REPLY

To the Editor:

It clearly is important to be able to reliably and safely evaluate fetal thyroid function in utero. We and others have been looking for ways to do so for several decades.[1] Drs Wu, Fisher, and their colleagues described a radioimmunoassay (RIA) for serum 3,3′-diiodothyronine sulfate (T_2S) in 1994 and noted increased serum T_2S levels in pregnant women.[2] However, they noted that the increase in serum T_2S levels in pregnancy was likely related to a substance other than T_2S, which they called "compound W." Compound W was described as T_2S-like since it reacted with anti-T_2S antibody, but it differed from T_2S in its stability at acidic pH and its migration in chromatography. In this and subsequent several studies, Wu, Fisher, and their coworkers have claimed that maternal serum compound W levels as measured by their T_2S-RIA reflected fetal thyroid function in utero.[2-7]

It is nearly 10 years now from the initial description of compound W, during which time we have awaited anxiously to learn more about the nature and structure of compound W, how it is formed, and what its detailed characteristics may be. Although it has been shown that compound W is abundant in sera and urine of pregnant women, the substance has not been available in purified form in any appreciable quantity to work with. No specific anti–compound W antibodies have been prepared, and it remains to be clearly established that compound W is indeed clearly different from T_2S in all or most aspects. Two coauthors of the initial report[2] (Huang and Chen)[8] have set up a similar RIA for T_2S in Taipei, Taiwan and confirmed their original findings. Curiously, however, Huang, Chen, and their coworkers described the increase in immunoreactivity in sera of pregnant women as due to T_2S and did not note it as compound W in their abstract.[8]

In view of the importance of a reliable tool to evaluate fetal thyroid function in utero, we chose to prepare another anti-T_2S antibody and employed it in a separate RIA using this new antibody. Our results using this RIA were the subject of a recent report.[9] While we confirmed Wu, Fisher, and coworkers' findings of an increased serum T_2S levels in sera of pregnant women and newborn cord blood, our data did not support the notion that fetal thyroid function is the only or the main factor responsible for high serum T_2S in pregnant women.[9]

Wu and Fisher are concerned[3] that mean serum T_2S level measured in our normal (male and female) subjects (~50 ng/dL) was substantially higher than that of approximately 10 ng/dL observed by them in a small number of female subjects. We have discussed this difference in normal values, to the extent it was possible, in our paper.[9] We believe that Wu and Fisher do not have comprehensive data in normal subjects to adequately compare their normal values with those in our normal subjects. For some unclear reason, Wu and Fisher have noted in their letter[3] an average normal serum level of 3,3′-T_2 of about 5 ng/dL. This value may have been noted in an attempt to reflect their anticipation that there should be some (roughly 1:1 or 2:1) relationship between serum T_2 and T_2S levels. However, their basis for such a notion is not known. Serum T_2 levels in various studies have ranged approximately between 0.9 to 18 ng/dL and individual values up to 29 ng/dL have been recorded.[10-14] No data are available at present on metabolic clearance rate (MCR) of T_2S. However, Wu and Fisher[3] go on to assume that it is about 700 L/d. We suspect that this assumption is incorrect, and we should await adequate actual data before calculating production rate (PRs) of T_2S.

In our studies,[9] we could not clearly explain the increase in serum T_2S levels in pregnancy simply as a function of gestational age. Additionally, we observed that administration of estrogen to normal women can be associated with a substantial increase in serum T_2S levels.[9] This turned out to be the case even though our studies showed that T_2S binds poorly to thyroxine-binding globulin (TBG), known to be increased after estrogen administration.[9] These various findings led us to argue that fetal thyroid function may be a contributor but not a major factor influencing serum T_2S levels in pregnant women.[9]

Our data suggesting that serum T_2S levels in pregnancy may not reliably reflect fetal thyroid function led us to consider a possibility that our T_2S antibody may not be reacting with compound W. However, Wu and Fisher note in their letter (paragraph 2) the observation that the majority of T_2S-like (anti-T_2S reactive) material in pregnant and cord blood sera is not T_2S per se but compound W.[3] This observation would indicate that markedly elevated T_2S levels that we have observed in sera of pregnant women and newborn cord blood were actually related to the so-called compound W.

Wu and Fisher assert that serum levels of compound W as measured by their T_2S RIA mainly reflect fetal thyroid function.[2,3] However, there are important inconsistencies with this notion in their data. Thus, they found that serum T_2S (compound W) levels increased about 4.5-fold (from 10 to 45 ng/dL) during the first trimester of pregnancy. Since fetal thyroid begins to form thyroid hormones only at or after about 12 weeks gestation,[15] a 4.5-fold increase in serum T_2S levels observed by Wu, Fisher, and colleagues in that first trimester of pregnancy[2] cannot be ascribed to fetal thyroid function. Similarly, Wu, Fisher, and colleagues observed that serum T_2S (compound W) levels at 1 day postpartum averaged 90 ng/dL,[2] which was about 56% of the value before delivery and 9-fold greater than the average value of serum T_2S (compound W) level of 10 ng/dL in normal (nonpregnant) women. This markedly (9-fold) elevated maternal serum T_2S (compound W) level 1 day after delivery cannot be ascribed to fetal thyroid function. Although no data are available on MCR and volume of distribution (VD) of T_2S, a consideration of some estimates of these parameters is of interest. Thus, if MCR of T_2S were 700 L/d as suggested by Wu and Fisher[3] and its VD approximated 50 L, the half-life of T_2S can be calculated to be about 1.18 hours. If fetal thyroid function were the main factor responsible for elevated serum T_2S level in pregnancy, this short half-life of T_2S suggests that Wu and Fisher and their colleagues would have found no elevation of serum T_2S 1 day postpartum. This would appear to be the case even if one considers much lower MCR of T_2S of about 200 L/d and its VD to be 50 L. Interestingly, however, Wu, Fisher, and colleagues found that serum

T_2S levels, while decreasing, remained elevated when measured up to 7 days postpartum.[3] Thus, it is obvious that there are important factors other than fetal thyroid function that influence maternal serum T_2S (compound W) levels.

It is clear that proponents for the existence of a compound W and its possible relation to fetal thyroid function should first determine what they are actually measuring in maternal sera using T_2S RIA, its structure and its relation to T_2S. If it is indeed an interesting compound that is different and distinct from T_2S, efforts should be focused on obtaining it in a purified form in quantities that can help develop a specific RIA or another assay to measure its serum levels specifically and then study its relation to fetal thyroid function. We feel that such studies are more needed than clinical studies attempted thus far[3-7] to define the utility of compound W measurements in evaluation of fetal thyroid function in uterus. In the meantime, however, our data and analysis of other available data do not support the notion that measurements of T_2S or compound W using T_2S RIA will yield adequate data to evaluate fetal thyroid function in utero.

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