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A 3,3'-Diiodothyronine Sulfate Cross-Reactive Material (Compound W), a Potential Marker for Fetal Hypothyroidism

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1. Introduction

In developing mammals (including humans), a deficiency or excess of thyroid hormone (TH) in the developing brain during the fetal and neonatal periods can lead to morphological and functional abnormalities (Nunez et al., 1992; Pasquini & Adamo, 1994; Morreale de Escobar et al., 2004; Harakawa et al., 1989). The most severe form of hypothyroidism in human fetus and neonate is the syndrome of cretinism. Recent studies indicate that abnormalities in intelligence quotient (IQ) and other neuropsychological tests may be found in children of women with subclinical hypothyroidism during pregnancy (Haddow et al., 1999; Mitchell & Klein, 2004; Casey et al., 2005). Subtle health impairment and reduced socio-educational achievement are observed in young adults with congenital hypothyroidism identified by neonatal screening and subsequently treated (Leger et al., 2011). This suggests the inadequacy in the current strategy with neonatal screening – it may already be too late to secure normal neurological development. Studies of populations indicate that congenital hypothyroidism affects 1 in 3,000 to 4,000 newborns; twice as many females as males. A recent report showed that the incidence in the United States increased from ~ 1:4100 in 1987 to ~ 1:2400 in 2002 (Rastogi & LaFranchi, 2010; Harris & Pass, 2007). The causes for this change are not entirely clear even though the screening strategy may have contributed to the increase (Rastogi & LaFranchi, 2010).

2. Etiology of congenital hypothyroidism

Most cases of congenital hypothyroidism are sporadic. But an estimated 15 to 20 percent of cases are inherited including mutations in the *DUOX2*, *PAX8*, *SLC5A5(NIS)*, *SLC26A4(PDS)*, *TG*, *TPO*, *DEHAL1, TSHB*, and *TSHR* genes (Table 1; Rastogi & LaFranchi, 2010; Grasberger & Refetoff, 2011). Many inherited cases are autosomal recessive but those with a mutation in the *PAX8* gene or certain *TSHR* gene mutations have an autosomal dominant pattern of inheritance. Another possible cause of fetal hypothyroidism is anti-thyroid medication treatment for maternal hyperthyroidism during pregnancy (Rastogi & LaFranchi, 2010; Rovet et al., 1999; Mirabella et al., 2000; Vanmiddlesworth et al., 2011). In severe iodine-deficient regions, the prevalence of cretinism can reach 10% of the local population; WHO

estimates indicate a prevalence in the millions worldwide (World Health Organization [WHO], 2004; WHO et al., 2007).

Category	Etiology	Mechanism	Note
Thyroid Failure	Developmental Anomaly	Dysgenesis	98% unknown; others associated genetic mutation: TTF, NKX2.1, NKX2.5, PAX-8
	Impaired production	Mutations on TH synthesis	NIS**, Peroxidase (DUOX2, DUOXA2), Pendred syndrome, Tg, Iodotyrosine deiodinase (DEHAL1, SECISBP2)
	TSH Binding	Receptor defect	
	TSH Signaling	G-protein	
Secondary Hypothyroidism	TSH Recetor	TSH β	
	TRH	Synthetic defect	PSIS**, Hypothalamic lesion
		Resistance	Receptor mutation
	Pituitary development/ function	Deficient transcription factors	HESX1, LHX3, LhX4, PIT1, PROP1 gene mutations
Peripheral Tissue	TH resistance	TSH β	
	Transporter	Abnormal TH transporter	MCT8 mutation
Transient	Antithyroid medication	Maternal Hyperthyroidism	
	Antibodies	Autoimmune	TSHR blocking antibody
	Iodine	Excess or deficient	Endemic goiter, a major world health problem
	Hepatic Hemangioma	Excess TH degradation	Type III deiodinase
Associate with other Abnormalities	Cleft palate		TTF-2 mutation
	Respiratory distress, Benign Chorea	Choreoathetosis	NKX2.1/TTF-1 mutation

** NIS: Sodium-iodide symporter; ** PSIS: pituitary stalk interruption syndrome

Table 1. Causes of Congenital Hypothyroidism

Concerns regarding fetal hypothyroidism and timely treatment warrant close monitoring of fetal thyroid status. One method, cordocentesis, is invasive and has a fetal loss rate of 0.5 to 1% (Daffos, 1989). Recently, ultrasonography has been utilized to assess the fetal thyroid

gland (Harris & Pass, 2007; Polak & Van Vliet, 2010; Luton et al., 2005; Abuhamad et al., 1995; Ribault et al., 2009). Cordocentesis and serial ultrasonographic measurements are either invasive or laborious. The development of a convenient non-invasive means to monitor fetal thyroid function is definitely needed.

