Re-Evaluating "Transitional Neonatal Hypoglycemia": Mechanism and Implications for Management

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A Committee of the Pediatric Endocrine Society was recently formed to develop guidelines for evaluation and management of hypoglycemia in neonates, infants, and children. To aid in formulating recommendations for neonates, in this review, we analyzed available data on the brief period of hypoglycemia, which commonly is observed in normal newborns during the transition from fetal to extrauterine life, hereafter referred to as transitional neonatal hypoglycemia in normal newborns. The goal was to better understand the mechanism underlying this phenomenon in order to formulate recommendations for recognizing neonates requiring diagnosis and treatment during the first days of life for disorders causing severe and persistent hypoglycemia.

It has long been known that plasma glucose concentrations are lower in the first 1-3 days of life in normal newborn infants than at later ages. Not until the 1960s was it appreciated that hypoglycemia in neonates could sometimes be symptomatic and, as in older infants and children, cause seizures or permanent brain damage.[1,2] Although studies in laboratory animals have demonstrated postnatal developmental changes in specific enzymes involved in hepatic gluconeogenesis and ketogenesis,[3,4] it is unclear that such changes adequately explain transitional neonatal hypoglycemia in human newborns or if other mechanisms may be involved.[5,6] A National Institutes of Health conference outlined many of the "gaps in knowledge" about neonatal hypoglycemia and lamented the lack of a rational basis for defining hypoglycemia in neonates.[7]

For this re-evaluation of transitional neonatal hypoglycemia in normal newborns, we used the strategy routinely employed by pediatric endocrinologists for evaluation of hypoglycemia in older infants and children. This strategy, based on an examination of the major metabolic fuel and hormone responses to hypoglycemia, makes it possible to discover the mechanism of hypoglycemia and to make a specific diagnosis of the underlying cause (**Figure**; available at www.jpeds.com).[8] We reviewed published data in normal newborns on metabolic fuel and hormone responses during the period of transitional neonatal hypoglycemia. We focused on mean responses as being most likely representative of normal newborns, recognizing the possibility of heterogeneity, particularly with regard to peripartum stresses and feeding practices. We found that transitional neonatal hypoglycemia most closely resembles known genetic forms of congenital hyperinsulinism, which cause a lowering of the plasma glucose threshold for suppression of insulin secretion. This conclusion is based on strong evidence supported by 2 or more independent reports and provides a novel perspective on both the diagnosis and management of hypoglycemia in the first several days after birth.

AGA	Appropriate for gestational age
FFA	Free fatty acid
P1	Postnatal day 1
SGA	Small for gestational age

Patterns of Plasma Glucose Concentrations in Normal Newborns during the First Days of Life

Prior to birth, fetal fuel metabolism is based primarily on oxidation of glucose, which is supplied from maternal plasma glucose whose levels are regulated by maternal insulin secretion.[9] The fetal brain is exposed to circulating glucose concentrations only slightly below those of maternal plasma; with normal maternal glucose concentrations of 70-90 mg/dL (3.9-5.0 mmol/L), the mean fetal-maternal plasma glucose difference at term is only 9 mg/dL (0.5 mmol/L).[10] Fetal insulin secretion is responsive to fetal plasma glucose concentrations, but fetal glucose concentrations are determined primarily by maternal glucose concentration whereas fetal insulin primarily functions to regulate growth.[11]

Immediately following birth, in normal newborns, the mean plasma glucose concentrations drop by 25-30 mg/dL

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(1.4-1.7 mmol/L) to a nadir of about 55-60 mg/dL (3-3.3 mmol/L) by 1-2 hours of age; glucose levels then steadily rise over the first few days of life to return to the normal range for infants, children, and adults (70-100 mg/dL [3.9-5.6 mmol/L]). A large 1971 study by Lubchenco and Bard[12] found that plasma glucose concentrations prior to the first feeding at 8 hours of age were <70 mg/dL (3.9 mmol/L) in over 80% of 126 term-appropriate for gestational age (AGA) neonates and clustered around a mean of 54 mg/dL (3 mmol/L). The lowest glucose values (<30 mg/dL, 1.7 mmol/L) appeared to be especially associated with peripartum stresses (fetal distress, birth asphyxia, or low Apgar scores) and with low weight-for-length ratios, consistent with fetal growth restriction. This is noteworthy because perinatal stress is now recognized to be associated with hyperinsulinemic hypoglycemia that may continue until several weeks of age.[13,14] Also noteworthy is that by the third day of life, none of the 126 term AGA neonates had a plasma glucose concentration below 50 mg/dL (2.8 mmol/L). Thus, extreme low glucose levels in normal neonates on the first day of life largely reflect peripartum factors.

