a female neonate who is now healthy and neurologically normal at 20 months of age.

**Discussion**

The present studies were undertaken to evaluate the possible use of compound W as a maternal marker of fetal thyroid dysfunction. An earlier report suggested that compound W, a T2S-like immunoreactive material present in maternal and fetal serum during pregnancy, is a thyroid hormone sulfoconjugate (5).

Our results suggest strongly that compound W is a metabolite of fetal thyroid hormone capable of transplacental fetal to maternal transfer. In fact, both maternal and fetal compound W levels increase progressively during gestation with significant direct correlation. Additionally, a positive correlation was observed between fetal compound W and fetal FT4, whereas no correlation was observed between maternal compound W and maternal FT4. Maternal compound W levels seem to reflect the effects of drugs on fetal thyroid function. In women on PTU, maternal compound W levels were in the low normal range, and did not show the usual increase with progression of gestation from the 2nd to 3rd trimester. A significant increase in maternal compound W was observed when the PTU dose was decreased to 50 mg/day, or was discontinued. Furthermore, we found that compound W levels were in the normal range also in the two women with goiter treated with L-T4 therapy at TSH-suppressive doses, supporting the view that such therapy (for the prevention of the increase of maternal goiter) is completely safe for the fetus.
Serial measurements of compound W in maternal serum can be considered a safe and practical test for the assessment of fetal thyroid function, particularly in hyperthyroid women treated with anti-thyroid drugs, whose fetuses could become hypothyroid due to the transplacental passage of the drug. Presently, the most precise way to diagnose fetal hypothyroidism is to perform cordocentesis and measure fetal TSH and FT4. However, this is an invasive procedure, associated with 1% fetal loss (12). However, this approach allows the early diagnosis of fetal hypothyroidism and the provision of substitutive therapy in utero (25, 26). Several recent studies have shown that intrauterine hypothyroidism is associated with decreased IQ values at 3–7 years even if a correct neonatal thyroid hormone replacement therapy is provided (27–32).

Since limited amounts of iodothyronines cross the placenta (33–36), administration of T4 or T3 to the mother is of limited value for therapy of fetal hypothyroidism and carries the risk of worsening of maternal hyperthyroidism. The amount of maternal hormone reaching the fetus in cases of severe fetal hypothyroidism appears insufficient to prevent the fetal pathology (36–38). Direct fetal therapy is now possible by periodic insertion of i-T4 into the amniotic fluid, at doses ranging from 120 to 500 μg, with intervals between intra-amniotic injection of 1 or 2 weeks (26, 39). One disadvantage of this technique is that it requires multiple invasive procedures. Another alternative is maternal TRIAC therapy (15, 40). Our results on transplacental passage of TRIAC confirm that TRIAC administered to the mother does cross the placenta. In fact, in the fetuses whose mothers received TRIAC, FT3 levels were 1.6– to 6-fold higher than the upper limit of the reference range (2, 41). Due to the 100% cross-reactivity with TRIAC of anti-T3 antibodies employed in our FT3 measurement method, this finding confirms the transplacental passage of the analog. Interestingly enough, the transplacental passage of TRIAC was highest in the only fetus who appeared to be hypothyroid, as documented by high circulating TSH levels. T3 given highest in the only fetus who appeared to be hypothyroid, transplacental passage of the analog. Interestingly our FT3 measurement method, this finding confirms the reaction with TRIAC of anti-T3 antibodies employed in the reference range (2, 41). Due to the 100% cross-reactivity of TRIAC in T3 RIA, the crossreactivity of 3,3′-DIACS in 3,3′-T2S RIA should be substantial. One may question whether the 3,3′-DIACS is produced in the fetal or in the maternal compartment. It is presumed that this sulfated DIAC is produced in the fetal or placental compartment and transported back into maternal serum, a process similar to the metabolism of T2S in sheep (43) and compound W in humans (5, 6).

Further study in non-pregnant women or in the thyroid hormone resistance syndrome patients who are treated with similar doses of TRIAC (44) would shed light on the origin of DIACS.

In conclusion, our data suggest that a random compound W measurement as a pregnant population screening may not be conclusive, whereas longitudinal evaluation of compound W appears to be a useful parameter of fetal thyroid function. Nevertheless, serial measurements of 3,3′-T2S crossreactive materials (compound W and 3,3′-DIACS) in maternal blood and the administration of TRIAC to the mother may represent a useful and safe alternative to invasive techniques for the diagnosis and therapy of fetal hypothyroidism.

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