3. Alternate pathways of Iodothyronines

The alternate pathways of thyroid hormone metabolism include conjugation (sulfation or sulfonation, and glucuronidation of the phenolic hydroxy group) and, to a lesser extent, oxidative deamination of the alanine side-chain leading to the formation of the corresponding iodothyroacetates and ether link cleavage (Fig. 1; Wu et al., 2005).
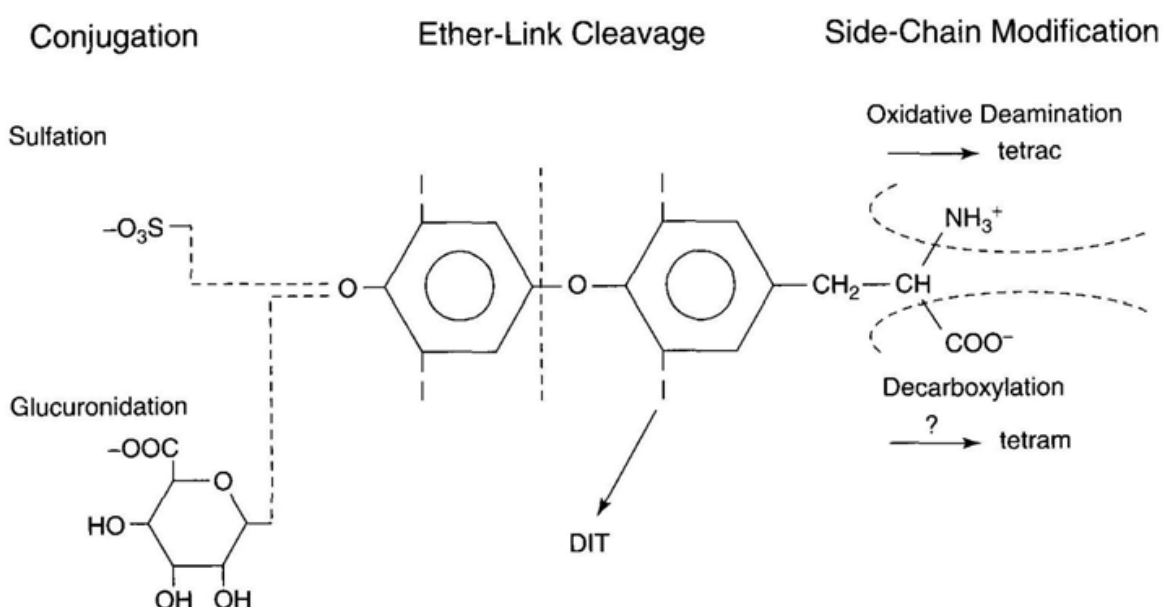

Fig. 1. Alternate pathways of thyroid hormone metabolism. The alternate pathways of thyroid hormone metabolism include conjugation (sulfation or sulfonation, and glucuronidation) and oxidative deamination of the alanine side-chain leading to the formation of the corresponding iodothyroacetates and ether link cleavage. DIT: diiodotyrosine; tetrac: tetraiodothyroacetic acid; tetram: tetraiodothyronamine.

Alternate pathways may serve as mechanisms for further regulation of the bioavailabilities of thyroid hormones in tissues, in addition to deiodination in various physiological and pathophysiological states. Sulfoconjugation of iodothyronines, for example, is an important pathway in developing mammals (Wu et al., 2005); and sulfated iodothyronines can also be deiodinated, even at a faster rate. Likewise, iodothyroacetates can be sulfated and further deiodinated. Iodothyronine glucuronides are rapidly excreted in the bile. Furthermore, sulfoconjugation and glucuronidation are not irreversible pathways for thyroid hormone metabolism. Glucuronides can be hydrolyzed in the intestine and reabsorbed, and sulfoconjugates can be desulfated in selective tissues, e.g. liver and brain, and become available to nuclear receptors, especially in fetuses where type I deiodinase (D1) activity is low. The *in vivo* occurrence of the decarboxylated metabolites of T_4 and T_3, 3,3',5,5'-

tetraiodothyronamine (T_4AM), and 3,3′5-triiodothyronamine (T_3AM) have not been demonstrated (Leonard & Kohrle, 2000). However, recently, 3-monoiodothyronamine (3-monoam or 3-T_1AM) and thyronamine (T_0AM) have been identified in brain and other tissues in rodents (Scanlan et al., 2004); monoam was found to have rapid effect on reducing rectal temperature in mice and is a potent agonist of the G protein-coupled trace amine receptor TAR1 (Scanlan, 2009). A single dose of T_1AM administered to rodents induces a hypometabolic state that in certain ways resembles hibernation. Monoam may be derived from low iodinated iodothyronines by aromatic amino acid decarboxylase (Fig. 1 & 2), however, its role in developing mammals is not known.
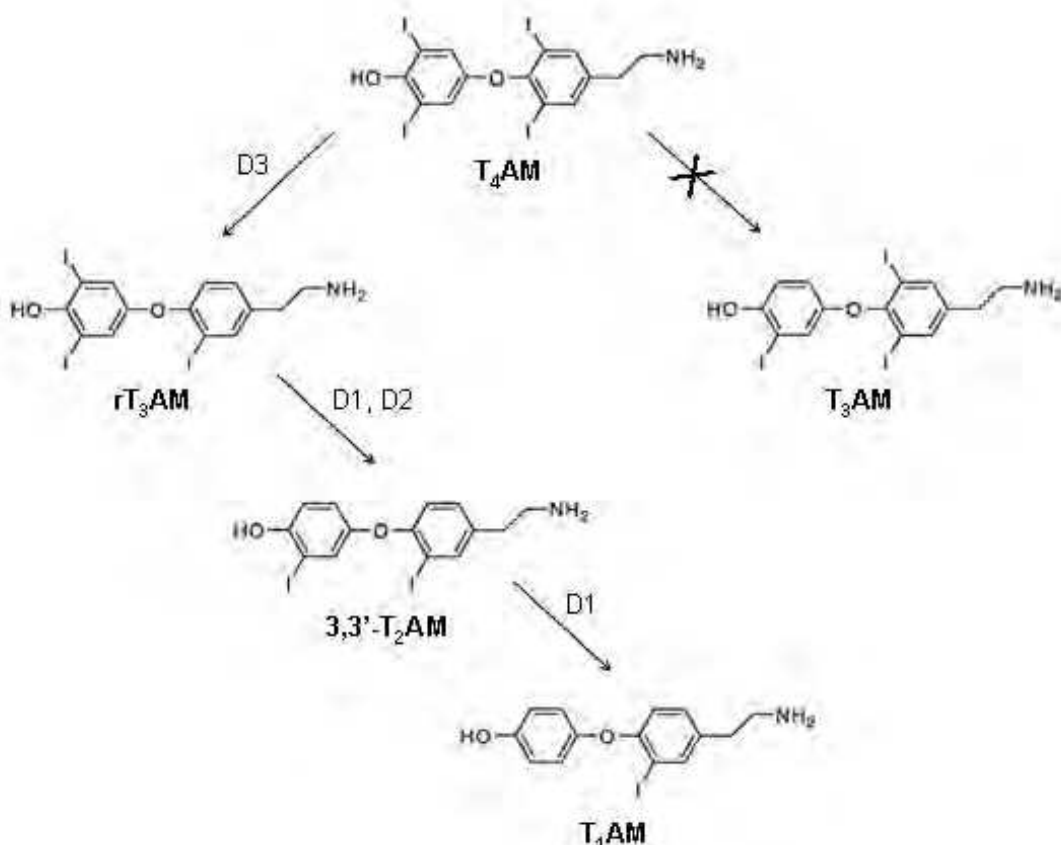

