Revisión de Hipoglicemia Neonatal. 2016.

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Propósito de la revisión

La detección y el manejo de la hipoglucemia neonatal sigue siendo un problema confuso y polémico en neonatología. El propósito de este artículo es contrastar las recientes recomendaciones de la Academia Americana de Pediatría y la Sociedad Pediátrica de Endocrinología.

Hallazgos recientes.

Usando diferentes metodologías, las organizaciones tienen diferencias significativas en cuanto a los screening y los niveles de glucosa que se deben utilizar para el manejo de hipoglicemia. La identificación de las primeras 48 h como un estado de hiperinsulinemia de transición es un nuevo concepto importante. El enfoque neuroendocrino se contrasta con una estrategia de desarrollo neurológico para encontrar los niveles que exceden los asociados a neuroglucopenia.

Resumen

Las preguntas siguen siendo las mismas cuando se trata de la detección y manejo de niveles bajos de glucosa. Recientes estudios de outcomes con diferentes resultados siguen añadiendo controversias en cuanto a qué hacer en aras del paciente. Es incierto si el cribado universal de los niveles de glucosa en las primeras horas se debe aplicar a todos los recién nacidos. Los síndromes hipoglucémicos persistentes deben ser identificados antes de la descarga.

El objetivo principal de la recomendación de la Sociedad Pediátrica de Endocrinología (SPE) es aumentar la conciencia para descartar síndromes hipoglucémicos persistentes cuando se trata de bebés con niveles bajos de glucosa que persisten. Es relevante identificar pacientes con síndromes hipoglucémicos persistentes para prevenir lesiones neurológicas graves. Es posible que bajos niveles de glucosa de las primeras 48 horas pudieran ser precursores de trastornos metabólicos.

Por lo tanto, nosotros debemos seguir a estos recién nacidos a las 48 h y cuidadosamente supervisarlos para pesquisar el desarrollo de cualquier signo clínico asegurándonos de que alcancen glicemias mayores de 70 mg / dl después de los primeros días de vida mantenidos a través de varios ciclos de alimentación rápida.

Estamos de acuerdo con los autores que vale la pena de estudiar hasta las 6 horas de ayuno antes de la descarga en algunos recién nacidos que están con mayor riesgo de un síndrome de hipoglucemia persistente. La descarga de la guardería no debe ocurrir hasta que estos diagnósticos se descarten.

La práctica actual del manejo de niveles bajos de glucosa en las primeras 48 h de vida se basa en gran medida en la opinión de los expertos, y no hay acuerdo sobre si trata o no de una transición de hipoglucemia neonatal en recién nacidos sanos en el contexto de una variación fisiológica normal o si se trata de un marcador de una adaptación metabólica inadecuada y, en algunos casos, asociados con neuroglucopenia.

Sabemos que un nivel bajo de glucosa en la sangre puede causar convulsiones, y que puede causar daño cerebral permanente. Sin embargo, en el estudio de McKinley Et. al. , niveles más altos de glucosa después del tratamiento se asociaron con deficiencia neurosensorial, especialmente con compromiso cognitivo. En aquellos en que pasó una mayor proporción de tiempo fuera del rango central de 54-72 mg / dl en las primeras 48 h de vida tuvieron peores resultados [29 & &]. Esto sugiere que la rápida corrección de glucosa inferior a 47 mg / dl puede estar asociada con malos resultado a una concentración de glucosa sanguínea más alta.

Se hace evidente que un umbral de glucosa de 47 mg / dl no es un número "mágico" para el tratamiento de la hipoglucemia neonatal. La evidencia de datos de 'hipoglucemia' desapercibida con el monitoreo intersticial también sugiere que es necesario considerar un margen de seguridad en el establecimiento de un determinado umbral, pero por desgracia, no ha habido acuerdo sobre cuál debería ser éste. El informe sobre resultados usando cifras menores de 47 mg / dl como manejo umbral es al menos tranquilizador en el sentido de que el protocolo tiene mucha similitud con las recomendaciones del Comité de AAP sobre el feto y el recién nacido, informado en 2011 y el cual fue de nuevo recientemente ratificado.

Los niveles de glicemia más bajos documentados en la AAP, con una más prolongada y mejor vigilancia para identificar síndromes de hipoglucemia persistente después de 48 h, podría ser el mejor compromiso para evitar un overscreening, y por lo tanto sobretratamiento, sin descuidar el diagnostico de hipoglucemia persistente después del período transición antes del alta hospitalaria.

