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# AN ALTERNATE APPROACH TO NEONATAL SCREENING OF THYROID FUNCTION

**Sing-Yung Wu*[1,2,3] M.D. Ph.D., Mark Chambers[1,2] D.V.M. M.D., Mazhar Khan[1] M.D., Haibo Zhao[3] M.D. Ph.D.**

[1]Department of Radiology, Veteran Administration, Long Beach, CA 90822.
[2]Department of Radiology, University of California, Irvine, CA 92697.
[3]Department of Research, Veteran Administration, Long Beach, CA 90822.

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***Corresponding Author: Sing-Yung Wu**

Department of Radiology, Veteran Administration, Long Beach, CA 90822.

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## ABSTRACT

**Background**: Thyroid hormone (TH) plays a critical role in early fetal brain development during the first trimester, including the proliferation, migration, and differentiation of neuronal cells. Because this developmental window occurs before birth, some neurological defects may be irreversible by the time treatment begins after birth according to the current neonatal screening. There are persistent reports of mild brain damage and lower IQ in some children with congenital hypothyroidism (CH), despite early detection and treatment after birth, reveal potential shortcomings in the current neonatal screening strategy and underscore the need for improvement. **Methods:** In this report we propose an alternate approach to assess fetal thyroid function in utero by examining the characteristic fetal thyroid hormone (TH) metabolism —specifically, the sulfation pathway. **Results:** Sulfoconjugation is a major metabolic pathway for TH in developing mammals due to low type 1 monodeiodinase. 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 become more mature. This transfer may be a novel mechanism to maintain low T3 states or regulate serum T2, a thermogenic hormone that is important for normal tissue maturity. The possibility that the transferred iodothyronine sulfate, especially T2S and its metabolite may serve as a marker of fetal thyroid function needs to be further explored. **Conclusions:** Further investigation into fetal TH metabolism and function may provide a rational alternative for managing CH at the early stage of fetal development and mitigating long-term adverse outcomes from neonatal-screen-associated “catch-up” treatment postnatally.

**KEYWORD:** Congenital Hypothyroidism, Fetal Thyroid Function, W-Compound, Biomarker, Neonatal Screening.

## INTRODUCTION

Neonatal screening programs for congenital hypothyroidism (CH) have been in place for over 50 years.[1,2] Currently, around 38 million newborns worldwide are screened each year for this disorder. These programs facilitate early diagnosis and treatment, leading to significantly improved long-term outcomes. However, despite systematic screening and timely intervention, some children with CH still experience mild brain damage and lower IQs.[3]

Thyroid hormone (TH) plays a crucial role in fetal brain development during the first trimester, influencing the proliferation, migration, and differentiation of neuronal cells.[4–6] Since this developmental window occurs before birth, some neurological defects may become irreversible by the time treatment is initiated postnatally. These enduring changes can impact IQ, as well as cognitive and motor development.[3, 7, 9–11] Children affected by congenital hypothyroidism may also experience reduced socio-educational achievement[12–14], an increased risk of autistic traits[10], and a higher prevalence of attention-deficit/hyperactivity disorder (ADHD) symptoms.[15]

Evidence indicates that higher maternal iodine intake prior to conception is linked to higher IQ in children[16], underscoring the potential benefits of nutritional and hormonal interventions before or during pregnancy.

Unfortunately, the incidence of congenital hypothyroidism (CHT) in the United States has been on the rise, increasing from approximately 1 in 4,100 live births in 1987 to about 1 in 2,400 by 2002.[17] Similar upward trends have been observed in other countries, including Australia[18], Italy[19], and Ireland.[20] A meta-analysis has estimated that the global prevalence of CHT among newborns has increased by 127% since 1969.[21] In contrast to recent reports from around the world, the incidence of congenital hypothyroidism in Finland has remained unchanged between 1994 and 2017.[22] Additionally, some infants may exhibit a delayed rise in thyroid-stimulating hormone (TSH), which might not be detected by standard neonatal screening protocols.[23] Emerging evidence suggests that this delayed TSH elevation may be more prevalent and clinically significant than previously recognized.

In addition, while the United States is generally regarded as iodine-sufficient, dietary iodine intake has significantly declined since the 1970s. As a result, iodine deficiency has reemerged among vulnerable populations, particularly women of reproductive age.[24] These trends, coupled with ongoing reports of mild brain damage and lower IQ in some children with congenital hypothyroidism (CH) despite early detection and treatment after birth, highlight potential shortcomings in the current neonatal screening strategy and underscore the need for improvement.

