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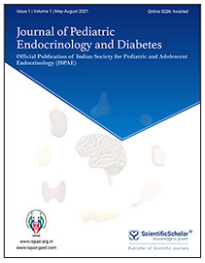

Editorial

Maternal hypothyroidism and mildly elevated thyroid-stimulating hormone levels during newborn screening – Is it clinically important?

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Untreated congenital hypothyroidism (CH) leads to severe intellectual disability. This points out the great importance of universal newborn screening for CH (as well as for other conditions), as devastating for the affected child/adult, family, and society. In India, such screening is performed by certain hospitals in certain population centers, but not universally in all infants born in the country.

Among those screened globally, mild thyrotropin (TSH) elevation presents several dilemmas. Is mild TSH elevation of clinical importance, that is, does it lead to adverse consequences? How long should the clinician wait for resolution of mild TSH elevation before starting thyroid hormone replacement therapy? The definition of "transient" neonatal hyperthyrotropinemia (TNH, as abbreviated in the paper by Sanjeev *et al*., 2022) depends on resolution of the mild TSH elevation, typically by 2 weeks and in "persistent" TNH by 4 weeks.[1]

What if the TSH is still elevated at 6 weeks?…8 weeks?...3 months? One cannot call it transient, until after the condition has resolved, until then mild TSH elevations has to be considered to be mild hypothyroidism, with close follow-up required. Other authors have labeled this "neonatal hyperthyrotropinemia."[2,3] Current guidelines state that infants with persistent TSH elevation remaining above the level of 5 mU/L at 4 weeks should be started on therapy.[4-6] Sanjeev *et al*. use the TSH values of 10–20 mU/L as persistent elevation.[1]

An even larger literature deals with "transient hypothyroidism" where infants clearly have CH and are treated for years. Then when they are taken off therapy at age 3 years as recommended or at another age, their TSH is normal.[4-6]

There has been controversy in the literature about the potential effect of maternal hypothyroidism on infant neurological development and infant thyroid function, ever since publication of the article by Haddow *et al*. which showed full scale intelligence quotient scores in 48 children whose mothers were not treated to be 7 points lower than those of control children at ages 7–9 years of age.[7] Li *et al*. showed similar effects (a difference from controls of about 9 or 10 points) of maternal subclinical hypothyroidism, hypothyroxinemia, or elevated thyroid peroxidase antibody titers in 81 infants evaluated at 25–30 months of age.[8] In contrast, Monaghan *et al*. did not find that maternal thyroid function was associated with neurodevelopmental outcomes in their "high fish-eating population" evaluated at 20 months of age.[9] Maternal hypothyroidism and offspring development might be observed to be more associated in an iodine-deficient population.

Other factors proposed have been transplacental passage of maternal thyroid antibodies, drugs, small for gestational age, newborn illness, and prematurity.[10,11]

Among the 50 infants in this study born to hypothyroid mothers and followed until 6 months of age, 6% had TNH, 2 with resolution by 2 weeks and one by 4 weeks.[1] All 50 (including the 3 with TNH) had normal development at 6 months of age. However, all mothers had been treated from the time of identification of their TSH elevation early in the first or second trimester. In addition, the article's statistics were done after excluding 13 additional infants (21% of the total of 63) who were born premature, with APGAR score of <6, or who required care in an intensive care unit. These are conditions that might also result from maternal hypothyroidism. Therefore, if the 13 had also been followed in the study, there might have been additional infants with TSH elevation. Thus, 6% might be an underestimation of occurrence of TNH or true CH.

All 50 infants in the current study had normal thyroid function by 4 weeks of age and normal development at 6 months of age, thus no adverse effects of maternal hypothyroidism were evident in assessable development in these 50 at 6 months of age.

However, this observation does not remove the need to keep track of thyroid function and development in infants born to hypothyroid mothers. To establish a clear slate free of concern for infants born to mothers who had hypothyroidism during pregnancy requires a larger study group, a control group, and a longer developmental follow-up. A longer follow-up is critical to discern differences from normal in skills that are not evident at 6 months of age, such as language, memory, vision, hearing, reading ability, attention, and persistence. Fortunately, Sanjeev *et al*. plan to continue follow-up of this cohort.

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