Fig. 2. Postulated T_1 AM (monoam) formation. T_4AM is not a substrate for type I or II deiodinase (D1 or D2) and cannot be deiodinated to T_3AM. However, T_4AM is readily deiodinated to rT_3AM by D3, and rT_3AM can be further deiodinated to ultimately provide T_1AM. This suggests a unique biosynthetic deiodination pathway for T_1AM starting from the decarboxylation products of either T_4 or rT_3.

4. Sulfoconjugation of Iodothyronines

Sulfoconjugation has been found to be a major pathway for thyroid hormone metabolism in mammalian fetuses (Fig. 1; Burrow et al., 1994; Wu et al., 2005; Simpson et al., 2005). The sulfation of thyroxine (T_4) and triiodothyronine (T_3) and their metabolites [reverse T_3 (rT_3) and 3,3′- diiodothyronine (T_2)] may accelerate their further degradation and excretion. The sulfation of T_4 completely blocks the outer-ring deiodination to T_3S. In addition, sulfated

iodothyronines may serve as a reservoir for biologically active hormones such as T_3, which can be recovered from T_3S by sulfatases in selective tissues (Wu et al., 2005).

By far, T_2 is the preferred substrate for various mammalian sulfotransferases (SULTs). The purpose of rapid sulfation of T_2, as well as rT_3 in some tissues studied, is unknown. It is interesting that T_2 has been found to stimulate mitochondrial respiration in various rat tissues (Moreno et al., 1997) and rT_3 may play a role in regulating actin polymerization in brain cells (Leonard & Farwell, 1997). Also, sulfated T_2 is the preferred substrate for both human and rat arylsulfatase (ARS) in the microsomal fraction of liver and placenta (Wu et al., 2005). Thus, the possibility that these T_4 metabolites may play a physiological role in developing animals cannot be excluded.

5. Sulfoconjugation of Iodothyronines and their placental transfer in sheep

Before the onset of active synthesis and release of TH, iodothyronines detected in the fetus clearly are maternal in origin. This period is approximately the first 17 gestational days (d) in rats, 50d in sheep (Fig. 3) and 90d in humans.
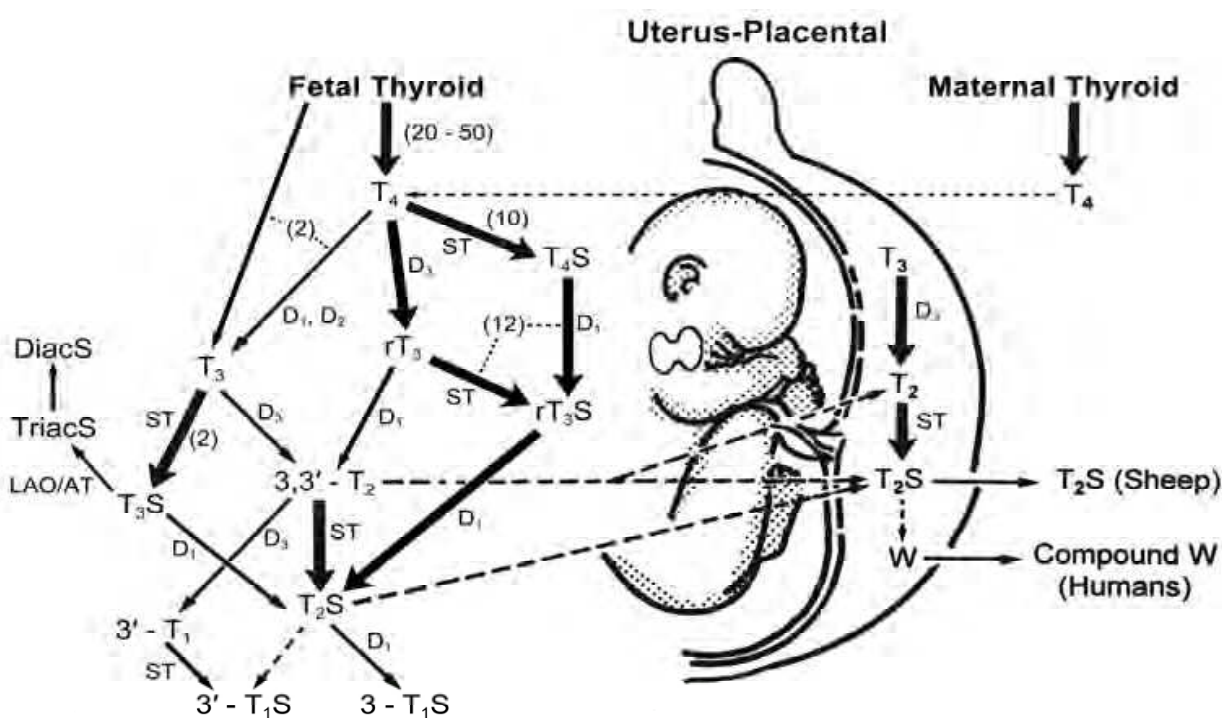

Fig. 3. Postulated metabolic pathways for ovine fetal thyroid hormones. D1, D2, and D3: type I, type II, and type III iodothyronine deiodinases; ST: iodothyronine sulfotransferases (SULT). LAO/AT: L-amino acid oxidase/aminotransferase; DiacS: sulfated 3,3'-diiodothyroacetic acid. Heavy solid lines indicate pathways that are more active in fetuses than in adults; thin solid lines, pathways that are less active in fetuses. The upper horizontal light dotted line depicts T_4 of maternal origin moving to the fetal compartment in the first trimester, before the fetal thyroid begins functioning. Other broken lines represent unconfirmed pathways. Numbers in parentheses indicate published production rates ($\mu g/kg/d$).

