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A fresh look at W- compound: A potential marker for fetal thyroid function – Fetal to maternal transfer of sulfated thyroid hormone metabolites

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Background

Thyroid hormone (TH) plays a profoundly important role in fetal neurological maturation. The differentiation and maturation of the brain is chronologically programmed by TH [1]. The changes in TH levels in fetuses may have serious and long-term neurodevelopmental consequences. In humans, early diagnosis and treatment are essential to ensure the normal Central Nervous System (CNS) development and prevent the sequelae of congenital hypothyroidism; cretinism is the most serious form. Currently, screening for congenital hypothyroidism is initiated at 2 to 3 days after birth by measuring TSH levels in the neonatal heel blood and starting therapy in the postnatal period. This neonatal screening strategy may be late for securing a normal brain development that starts at first trimester of pregnancy [2,3]. A significant number of school age children diagnosed hypothyroidism *in utero* had mild to moderate leaning attentional problems, despite early diagnosis and treatment postnatally [4,5]. A fetal functional marker in maternal serum or urine would provide a convenient method for screening congenital hypothyroidism in utero, rather than postnatally.

Sulfoconjugation is the major pathway for thyroid hormone metabolism in mammalian fetuses

In sheep study, we have demonstrated that the high production rate (μg/kg/d) of T_4 sulfate (T_4S) in fetuses reflects the dominate role of the sulfation pathway in TH metabolism. It also predicts that 3,3'-diiodothyronine sulfate (T_2S) is a major thyroid hormone metabolite in the fetus [6]. 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 sulfated TH metabolites (iodothyronine sulfoconjugates). When the ovine fetus was infused with pharmacological amounts of T_3 or T_3S, significant fetal to maternal transfer of T_2S and T_3S occurred [6-8]. In humans, we found high levels of radioimmunoassayable T_2S in maternal serum [9] and urine [10].

W-Compound, a T_2S-Crossreactive Material, as a Potential Marker for Fetal Thyroid Function:

In humans, we found high levels of radioimmunoassayable T_2S in maternal serum [9,11] ; 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 (Figure 1,2). On a closer examination, the radioimmunoassayable "T_2S" did not cochromatography with synthetic T_2S by HPLC [9]. Over 40 known synthetic thyroid hormone analogs were examined and none was found to be identical to the T2S-like material in pregnant women's serum [11]. Thus, the name W-Compound was given. It is postulated that W-Compound is a side-chain modification of T_2S, which cross-reacts with T_2S antibody but is slightly more hydrophobic than T_2S. Consistent with being an analogue of iodothyronine, we recently found high level of iodine content in highly purified W-Compound preparation analyzed by a Triple Quadrupole ICP-MS (Inductively Coupled Plasma Mass Spectrum) (Xi BX, Synold T, Wu SY. unpublished results).

In normal pregnancies, both maternal and fetal W-Compound levels increased progressively with a significant direct correlation ($p<0.001$, in both mothers and fetuses) [12] (Figure 2). In addition, in 436 paired cord and maternal sera obtained from women at delivery, a highly significant correlation was found between the concentrations of Compound W in newborn cord and maternal serum ($p<0.01$) [12]. A significant positive correlation was observed in serum levels between fetal W-Compound and fetal T_4 ($p<0.003$) and between maternal and fetal W-Compound ($p<0.0001$) [12] whereas no correlation was observed between maternal serum W-Compound and maternal serum T_4 in euthyroid or hyperthyroid women. Thus, these data strongly suggest the fetal origin of W-Compound.

To further explore the possible origin of W-Compound, 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 reverse-T_3S (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 nine pairs of cord serum was found to be significantly higher in venous samples than in arterial samples [11]. 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 [9] (Figure 1). A similar disappearance slope of serum W was also found in newborn infants