Neonatal hypoglycemia

David H. Adamkin

Purpose of review
The screening and management for neonatal hypoglycemia remains a confusing and contentious problem in neonatology. The purpose of this article is to contrast recent recommendations from the American Academy of Pediatrics and the Pediatric Endocrine Society.

Recent findings
Using different methodologies, the organizations have significant differences on whom to screen and what levels of glucose should be used for management. The identification of the first 48 h as a transitional hyperinsulinemic state is a new important concept. The neuroendocrine approach is contrasted with a neurodevelopmental strategy to find levels that exceed those associated with neuroglycopenia.

Summary
The questions remain the same when it comes to screening and management of neonatal low-glucose levels. Recent outcome studies with differing results continue to add to the controversy as to what to do at the bedside. It is uncertain if universal screening of glucose levels in the first hours should be applied to all newborn infants. Persistent hypoglycemic syndromes must be identified prior to discharge.

Keywords
brain damage, developmental delay, hypoglycemia, risk factors, seizures, transitional hyperinsulinemia

INTRODUCTION

Over 50 years ago, Cornblath *et al.* [1] recognized that low-blood glucose levels in small for gestational age (SGA) and preterm infants were associated with seizures. It became clear that symptomatic hypoglycemia could lead to long-term neurologic deficits. However, the definition of clinically significant hypoglycemia remains among the most confused and contentious issues in neonatal medicine [2▪]. We still have limited evidence-based consensus regarding the screening and management of infants at risk for hypoglycemia. Although there is agreement that recurrent severe hypoglycemia causes brain injury, there have been few high-quality studies to shed light on the neurodevelopmental outcomes related to transient neonatal hypoglycemia [3▪]. The last 2 years or so has seen new recommendations from the Pediatric Endocrine Society (PES) for the evaluation and management of hypoglycemia in neonates, infants, and children [4▪▪,5▪▪]. This guidance has differed significantly in approach and 'recommended critical thresholds' for hypoglycemia from those previously provided by the Committee on Fetus and the Newborn and the American Academy of Pediatrics (AAP) [6]. The purpose of this review is to contrast the approaches taken by the two organizations and explain how these groups came to differing recommendations. To make this comparison, we review transitional hypoglycemia, postnatal glucose homeostasis, and risk of injury from hypoglycemia using a metabolic fuel neurohormonal analyses approach versus one based on neurodevelopmental outcome.

TRANSITIONAL NEONATAL HYPOGLYCEMIA

The PES focused on the brief period of hypoglycemia that occurs in the first 48 h of life called 'transitional neonatal hypoglycemia' [2▪]. They examined major metabolic fuel and hormonal responses to low-blood glucose levels during this transition. Their conclusions were that this period resembled known forms of congenital hyperinsulinism, causing a lowering of the plasma glucose threshold for suppression of insulin secretion [2▪]. The 'fetal' glucose concentration of approximately 60 mg/dl versus

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KEY POINTS

- Screening and management for neonatal hypoglycemia remains an important part of newborn care.
- The methods used to recommend treatment levels are imperfect but do provide the clinician with ranges to decide on action based on the individual patient characteristics.
- After 72 h of age, all infants should maintain glucose concentrations of more than 70 mg/dl.

the maternal level approximated at 80 mg/dl, persists for the first 48 h of life. After the first days of life, the glucose levels become similar to adult values. The PES approach was to focus on mean glucose values as being most representative of normal newborns while the AAP guideline used the lower ranges of glucose concentrations found in the fetus and asymptomatic infants [7,8]. The endocrine-based mechanisms used to determine critical levels of glucose showed hyperinsulinemia accompanied by suppressed levels of ketones [9] and large glycemic responses to glucagon and epinephrine [10,11]. The absence of alternative fuels and the inappropriate preservation of glycogen in a newborn with low-glucose levels are consistent with a hypoketotic hyperinsulinemia [2▪].