In this review, we propose an alternate approach to assess fetal thyroid function in utero by examining the characteristic fetal thyroid hormone (TH) metabolism—specifically, the sulfation pathway. Further investigation into fetal TH metabolism and function may provide a rational alternative for managing CH at the early stage of fetal development and mitigating long-term adverse outcomes from neonatal-screen-associated "catch-up" treatment postnatally.

**Alternate Pathways of Thyroid Hormone Metabolism in Fetuses**

The observation that the fetal $T_4$ production rate (35 – 50 µg/kg/d) (Table 1) exceeds the combined production rates for $T_3$ (2 – 7 µg/kg/d) and $rT_3$ (4 – 6 µg/kg/d) suggested that there are alternate pathways of TH metabolism might be significant during development.[25] We have carried out studies to characterize the patterns of maturation of thyroid hormone metabolism in fetal and adult sheep.[26] The patterns of ontogenesis of Type I deiodinase in sheep liver, kidney, and thyroid glands are summarized in Fig. 1.

The fetal liver has substantially lower Type I mono-deiodinase activity than maternal liver.[26] As shown in Fig. 2, serum T3 is undetectable in the ovine fetus until about 90 days of gestation, while human fetus until about 50 weeks gestation. Serum rT3 is elevated in early pregnancy.[25] The Ontogeny of the three mono-deiodinases that catalyze the progressive deiodination of T4 differs in the developing fetuses. Type II and III mono-deiodinases appear at mid-gestation, whereas Type I is not evident until later.[26,27] This explains fetal T3 concentrations are low. The preterm increase in fetal serum T3 concentrations is due to the maturation of Type I mono-deiodinase activity. Serum concentrations of rT3, T4 sulfate, T4 sulfate and rT3 sulfate in the fetuses are high.[28-31] Since Sulfated iodothyronines are not substrate to Type III, the sulfated metabolites accumulate in fetal serum due to low Type I mono-deiodinase activities in fetal tissues.[26] Our studies have shown that sulfation pathway is the major route of thyroid hormone metabolism in developing mammalians (Fig. 3).[27]

**Sulfoconjugation is the major pathway for fetal thyroid hormone (TH) metabolism**

In order to study the sulfation pathway in developing mammals in utero, the Thyroid Research Lab at VA Long Beach has developed following tools including methods of measuring the enlisted thyroid hormone analogs and specific antibodies to the following TH analogs.

1. Specific antibody and radioimmunoassay of Thyroxine Sulfate (T4S).[29, 30]
2. 3,3',5'-Triiodothyronine Sulfate (rT3S).[31]
3. 3,3'-Diiodothyronine Sulfate (T2S).[32-36]
4. Specific antibody and radioimmunoassay of 3'-Monoiodothyronine sulfate (3'-T1S).[37]
5. Specific antibody and radioimmunoassay of Triac Sulfate (TriacS).[37]

With these specific assays, we have found that sulfoconjugation is the major pathway for fetal thyroid hormone (TH) metabolism, converting $T_4$ to inactive metabolites, $T_4S$, $rT_3S$, and $T_3S$, via sulfotransferases (SULT) and type 3 deiodinase in gestation.[27] Consistent with high production rate of $T_4S$ and $rT_3S$, there are high serum sulfated iodothyronine analogs, including $T_4S$, $T_3S$, $rT_3S$, and 3,3'-$T_2S$ ($T_2S$), in ovine and human fetal and preterm infants. Since maternal $T_2S$ appears to be quantitatively derived from fetal $T_3$ (the active TH), the amount of $T_2S$ in the maternal compartment correlates with fetal thyroid function in sheep. Maternal serum levels of $T_2S$ significantly correlate with fetal $T_4$ or immuno-assayable $T_2S$ but not maternal serum $T_4$ in euthyroid or hyperthyroid women, showing a distinct difference between fetal and maternal in TH metabolism. Fetal $T_2S$ is actively transferred to the mother via placenta and the quantity of $T_2S$ in maternal compartment reflects fetal thyroid function (*vide infra*). Thus, maternal serum immuno-assayable $T_2S$ may be a biomarker for monitoring fetal thyroid function in utero, although more investigations are needed to determine if it can be used as an alternative strategy for

screening/managing congenital hypothyroidism due to dysregulated thyroid hormone metabolism.[27]

**3,3'-T2S is the major thyroid hormone metabolite in the fetus - the fetal to maternal transfer**

Thyroid hormone (TH) plays an important role in early fetal neurological maturation. Iodothyronines detected in the fetus before the onset of fetal thyroid function is of maternal origin. The maternal-fetal transfer of TH and their metabolites are apparently a two-way street.[38, 39] The high gradient between fetal and maternal serum concentrations of iodothyronine sulfates raises the possibility of significant fetal to maternal transfer of iodothyronine sulfoconjugates.