The proposed scheme for ovine fetal iodothyronine metabolism in late gestation (near term) depicts the production rates for sulfoconjugated thyroid hormone analogs (shown as numbers in parentheses along the thick arrows in Fig. 3). The high production rate (ug/kg/d) of T_4 sulfate (T_4S) reflects the activity of the sulfation pathway. The rT_3S production rate likely represents both sulfation of rT_3 and inner-ring deiodination of T_4S. This scheme shown in Fig. 3 also predicts 3,3'-T_2S is a major thyroid hormone metabolite in the fetus.

The transfer of TH and their metabolites may be a two-way street. We have shown high concentrations of sulfated iodothyronine analogs in human and ovine fetal serum. These include T_4S, T_3S, rT_3S, and 3,3'-T_2S (T_2S) (Wu et al., 2005). The high gradient between fetal and maternal serum concentrations of iodothyronine sulfates raises the possibility that there may be significant fetal to maternal transfer of iodothyronine sulfoconjugates. When the ovine fetus was infused with pharmacological amounts (0.46 μmoles) of T_3 or T_3S, significant fetal to maternal transfer of T_2S and T_3S occurred (Wu et al., 1995; Wu et al., 1999; Wu et al., 2006). It is noteworthy that significantly more T_3S than T_2S of fetal origin was recovered in maternal urine following the fetal infusion of either T_3 or T_3S.

Furthermore, maternal T_2S and T_3S levels were significantly higher after fetal T_3 than after T_3S infusion despite the fact that the mean fetal serum concentration of T_3S after fetal T_3S infusion was 20 times higher than following T_3 infusion (Wu et al., 1995). On the other hand, after fetal infusion of ^{125}I-T_3, without disturbing the fetal stable T_3 pool, a mean of 19% of infused radioactive dose was recovered in maternal urine in 4 h. T_2S, not T_3S, was identified as the major radioactive iodothyronine in fetal to maternal transfer; only minimal amounts of T_3S or T_3, were found (Wu et al., 2006).

We also assessed the contribution of fetal TH to the urinary T_2S and T_3S pool in ewes. Maternal urinary T_2S excretion (pmol/g creatinine) is significantly reduced by fetal thyroidectomy (Tx) but not by maternal Tx (Wu et al., 2001). Maternal urinary T_2S excretion correlated positively with fetal serum T_4 concentrations but not with maternal serum T_3 or T_4 levels (Wu et al., 2001). In view of a possible functional role of T_2 to stimulate mitochondrial respiration, the removal of T_2 from fetal compartment may be necessary for normal maturation of mammalian fetuses (Wu et al., 2005). Furthermore, recent study showed that ARSC, the only sulfatase that hydrolyzes iodothyronine sulfates, has a substrate preference for T_2 (Kester et al., 2002), which raises the possibility that T_2S could be readily reversed back to its precursor, an active iodothyronine. This would suggest a need for the fetus to remove T_2S from fetal compartment. Furthermore, in the sheep model, T_2S of fetal origin contributes significantly to maternal urinary T_2S excretion and may reflect fetal iodothyronine production.

6. The Evaluation a T_2S-crossreactive material (compound w) as a potential marker for fetal thyroid function

In humans, we found high levels of radioimmunoassayable T_2S in maternal serum (Wu et al., 1994) and urine (Wu et al., 1998). Levels increased with the progression of pregnancy and peaked before parturition. At delivery, a 20-fold increase in serum "T_2S" was found compared to non-pregnant women and "T_2S" levels returned to non-pregnant values in 7 to 10 days (Fig. 4 & 5). On closer examination, the radioimmunoassayable "T_2S" did not cochromatograph with synthetic T_2S by HPLC (Wu et al., 1994). The authentic T_2S was

hydrolyzed by hot-acid digestion (Wu et al., 1994). Using this procedure, the recovery of T_2S-crossreactive material was near 82% in fetal and maternal serum (Fig. 6; Wu et al., 2007).
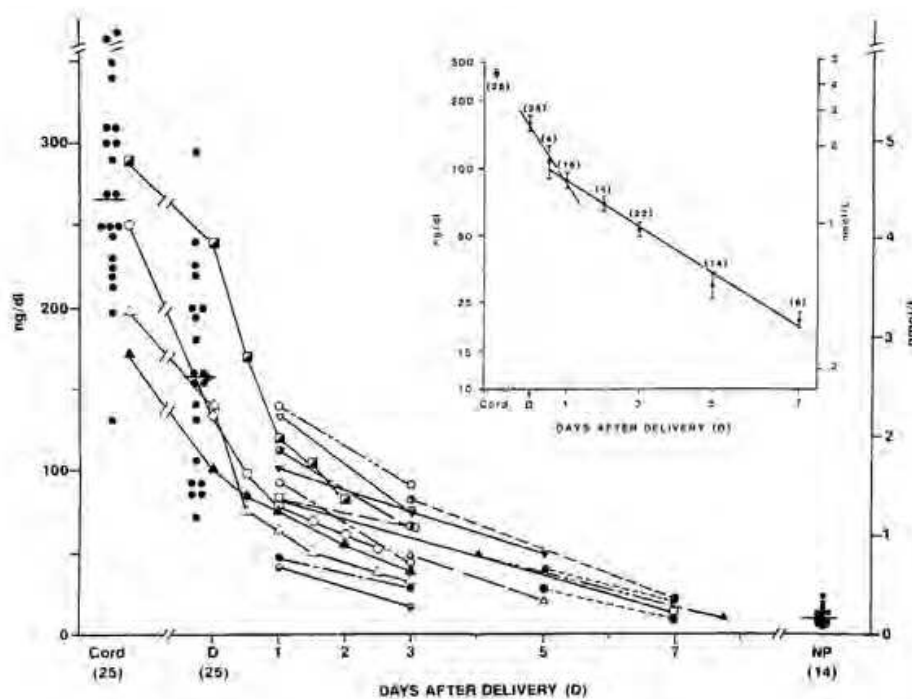