The AAP algorithm during asymptomatic transitional neonatal hypoglycemia uses the lower ranges of glucose values from fetal and neonatal data [7,8], and suggests that the lower range is 25 mg/dl and the actionable levels are 25–40 mg/dl during the first 4 h of life. These levels approximate the fifth to tenth percentile for glucose rather than 55–60 mg/dl from the PES approach. From 4 to 24 h of age, the AAP lower range moves to less than 35 mg/dl and the actionable values 35–45 mg/dl [6]. The PES relies on data from the 1950s and 1960s where infants fasted from 8 to 24 h and found that mean glucose levels were remarkably stable, and relatively unaffected by timing of initial feeding and interval between feeds. The 8-h fast resulted in a mean plasma glucose level in normal newborn infants of 57–69 mg/dl [10]. PES suggests that the breastfed infant consumes very few calories from colostrum during the first days after birth, yet has mean plasma glucose concentrations that are only slightly lower than bottle-fed infants [12]. However, the range of values for term, appropriate for gestational age (AGA), breastfed infants from 3 h of age to 72 h is 25–144 mg/dl [13]. The interquartile range for the same period was 41–60 mg/dl [13]. Using means versus lower ranges in well, asymptomatic infants will lead to significant differences in the interpretation of thresholds. Feeding is probably more important at the lower ranges of plasma glucose and is affected by timing of initial feed and the interval between feedings. The AAP recommends breast milk feeding within first hour of life and a feeding interval, between 2 and 3 h to promote breastfeeding and maintenance of glucose levels. This represents another disconnect between the two sets of recommendations prompted by looking at mean values versus ranges for guidance.

The PES suggests a regulated process in normal newborns during the period of transitional hypoglycemia is initially maintained at approximately 55–65 mg/dl, but then increases to more than 70 mg/dl by 3 days of life. This pattern cannot be explained by developmental deficiencies in hepatic enzymes for glycogenolysis, gluconeogenesis, or ketogenesis identified in animal studies [4▪▪]. The Endocrine Society opinion for the first 48 h of life, therefore, is based on a mean value of 55–60 mg/dl in healthy normal newborns. This level is similar to the threshold for neurogenic symptoms in the older child or adult, but is above the threshold for neuroglycopenic symptoms in these individuals [5▪▪]. However, we do not know where a newborn develops neuroglycopenia, or the level at which cerebral energy deficiency occurs, and therefore the risk of brain injury [6]. The AAP approach, as we will see, uses levels from neurodevelopmental outcome studies that the AAP believes will provide a margin of safety; clinical decisions are based on the individual patient [6]. The goal is to balance safety while supporting breastfeeding and not overscreening and overtreating asymptomatic infants.

POSTNATAL GLUCOSE HOMEOSTASIS

The timing of the first feeding was important in the AAP statement on postnatal glucose homeostasis during the first hours of life [6]. At birth, the blood glucose concentration is about 70% of the maternal level. It falls rapidly to a low-range nadir by 1 h to a value as low as 20–25 mg/dl [7]. These levels are common in healthy neonates and the fall is seen in all mammalian newborns. These glucose levels are transient and the vast majority of the infants are well appearing. The decrease is considered to be part of the normal adaptation for postnatal life that helps establish postnatal glucose homeostasis [7,14,15]. Why do blood glucose concentrations fall to low levels after birth in all mammals? Are there advantages to having a lower blood glucose concentration compared with adults for the first 2 days of life? There are some speculations [16]. The decrease in glucose concentration soon after birth might be essential to stimulate physiological processes that are required for

postnatal survival, including promoting glucose production through gluconeogenesis and glycogenolysis. In addition, the decrease in glucose concentration enhances oxidative fat metabolism, stimulates appetite, and may help adapt to fast-feed cycles. Persistently lower glucose concentrations might be the result of mechanisms that were vital for the fetus to allow maternal-to-fetal glucose transport but not reversed after birth. The PES interpretation of these lower levels (<30 mg/dl) is that they appear to be associated with peripartum stresses (fetal distress, birth asphyxia, or low-Apgar scores) and with low weight-for-length ratios, consistent with fetal growth restriction. An important concern raised by the PES analyses is that perinatal stress may be associated with prolonged neonatal hyperinsulinemia that may continue until several weeks of age [17,18]. Therefore, the PES increases the risk categories from the AAP document from late preterm, and term small for gestational age, large for gestational age, and infant of diabetic mother infants to also include perinatal stress (birth asphyxia, ischemia, Cesarean sections for fetal distress), maternal preeclampsia/eclampsia or hypertension, meconium aspiration syndrome, erythroblastosis fetalis, premature, or postmature delivery. In addition, infants with a family history of genetic forms of hypoglycemia and congenital syndromes like Beckwith Wiedemann and neonates with abnormal physical findings (e.g., midline facial malformations, microphalus) should be screened [4▪▪].