The scheme shown in Fig. 3 also indicates 3,3'-$T_2S$ is the major thyroid hormone metabolite in the fetus. We have performed intravenous infusions of radioiodine labeled $T_3$ and $T_4$ into near-term ovine fetuses, demonstrated a rapid clearance of labeled $T_3$ from fetal serum (disappearance $T_{1/2}$ of 0.7 hours). Labeled $T_2S$ was identified as the major fetal iodothyronine metabolite in maternal urine.[33] Fetal $T_3$ undergoes rapid inner-ring monodeiodination to 3,3'-$T_2$ which is an excellent substrate for all known mammalian iodothyronine sulfotransferases.[27] The rapid sulfoconjugation of the hydroxyl group in the outer-ring of 3,3'-$T_2$ forms a hydrophilic sulfated $T_2$ ($T_2S$) with enhanced permeability through placental membranes, facilitating the transfer of THs to maternal compartments. The $T_2S$ of fetal origin appears to be rapidly cleared from the maternal circulation via excretion in urine.[38] Fetal $T_4$, on the other hand, disappears from the fetal circulation at a slower rate. The major metabolites in fetal circulation after infusion of $^{125}$I-$T_4$ were $rT_3$ and $T_3$ as well as their sulfates, $T_4S$, $rT_3S$ and 3, 3'-$T_2S$.[38]

Similar to fetal $T_3$ infusion, the most abundant metabolite found in maternal urine following radioactive $T_4$ infusion is $T_2S$. The $T_4$ infusion study also confirms previous data in ovine fetuses[38], indicating that the production of active thyroid hormone ($T_3$) is less than the production of inactive products, rT3, T2S, rT3S and T3S.[27]

$T_3$ derived from $T_4$ formed in the fetal circulation is converted to $T_2S$, which is then transferred to the maternal compartment for deiodination and excretion.[38] This process would contribute to the low circulating $T_3$ levels in the fetus. Since $T_2S$ appears to be quantitatively derived from circulating $T_3$ (the active TH in the fetus), a significant increase or decrease in $T_2S$ in the maternal circulation would suggest hyper- or hypothyroidism in the fetus. In thyroidectomized sheep model, we found that 3,3'- $T_2S$ excretion in maternal urine reflects fetal thyroid function.[35, 38]

**W-compound should be considered as a potential fetal thyroid function marker**

In humans, we have found high levels of radio-immunoassayable $T_2S$ in maternal serum.[33-36]; its levels increase with gestational age and peaked just prior to parturition. At delivery, a 20-fold increase in serum "$T_2S$" is present compared to nonpregnant women and "$T_2S$" levels return to nonpregnant values in 7 to 10 days after delivery. Serum levels were measured by a $T_2S$-specific radioimmunoassay (RIA) in 60 serum samples from newborns with hyperbilirubinemia, age 1 to 30 days. It is found that radio-immunoassayable $T_2S$ is cleared at similar rates in newborn as in postpartum maternal sera.[40] This is consistent with the hypothesis that this "$T_2S$" is produced in or transported through the placenta.

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 found high level of iodine content in highly purified W-Compound preparation analyzed by a Triple Quadrupole ICP-MS (Inductively Coupled Plasma Mass Spectrum).[39]

In normal pregnancy, both maternal and fetal W-Compound levels increase progressively with a significant direct correlation ($p<0.001$, in both mothers and fetuses). In addition, in 436 paired cord and maternal sera obtained from women at delivery, there is a highly significant correlation between the concentrations of Compound W in newborn cord and maternal sera ($p<0.01$) (27, Fig. 4).