Fig. 4. Change of serum concentrations of compound W in cord and maternal serum. Compound W, expressed as ng/dl of T_2S, in newborns and maternal serum samples at the time of delivery (D). The connected lines represent serial measurements in the same patients (n = 18). T_2S concentrations also were measured in 14 nonpregnant women (NP) for comparison. The decrease in serum compound W concentrations after parturition is depicted in the semilog plot in the inset. The closed circles and vertical bars represent the mean ± SEM and (n) represents the total number of samples studied at each time period in a total of 35 patients.
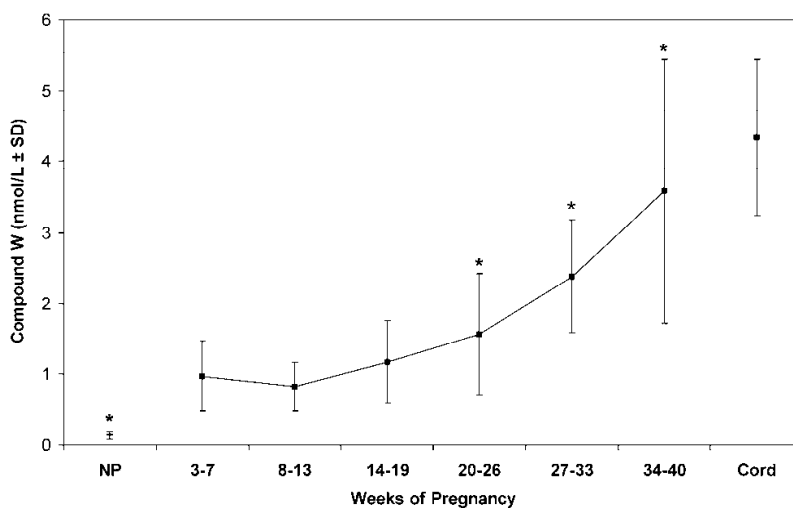

Fig. 5. Changes of compound W at different gestation periods. Normal values of T_2S-crossreactive material (compound W) in serum from pregnant women, nonpregnant women (NP), and newborns. Vertical bars are mean ± 1 SD. * p < 0.05 cf. 3-7 weeks pregnancy.
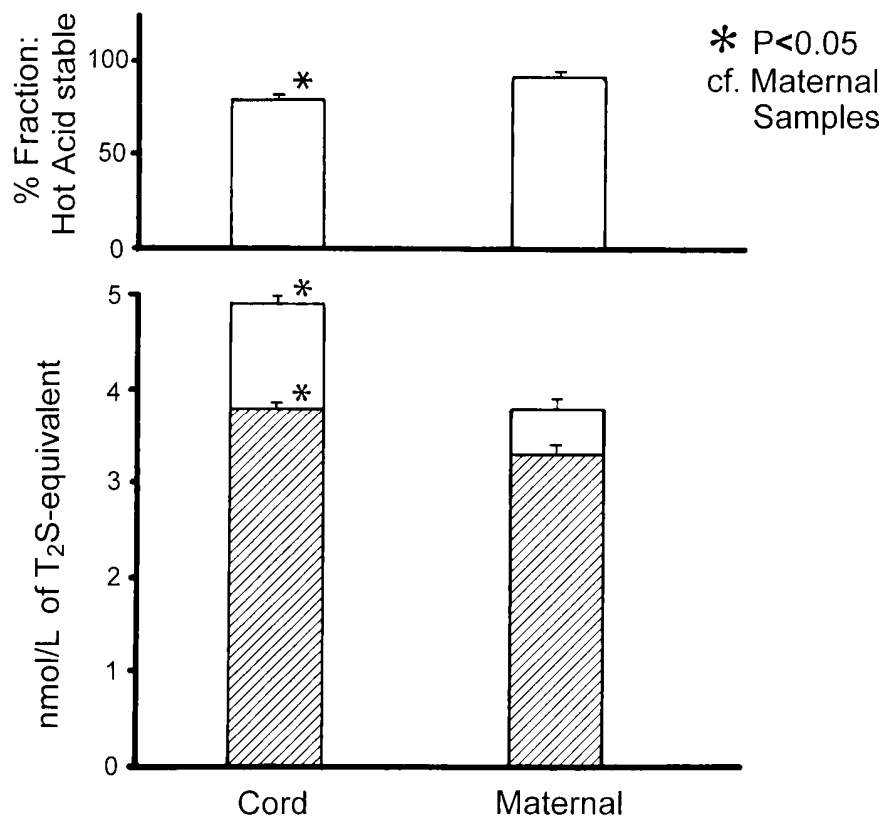
Fig. 6. Recovery of T_2S-crossreactive material following hot-acid treatment. Top: Percent of T_2S-crossreactive fraction that is hot-acid stable in cord (n = 6) and maternal (n = 12) serum samples.