The time-course of transitional neonatal hypoglycemia in normal newborns has been described in numerous, primarily cross-sectional, studies using relatively small groups of infants.[5,15-18] A representative example is the 1965 study by Cornblath et al, comparing glucose concentrations in normal weight and low birthweight newborn infants over the first 3 weeks of life.[5] Immediately after birth, mean plasma glucose concentrations fell in the normal newborns to ~60 mg/dL (3.3 mmol/L) at 2 hours (in this manuscript, whole blood glucose concentrations have been converted to equivalent plasma concentrations using a factor of 1.15). Glucose levels then rose steadily to stabilize at a mean plasma concentration greater than 80 mg/dL (4.4 mmol/L) by day of life 3. Similar patterns have been reported by others. For example, studies by Hawdon et al showed mean plasma glucose values of 56-59 mg/dL (3.1-3.3 mmol/L) in the first 12 hours of life compared with a mean glucose of 74 mg/dL (4.1 mmol/L) by day of life 4.[15] Thus, one important feature of transitional neonatal hypoglycemia in normal newborns is that plasma glucose levels are lowest early on the first day of life, and then progressively increase over the subsequent 2-3 days to reach the range of normal for older infants and children.

A second important feature of transitional neonatal hypoglycemia in normal infants is that the concentrations of plasma glucose are remarkably stable and relatively unaffected by the timing of initial feeding or interval between feedings. For example, in a study of fasting responses in 24 term AGA infants monitored hourly for the first 8-hour period of fasting after birth,[19] most maintained stable levels of plasma glucose throughout the 8 hours; the mean (± SD) plasma glucose concentration at 8 hours of age was 57 ± 12 mg/dL (3.2 ± 0.7 mmol/L). This apparent stability of low plasma glucose levels in transitional neonatal hypoglycemia is also demonstrated by data from older studies when the normal nursery feeding practice was to withhold feedings for a full day or more after birth. In a 1950 study by Desmond et al, mean plasma glucose levels in normal newborn infants who had received no calories for 24 hours after birth were 57-69 mg/dL (3.2-3.8 mM), which is similar to the values during the first hours of life from more recent studies.[5,15,20] In addition, infants who are breastfed consume very few calories from colostrum during the first days after birth, but have plasma glucose concentrations only slightly lower than bottle-fed infants.[21]

In summary, the pattern of plasma glucose levels during the period of transitional neonatal hypoglycemia suggests a regulated process in normal newborn infants in which the mean plasma glucose concentration is initially maintained at ~55-65 mg/dL (3.1-3.6 mmol/L), but then increases to >70 mg/dL (>3.9 mmol/L) by 2-3 days after birth. This pattern of a stable degree of hypoglycemia cannot be readily explained by the developmental deficiencies in hepatic enzymes of glycogenolysis, gluconeogenesis, or ketogenesis identified in animal studies.

Transitional Neonatal Hypoglycemia in Normal Newborns Is a Hypoketotic Hypoglycemia

As noted above, the underlying mechanisms of hypoglycemia are best elucidated by examining the hormonal and metabolic fuel responses as hypoglycemia develops. The approach was applied in 3 studies of transitional neonatal hypoglycemia in normal newborns between 1974 and 1992[15,19,22]; more recent studies are not available. They all demonstrate that low glucose concentrations on the first day of life are associated with remarkably low concentrations of plasma ketones.

For example, in the study mentioned above by Stanley et al, fuel and hormone responses were measured in 4 groups of neonates (term and preterm, AGA and small for gestational age [SGA]) at the end of their first 8 hour postnatal period of fasting.[19] In term AGA neonates with glucoses greater than or lower than 40 mg/dL (2.2 mmol/L), plasma total ketones were 0.37 and 0.18 mmol/L, respectively (ie, ~10-fold lower compared with 24-hour fasted normal older children [2.7 mmol/L])[8] despite similar degrees of hypoglycemia. The suppression of ketones in term AGA neonates was very similar to infants with hyperinsulinemic hypoglycemia (0.7 mmol/L).[8] This study also showed that plasma total ketones remained extremely low across the entire range of plasma glucose concentrations in preterm-AGA, term-SGA, preterm-SGA, as well as term-AGA infants. Similar data showing low ketones especially on the first day of life in both AGA and SGA neonates were reported by Haymond et al in 1974[22] and by Hawdon et al in 1992.[15]

Because rates of ketone utilization by the brain are directly proportional to their plasma concentrations,[23] the contribution of ketones to neonatal brain metabolism is less than one-tenth that of older children with similar degrees of hypoglycemia. Plasma free fatty acid (FFA) concentrations were not completely suppressed in the study by Stanley et al.[19] However, the values may have been artifactually elevated