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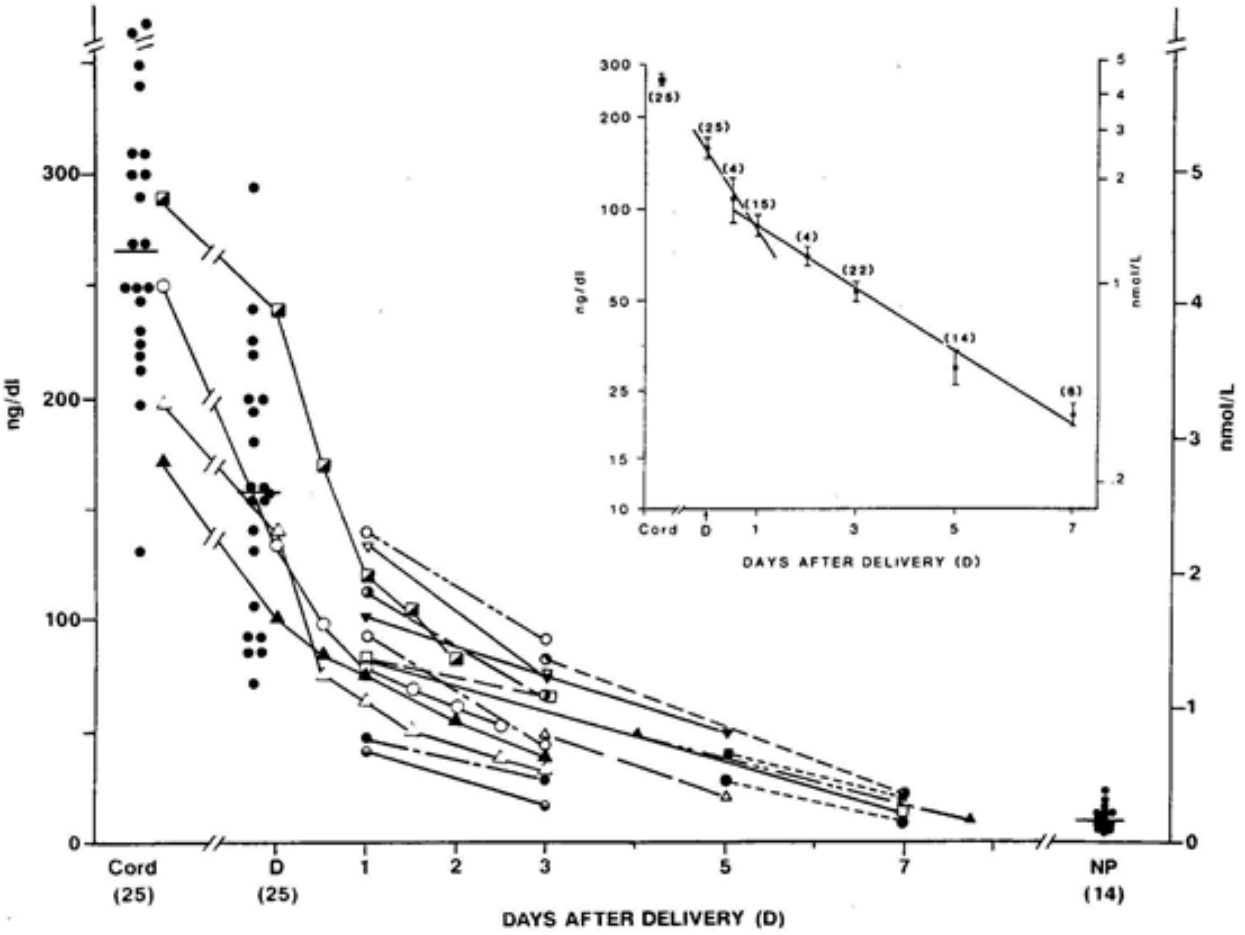

Figure 1. Concentrations of T_2S and W-compound in cord serum of newborns and W-compound levels in maternal serum samples at the time of deliver (D). The connected lines represent serial measurements in the same patients (n = 18). T_2S concentrations also were measured in 14 nonpregnant women (NP) for comparison. The decrease in serum W-compound concentrations after parturition is depicted in the semilog plot in the inset. The closed circles in vertical bars represent the mean (±SEM) and (n) represent the total number of samples studied at each time period in a total of 35 patients.

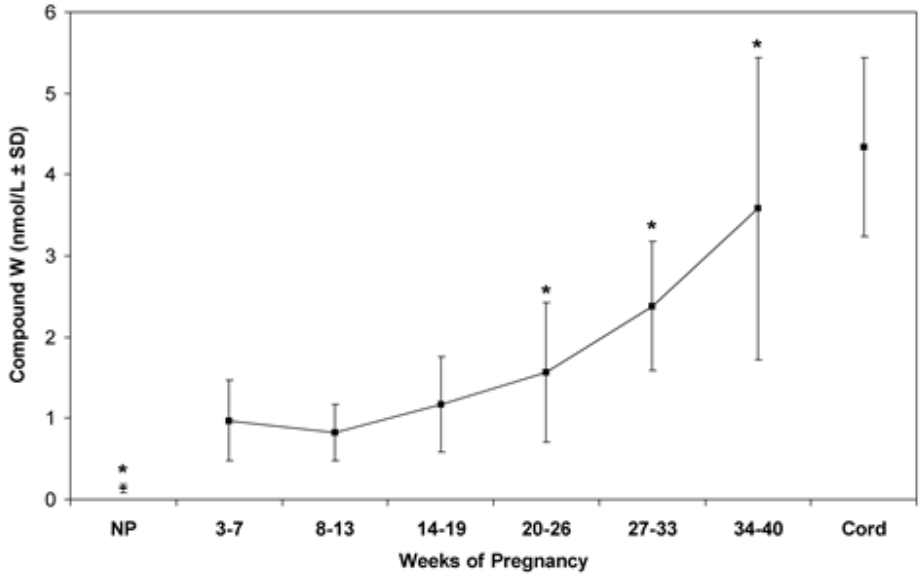

Figure 2. Normal values of T_2S-crossreactive material (W-Compound) in serum from pregnant women, nonpregnant women, and newborns. Vertical bars are mean ± 1 SD. * $p < 0.05$ cf. 3-7 weeks pregnancy.

[13]. These findings support the postulation that W is produced in the placenta with iodothyronine precursor of fetal origin.

Summary

Sulfoconjugation is a major metabolic pathway for thyroid hormone in developing mammals. The significant rise of sulfated iodothyronines in mammalian fetal compartments raises the possibilities that significant fetal to maternal transfer of the TH sulfoconjugates may occur in the late gestation as the fetal hypothalamic-pituitary-thyroid system become more mature. This transfer may be a novel mechanism to maintain low T_3 states or regulate serum 3,3'-T_2, a thermogenic hormone [14], that is important for normal tissue maturity. The possibility that the transferred iodothyronine sulfate, especially 3,3'-T_2S and its metabolite may serve as a marker of fetal thyroid function needs to be further explored. To facilitate the further study on W-Compound as a fetal thyroid function marker, we have recently developed a non-isotopic method [15].

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