The maternal and paired cord serum concentrations of T_2S-reactive material presented were adjusted by this percentage to obtain the hot-acid-resistant T_2S-equivalent activity, or the "corrected" value. Over 40 known synthetic thyroid hormone analogs were examined and none was found to be identical to the T_2S-like material in pregnant women's serum. Thus, the name Compound W was given. It is postulated that W is a side-chain modification of T_2S, which cross-reacts with T_2S antibody but is slightly more hydrophobic than T_2S. A possible candidate is N, N-dimethylated T_2S (Fig. 7; Wu et al., 2007).

To explore the possible origin of compound W, the serum concentrations of sulfated iodothyronines from cord arterial and venous samples were compared. There were no significant differences between the mean T_3S, T_4S, or rT_3S concentrations of arterial and venous serum samples. However, the venous T_2S-equivalent concentration was higher than arterial in seven of the paired samples and lower in two. The mean "corrected" W concentration in paired arterial/venous cord serum was found to be significantly higher in venous samples than in arterial samples (Wu et al., 2007). In addition, the mean of the maternal serum concentrations of T_2S-reactive material was significantly lower than that of the paired cord serum concentrations. The rapid disappearance of W from maternal serum immediately after delivery supports this hypothesis (Wu et al., 1994). A similar disappearance slope of serum W was also found in newborn infants (Chen et al., 2010). These findings support the postulation that W is produced in the placenta.
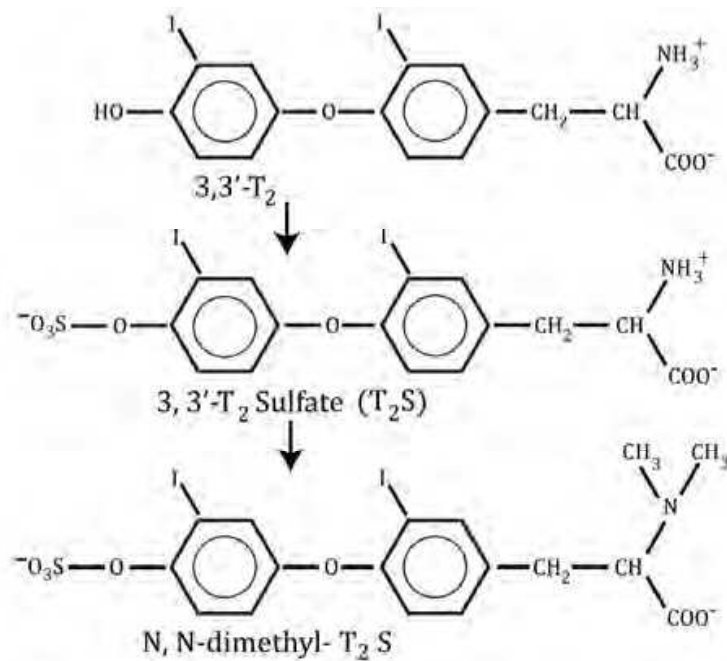
Fig. 7. Postulated pathway converting T_2S to N, N-methyl- T_2S. N, N-methyl- T_2S has the same physico-chemical characteristics on HPLC and reaction to T_2S-specific antibody.
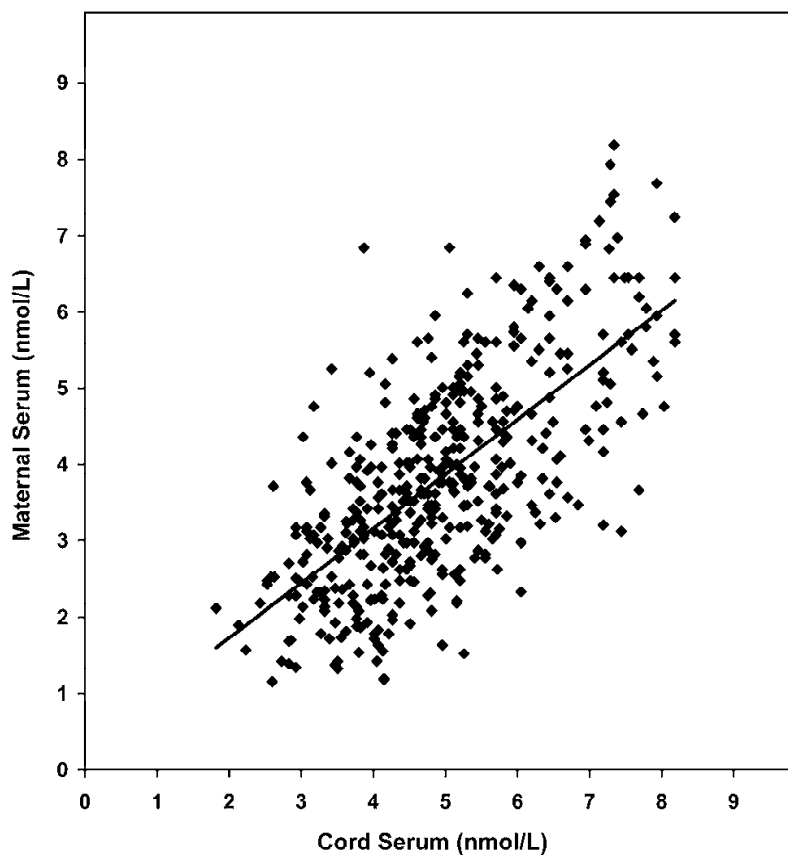

Fig. 8. Levels of T_2S-crossreactive material in paired maternal and cord serum at term. The solid line is the trend-line from lineal regression analysis for the correlation
(n = 436, R = 0.686).

