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COMMENT

Approaching the diagnosis of thyroid disorders in preterm infants

Francisca Grob [1,2]✉

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Children born prematurely display a unique and dynamic pattern of thyroid hormone concentrations that varies after birth depending on gestational and chronological age and other postnatal variables. Not only hypothalamic–pituitary–thyroid (HPT) axis immaturity but also withdrawal of maternal–placental thyroxine (T_4) transfer after birth, morbidities, medication, iodine exposure, low weight, the persistence of foetal metabolism of deiodinases and a smaller thyroid gland affect thyroid hormone physiology. Premature infants exhibit lower T_4 concentrations when compared with foetuses at the same gestational age,[1] usually called "hypothyroxinaemia of prematurity". Additionally, reductions in T_4 are even more pronounced in very low birth weight newborns when critically ill, reaching a nadir at the end of the first week of life and then gradually rising from this time onwards until overlapping levels seen in term infants.[2] Furthermore, thyroid-stimulating hormone (TSH) concentrations at birth are lower in this population than those observed in term infants, and in some cases present a late rise which is not seen in term babies.[3] This condition, entitled "hyperthyrotropinaemia", i.e. mild elevation of TSH with normal T_4 concentrations, is frequently characterised by having a normal thyroid gland anatomy and by being transient.[4]

Definition of normal postnatal serum thyroid hormones that take into account the particularities of preterm infant variability has not been established yet, and knowledge of physiological changes is essential for understanding and developing normal reference intervals. Clinical features suggestive of thyroid dysfunction are often present in this population regardless of their thyroid profile: they are often admitted to the Neonatal Intensive Care Unit with cardiac dysfunction, temperature instability, coagulation disorders, bradycardia, apnoea and hypotonia. These are therefore not useful to differentiate children at risk of hypothyroidism. Particularly during a critical period of brain development, thyroid hormone ranges that consider not only gestational age at birth but also postnatal age are needed.

In this issue of *Pediatric Research*, Ziegler et al. report thyroid hormone reference intervals in a cohort of preterm infants admitted at a single hospital in Ohio, United States, over 7 years. The postmenstrual age (PMA), reflective of both the gestational age at birth as well as the postnatal chronological age, was calculated to obtain TSH and T_4 concentrations in a cohort of children with neither HPT disease nor thyroxine treatment. An overall small and gradual rise in free T_4 values with increased PMA was found, but TSH did not show such a significant change. Few studies have assessed postnatal trends in thyroid hormones, corrected for gestational age, beyond the first week of life. The Scottish preterm thyroid group published reference values for a smaller group of preterm infants during the first month of life and compared them to those of term infants.[2] Similar to the study of Ziegler et al., a lower postnatal increase in FT_4 levels with concomitant reductions in T_4 and T_3 in infants requiring maximal intensive care and similar TSH values was observed in all gestational groups.[5] Others have proposed the use of a single reference interval across all gestational ages.[6] However, significant variability between thyroid hormone assays limits the wide use of single reference intervals, which should derive from the same assay used to test the patient.

The decision to treat children with a certain thyroid hormone profile must incorporate the potential long-term neurodevelopmental and cognitive impairment of children with mildly elevated or reduced neonatal TSH and T_4 levels, respectively. Outcome studies of duration and cognitive consequences of thyroid hormone abnormalities in preterm infants are scarce and confusing, as a threshold selection for TSH or T_4 and primary outcomes vary among studies. In neonatal hyperthyrotropinaemia, a systematic review including 82% of infants who received levothyroxine did not show adverse developmental outcomes during infancy or childhood.[7] Studies in term infants have shown that mildly elevated neonatal TSH levels are linked with being exempt from school testing due to significant or complex disability[8] and poor educational and developmental outcomes.[9] Similar studies are lacking in the preterm population. However, smaller follow-up studies have reported that the 3% of infants consistently in the top decile of gestationally age-adjusted TSH levels had a significant reduction in cognitive, motor and fine motor scores when compared with those not in the top decile.[10] Hyperthyrotropinaemia appears to behave differently within the preterm population, where often mild and transient TSH elevation with no long-term developmental consequences is observed.[11] Nonetheless, more studies are needed to determine the long-term developmental impact of a mildly elevated TSH and normal T_4, whether treated or not.

The selection of different definitions of hypothyroxinaemia of prematurity among studies makes the interpretation of the reported outcomes difficult. Neurocognitive outcomes in premature infants with persistent low T_4 concentrations for gestational and chronological age seem to be adverse in those persistently affected by low T_4 concentrations[10] but not in those

[1]Division of Pediatrics, School of Medicine, Pontificia Universidad Católica de Chile, Santiago, Chile. [2]Murdoch children's research institute (MCRI), Melbourne, Australia.
✉email: fgrob@med.puc.cl

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having a single postnatal isolated low measurement.[12] Similarly, after adjustment for confounders, hypothyroxinaemic infants have scored significantly lower than euthyroid infants on the general cognitive and verbal scales at 5 years old.[13] Conversely, others have also suggested that higher postnatal free T_4 may be a marker of adverse neuropsychological development in a small sample of preterm infants.[14] The effects of thyroxine supplementation on long-term neurologic development remain to be established. In 2007, a Cochrane systematic review did not support the administration of prophylactic postnatal thyroid hormones to prevent morbidity and mortality or to improve neurodevelopmental outcomes in preterm infants. Subsequent randomised controlled studies with thyroid hormones[15,16] and a systematic review assessing the evidence from randomised controlled trials on dietary supplementation with iodine[17] have also failed to demonstrate the benefits of treatment on mortality or cognition.

Establishing normal ranges for thyroid hormones in premature infants is a valuable tool not only for identifying children at risk of adverse cognitive outcomes, but also to avoid the overdiagnosis of hypothyroidism in this fragile population.[18] Extrapolation and comparison of these results to different preterm populations need to be carefully considered, as reference values are affected by many variables, such as the patient population and the laboratory methods used.

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COMPETING INTERESTS

The author declares no competing interests.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Patient consent was not required.

ADDITIONAL INFORMATION

Correspondence and requests for materials should be addressed to Francisca Grob.