A significant positive correlation is also observed between fetal serum concentrations of W-Compound and fetal $T_4$ ($p<0.003$) and between maternal and fetal W-Compound concentrations ($p<0.0001$) (41, Fig. 5). However, no significant correlations were observed between maternal serum W-Compound and maternal serum $T_4$ in euthyroid or hyperthyroid women. 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 blood samples were compared.[36] There were no significant differences between the mean $T_3S$, $T_4S$, or reverse-$T_3S$ concentrations of arterial and venous serum samples. However, the venous concentration of the $T_2S$-equivalent material was higher than that in arterial blood in seven of the paired samples and lower in two. The mean "corrected" concentration of W-Compound in nine pairs of cord sera was found to be significantly higher in venous than arterial blood samples suggesting the fetal origin of W.[36] 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 Measurement of W-Compound**

The original method for the measurement of W-Compound involves the use of RIA which was

developed by Wu et al.[32,36] Radioimmunoassay, in general, is not convenient to most clinical laboratories due to the involvement of using a radioisotopeI.[125]

In a recent study, we have applied a highly sensitive and rapid homogeneous time-resolved fluorescence immunoassay to establish an indirect competitive W-Compound quantitative detection method called AlphaLisa (ICW-AlphaLisa), to measure the levels of W-Compound in maternal serum during pregnancy.[42] We developed specific polyclonal antibodies against W-Compound [a 3,3′-diiodothyronine sulfate ($T_2S$) immuno-crossreactive material] and established an ICW quantitative detection method using AlphaLISA. In this method, photosensitive particles (donor beads) were coated with purified W-Compound or $T_2S$ and rabbit anti- W-Compound antibody, followed by incubation with biotinylated goat anti-rabbit antibody. This constitutes a detection system with streptavidin-coated acceptor particle. We have optimized the test conditions and evaluated the detection performance. The sensitivity of the method was 5 pg/ml in a detection range of 5-10,000 pg/ml. The intra-assay coefficient of variation averages <10% with stable reproducibility. The ICW-AlphaLISA shows good stability and high sensitivity and can measure a wide range of W-compound levels in extracts of maternal serum samples.[42]

**Abbreviations**

ADHD: Attention Deficit/Hyperactivity Disorder
CH: Congenital Hypothyroidism
D1, D2, and D3: Type I, Type II, And Type III Iodothyronine Deiodinase
DiacS: Sulfated 3,3'-Diiodothyroacetic Acid
LAO/AT: L-Amino Acid Oxidase/Aminotransferase
SULT or ST: Sulfotransferases
T1, T2 and T3: Mono-, Di-, and Tri-iodothyronine
T4: Thyroxine
T4S, T3S, rT3S, T2S and T1S: Sulfated T4, T3, rT3, T2 and T1
TH: Thyroid Hormone
TriacS: Sulfated 3,3',5-Triiodothyroacetic Acid
TSH: Thyroid Stimulating Hormone
TSHR: TSH Receptor
W-Compound: A T2S-immuno-cross-reactive material in maternal circulation in human pregnancy displays as a peak adjacent to but unidentical to synthetic T2S on HLPC, which is named as the W-compound whose levels significantly correlate with fetal thyroid function in humans.

**Table 1: The Production Rates (PR, µg/kg/d) and Clearance Rates (CR, l/kg/d) in adult, newborn and fetal sheep in T4, T3 and rT3 ontogeny. Data are presented as mean (+ SEM) and are summarized from Reference 25.**

| | $T_4$ | | $T_3$ | | $rT_3$ | |
|---|---|---|---|---|---|---|
| Animal Age | CR (l/kg/d) | PR (µg/kg/d) | CR (l/kg/d) | PR (µg/kg/d) | CR (l/kg/d) | PR (µg/kg/d) |
| Adult | 0.06 ± 0.01 | 3.3 ± 0.7 | 1 ± .1 | 0.6 ± .01 | 1.7 ± .4 | 0.9 ± .1 |
| Newborn (1st wk) | 0.7 ± .1 | 51 ± 7 | 4 ± 1 | 9.6 ± .6 | 2.8 ± .3 | 2.9 ± .2 |
| Fetus | | | | | | |
| <125 d | 0.4 ± .01 | 35 ± 11 | 43 ± 20 | 2.4 ± 0.8 | — | — |
| >135 d | 0.6 ± 0.2 | 50 ± 13 | 84 ± 32 | 6.4 ± 2.1 | 1.1 ± 0.1 | 5.9 ± 0.7 |

