Transient Hypothyroxinemia of Prematurity: Does it Have Clinical Relevance?

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Rapid advances in neonatal care have led to a dramatic surge in survival of the very- and extremely-premature infants. This is, however, tempered by a concomitant increase in the incidence of severe neuromorbidity in the survivors, including cognitive delay, cerebral palsy, hearing loss, blindness, mental retardation, and epilepsy. Thus, an emerging challenge in newborn care is to translate the gains in survival achieved into gains in healthy survival, without the current high frequency of neurodevelopmental impairments.

Transient hypothyroxinemia of prematurity (THOP), though a self-limiting condition seen in newborns <34 weeks of gestation, assumes significance since its occurrence coincides with the period critical for brain development. In newborns with congenital hypothyroidism, a delay of even two weeks in instituting thyroxine (T_4) replacement has an adverse impact on the intelligence quotient (IQ). Motor and cognitive deficits are seen in these children despite early thyroxine replacement. Thus, even transiently low thyroxine levels are considered to be a potent risk factor for adverse neurodevelopmental outcome in preterm infants and have been the subject of many elegant long-term studies [1-5]. All cohorts have documented a measure of abnormal mental development in children with THOP. Concern about the possible consequences of hypothyroidism has also led to several trials of treatment with thyroxine.

In the article published in this issue of the journal, Dilli, *et al.* [6] have reported the neurodevelopmental status of preterm infants born at ≤ 32 weeks gestation with a birth weight of ≤1500 g, at 18-24 months corrected age. They have reported similar mean mental and psychomotor developmental index scores in infants with and without THOP. After adjustment for gestational age and multiple perinatal and neonatal variables, they found that THOP is not associated with an increased risk of disabling cerebral palsy or reduction in MDI or PDI scores. Based on these observations, the authors have concluded that THOP may not be an important cause of neurological problems or delayed mental development in these infants. The results of this study; however, need to be interpreted with caution. Firstly, the very cut-off value of T_4 used by the authors to define THOP is much higher that the usually accepted definitions. Though there is no consensus on the level of thyroxine for defining hypothyroxinemia in the preterm, definitions used by other authors have been 2 [1], 2.6 [2], or 3 [3,4] SDS below the mean thyroxine level seen on newborn screening of the reference population. Other authors have used an absolute cut-off level like 40 nmol/L [7] or 6 mcg/dL for T_4 [8]. All these are significantly lower that the 25th centile used by the authors of the present study, which corresponds to more than -1 SDS (-1 SDS = 15.9 percentile). Thus many infants classified as hypothyroxinemic in this study do not meet the criterion used by others. In fact, for preterm infants more appropriate levels for comparison of thyroxine values are T_4/free T_4 levels in cord blood corrected for an equivalent gestational age had the infant remained in utero [5]. Using a cut-off of 10th centile of cord T_4 corrected for gestational age, Delahunty, *et al*., [5] found that 20% of all infants born at <34 weeks gestation were hypothyroxinemic, with only 10% being between 31-34 weeks, and rest more premature. Reuss, *et al*. [2] found a 15% incidence of THOP in infants born at <33 weeks gestation using a cut-off of -2.6 SD. Dilli, *et al*. [6], on the other hand, have classified nearly 29% of their subjects to have THOP using a higher cut-off value. It is therefore not surprising that results reported in this study are better than those reported by other authors. Another important factor that could have a bearing on the results of this study is the small number of subjects, despite using a higher cut-off criterion. This is evident by the wide range of 95% CIs reported for the odds ratios. Absence of a significant association of adverse neurodevelopmental outcome with not only THOP, but also with other important medical morbidities is also a likely reflection of the small sample size.

Thus, concerns about long-term effects of THOP remain, and establishing the role of thyroxine

supplementation, especially to extremely premature infants or those with documented hypothyroxinemia remains a research priority.

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Late Preterm Births: Major Cause of Prematurity and Adverse Outcomes of Neonatal Hyperbilirubinemia

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Occurrence and consequence of late preterm births (239 to 259 days of gestational age, GA) is a public health problem that is preventable. These infants account for the bulk of a nation's preterm population (of all USA preterm births, 74% are late-preterm), adversely impact on national breastfeeding rates, increase direct healthcare cost by need for readmission of infants for severe hyperbilirubinemia and hypernatremic dehydration, as well as increase the risk for irreversible brain damage due to kernicterus [1-4].

As a sub-cohort of the preterm population, late-preterm infants masquerade as term infants (<37 weeks and 0/7 days of GA) on the basis of their relatively mature appearance, but remain physiologically and metabolically immature [2]. Currently, most late preterm infants are cared for by their mothers and discharged home with unmonitored home care. Consequently, late-preterm infants are at higher risk than term infants of developing medical complications that result in higher rates of mortality and morbidity, and have higher rates of hospital readmission during the neonatal period than term infants.

Maturational factors that impact postnatal adaptation include brain and autonomic nervous system growth and induction of hepatic metabolic pathways. The brain volume of an infant at 36 weeks GA is only about 60% of that for a term infant [5]. Reduced number of sulci and gyri reflect an anatomic in maturity that is defined by the white matter, myelination and cortical migration of neuronal cells. Late-preterm infants are also more susceptible to gray matter injury induced by hypoxia-ischemia than the term infant. Low oromotor tone, function, and neural maturation also predispose these infants to dehydration and hyperbilirubinemia that are associated with poor feeding in the breastfed infant. Breastfeeding of a preterm infant also requires special coaching of the mother [7]. Decreased maternal breast stimulation and decreased breast emptying and lead to suboptimal milk transfer to the baby as well as decreased maternal milk production. This leads to excessive weight loss and decreased bilirubin excretion leading to dehydration, slow postnatal weight gain and newborn jaundice. Jaundice and hyperbilirubinemia occur more commonly and are more prolonged among late preterm infants than term infants because of delayed maturation