Prior studies suggest strongly that compound W is a metabolite of fetal thyroid hormone capable of transplacental fetal to maternal transfer (Wu et al., 2005; Wu et al., 1994; Cortelazzi et al., 1999; Wu et al., 2007). Both maternal and fetal compound W levels increase progressively during gestation with significant direct correlation (in both mothers and fetuses). Additionally, in 436 paired cord and maternal sera obtained at delivery, a highly significant positive correlation was observed between fetal and maternal compound W (Fig. 8). A significant positive correlation was also observed between serum levels of fetal compound W and fetal FT_4 and between maternal and fetal compound W (Fig. 9; Cortelazzi
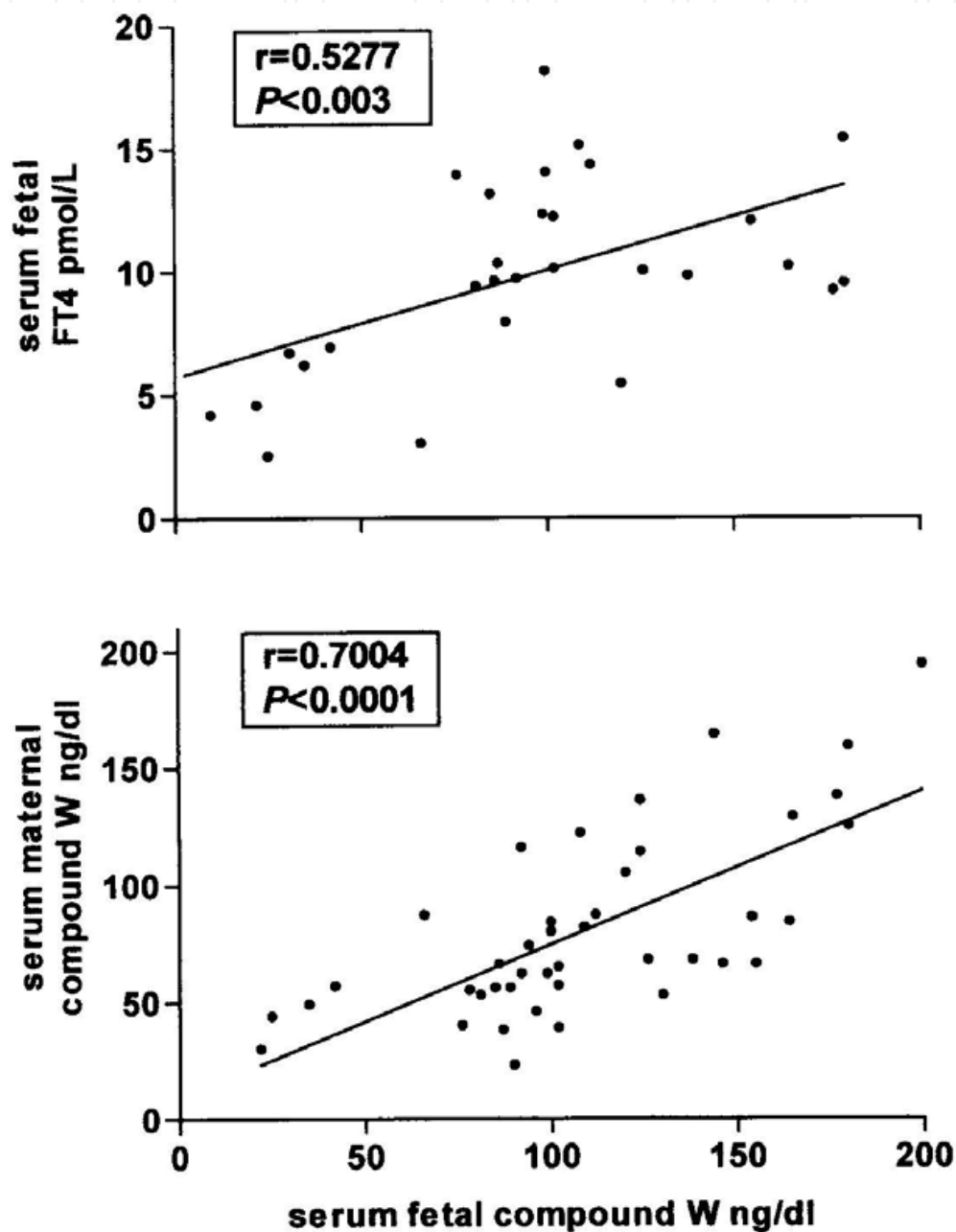

Fig. 9. Compound W levels in fetal serum: correlation with serum fetal FT4 (n=29) and maternal compound W (n=42). [Cortelazzi et al., 1999, reproduced with permission from European J. Endocrinology]