**Figures**

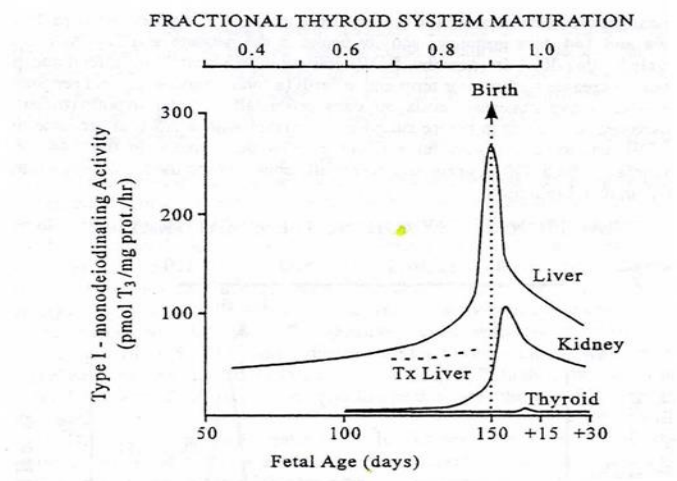


**Fig. 1: The maturation of type I mono-deiodinase activities in ovine liver, kidney and thyroid.**

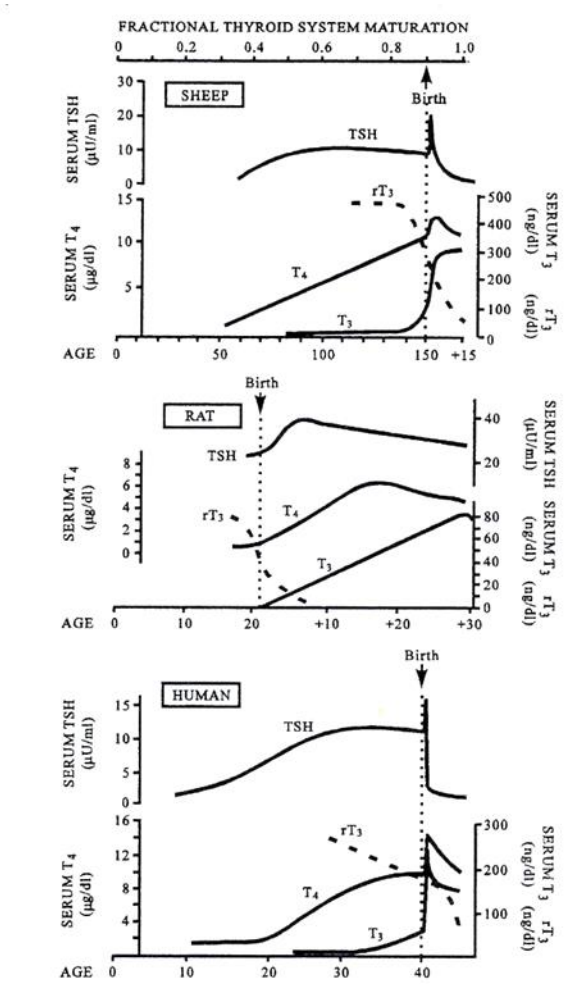


**Fig 2: Maturation of TH metabolism in the developing sheep, rat and human. Data are plotted as function of gestational age.**

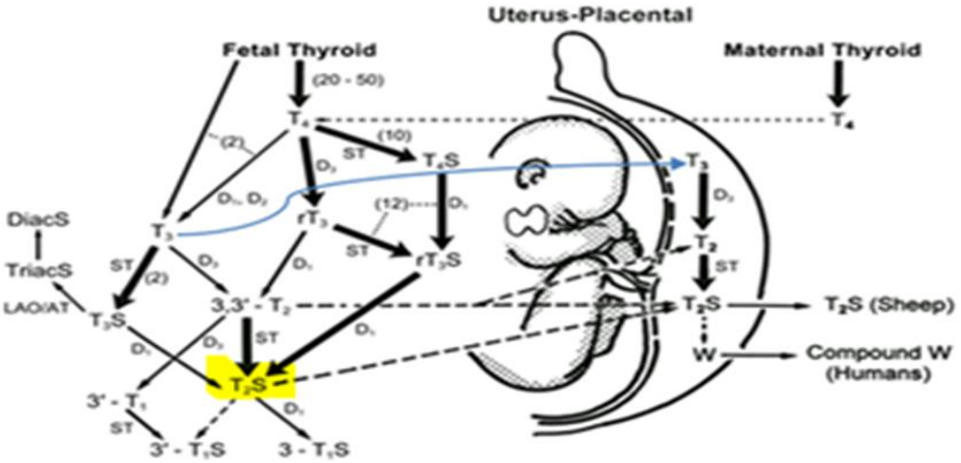


**Fig. 3: Postulated metabolic pathways for ovine fetal thyroid hormones. Heavy solid lines indicate pathways that are more active in fetuses than in adults; thin solid lines, pathways that are less active in fetuses. The upper horizontal light dotted line depicts T4 of maternal origin moving to the fetal compartment in the first trimester, before the fetal thyroid begins functioning. The blue line indicates the transfer of fetal T3, through placenta D3 and ST to form T2S, into maternal compartment. Other broken lines represent unconfirmed pathways. Numbers in parentheses indicate published production rates (μg/kg/d) (3). (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, TriacS sulfated 3,3',5-triiodothyroacetic acid).**

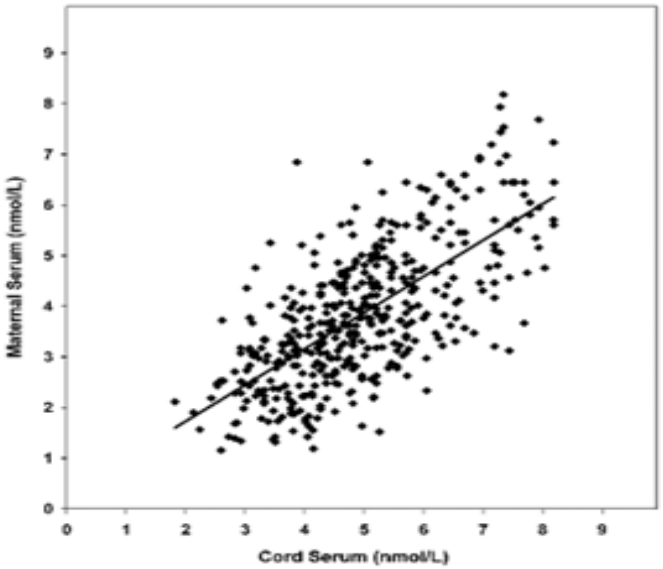


**Fig. 4: Levels of T2S-crossreactive material, W-compound, in paired maternal and cord serum at term. The solid line is the trend-line from lineal regression analysis for the correlation (n = 436, R = 0.686).**

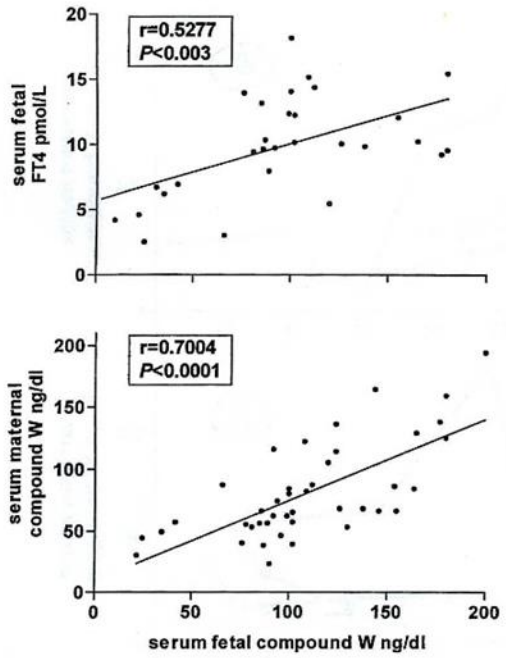


**Fig. 5: W-Compound levels in fetal serum correlation with serum fetal FT4 (n=29) and maternal W-compound (n=42).**

**SUMMARY**

Thyroid hormone (TH) plays a critical role in early fetal brain development during the first trimester, including the proliferation, migration, and differentiation of neuronal cells. Because this developmental window occurs before birth, some neurological defects may be irreversible by the time treatment begins after birth according to the current neonatal screening. There are persistent reports of mild brain damage and lower IQ in some children with congenital hypothyroidism (CH) despite early detection and treatment after birth, reveal potential shortcomings in the current neonatal screening strategy and underscore the need for improvement. In this review, we propose an alternate approach to assess fetal thyroid function in utero by examining the characteristic fetal thyroid hormone (TH) metabolism—specifically, the sulfation pathway. Further investigation into fetal TH metabolism and function may provide a rational alternative for managing CH at the early stage of fetal development and mitigating long-term adverse outcomes from neonatal-screen-ssociated "catch-up" treatment.

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