et al., 1999) whereas no correlation was observed between maternal serum compound W and maternal serum FT_4 in euthyroid or hyperthyroid women. Furthermore, maternal compound W levels seem to reflect the effects of drugs on fetal thyroid function (Cortelazzi et al., 1999). In women on propylthiouracil (PTU), maternal compound W levels were in the low normal range and did not show the usual increase with progression of gestation (Cortelazzi et al., 1999). The lack of progression in maternal compound W levels was confirmed in a recent study of 22 pregnant women treated with anti-thyroid medication (Fig. 10; Vanmiddlesworth et al., 2011). A significant increase in maternal compound W was observed when the PTU dose was decreased or discontinued.
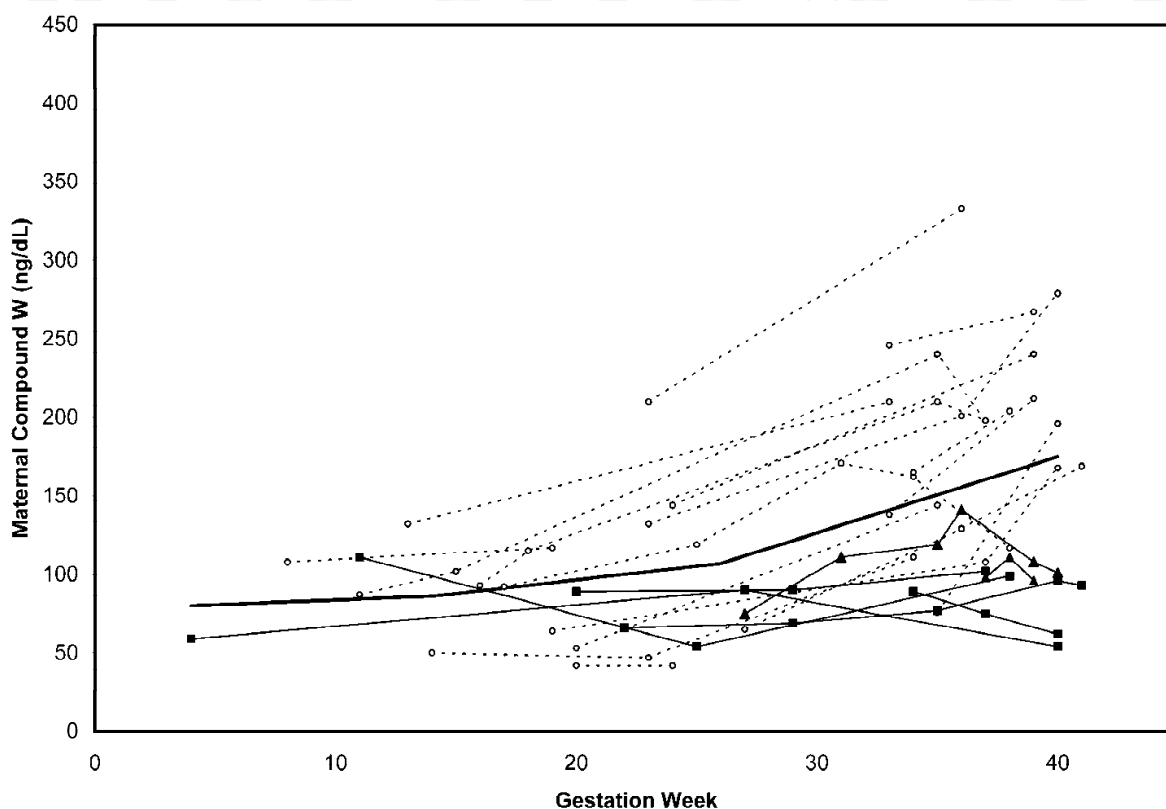

Fig. 10. Courses of compound W in serum of pregnant patients with hyperthyroidism receiving antithyroid therapy. Two or more points on dotted lines mark the course of compound W in each patient, and the thick continuous black line shows the marginal mean course. Thick gray lines represent the 10th (lower) and 90th (upper) percentiles. Square markers on solid lines indicate suppressed or nonprogressive serial measurements in 5 patients; triangular markers on solid lines denote 2 patients who had transient progression and then reduction below the 10th percentile at term.

Cortelazzi, et al. (Cortelazzi et al., 1999) suggest that abnormal thyroid function will be revealed by an absence of the normal rise of compound W during gestation. In comparison with relatively low incidence of congenital hypothyroidism in this population (Rastogi & LaFranchi, 2010; Harris & Pass, 2007), 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 can become hypothyroid due to the transplacental passage of the drug (Fig. 10; Vanmiddlesworth et al., 2011).

Further study is needed to include compound W levels in a greater number of hyperthyroid pregnant women treated with anti-thyroid medication or pregnant women with evidence of autoimmune thyroid illnesses, followed by long-term follow-up of psychomotor development in these seemingly euthyroid babies. Suppressed W levels may help to define the sub-group of children exposed to PTU in utero or born to mothers with autoimmune disease who have been shown to have an adverse cognitive outcome (Grasberger & Refetoff, 2011; Rovet et al., 1999; Mirabella et al., 2000; Mitchell & Klein, 2004; Casey et al., 2005).

7. Conclusion

Sulfoconjugation is a major metabolic pathway for thyroid hormone in developing mammals. The significant rise of sulfated iodothyronines in mammalian fetal compartments raises the possibility that significant fetal to maternal transfer of the conjugates may occur in late gestation as the fetal hypothalamic-pituitary-thyroid system becomes more mature. This transfer may be a novel mechanism to maintain low T_3 states or regulate serum T_2, a thermogenic hormone that is important for normal tissue maturity. The possibility that the transferred iodothyronine sulfate, especially T_2S and its metabolite, may serve as a marker of fetal thyroid function needs to be further explored.

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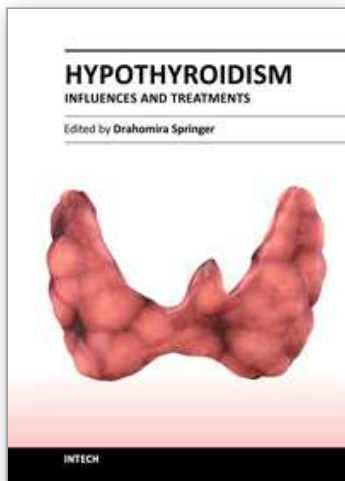
Hypothyroidism - Influences and Treatments
Edited by Dr. Drahomira Springer

Hypothyroidism is the most common thyroid disorder and it is significantly more frequent than presented - millions of people suffer from this disease without knowing it. People with this condition will have symptoms associated with slow metabolism. Estimates of subclinical hypothyroidism range between 3 to 8 %, increasing with age, whereas it more likely affects women than men. About 10% of women may have some degree of thyroid hormone deficiency. Hypothyroidism may affect lipid metabolism, neurological diseases or other clinical conditions. The book includes studies on advancements in diagnosis, regulation and replacement therapy, thyroid ultrasonography and radioiodine therapy for hypothyroidism. "Hypothyroidism - Influences and Treatments" contains many important specifications, results of scientific studies and innovations for endocrine practice.

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