These additions would add immensely to the number of infants screened and thus create the need to interpret and act on glucose levels in many asymptomatic infants. No one would argue with screening those with a family history of genetic forms of hypoglycemia, or those infants with dysmorphology suggesting the possibility of a hypoglycemic syndrome. However, screening of infants with perinatal stress would be burdensome, difficult to implement, and lead to a large number of difficult to interpret glucose levels in otherwise asymptomatic infants. A study that chose to use a value of less than 47 mg/dl to define hypoglycemia in the first 48 h of life for the four at-risk populations of neonates used in the AAP document found that 25% of all deliveries were at risk, and 51% of these four at-risk groups had at least one blood glucose concentration less than 47 mg/dl [19]. This study used the glucose oxidase method for the initial sampling as opposed to the less precise 'bedside' screening method. Therefore, applying this value to screening just these four groups means that in the United States, more than 550 000 neonates would be screened and 12.5% of all newborns would be diagnosed with hypoglycemia.

What is clear from this study is that the higher the glucose threshold for screening and the more often these tests are performed, the greater number of asymptomatic patients with low-blood glucose will be identified [20]. What does the individual clinician do with this information? Which set of imperfect recommendations does the clinician decide to follow?

NEURODEVELOPMENTAL OUTCOME

Similar to the glucose concentration epidemiologic data and neuroendocrine responses used to reach a decision about critical thresholds of glucose to prevent brain injury, the neurodevelopmental outcome approach has been as confusing and contentious. This 'story' begins with an influential study from the United Kingdom published in 1988 that profoundly influenced neonatal care around the world. That concluded that a glucose concentration less than 47 mg/dl was the threshold that reliably would predict adverse outcomes [20]. The study evaluated blood glucose levels drawn daily initially, then weekly until discharge on 661 infants weighing less than 1850 g, at birth that were enrolled in nutrition study looking at the effect of early diets on cognitive outcomes. They used statistical strategies to determine a threshold value that reliably predicted an adverse outcome. They found that the number of days that these infants experienced moderate hypoglycemia (their definition) was strongly related to reduced scores for mental and motor development at 18 months corrected age, even after adjustment for a wide range of factors known to influence development [20]. There were several study weaknesses. Sicker infants had more frequent determinations of blood glucose, and hypoglycemia was not really the focus of this prospective controlled feeding trial. In fact, some infants were permitted to have plasma glucose levels less than 20 mg/dl for as long as 3–7 days without intervention. Only the first glucose value of the day was used in the analyses [21]. They found that a first glucose value of less than 47 mg/dl in high-risk infants with a birth weight less than 1850 g on 5 or more days correlated positively with abnormal neurologic and developmental outcomes at 18 months of age [20]. This value suddenly was used worldwide, and applied to even term AGA healthy neonates, as the gold standard and critical threshold defining hypoglycemia and risk of brain injury. However, less dramatic differences were found when the children were seen again as part of a larger study when they were 7–8 years of age [22]. The authors themselves noted the difficulty of providing causation when an observational approach is used, saying that 'when such

observations generate hypotheses or legitimate clinical concerns this should stimulate future studies and randomized controlled trials' [22].

A study also performed in the United Kingdom, and published almost 25 years later, did exactly what the previous investigator suggested and found no evidence to support that recurrent low-blood glucose levels of less than 45 mg/dl pose a hazard to preterm infants [23]. In this randomized controlled trial, which included infants less than 32 weeks gestation that had blood glucose levels measured daily for the first 10 days of life, there were no differences in developmental outcomes at 2 years of age. At 15 years of age, outcomes (including full-scale intelligence quotient, behavioral and emotional outcomes, and adaptation to daily living as adolescents) were nearly identical between controls and those with blood glucose concentrations less than 45 mg/dl on at least 3 days of the first 10 days of life [23].

Another large study published the same year as the randomized trial from the United Kingdom included over 800 moderate preterm infants (32–35 6/7 weeks) from the Netherlands [24]. Using a community-based, stratified cohort, the parents of these children completed the Ages and Stages Questionnaire when their children were 43–49 months of age. The odds of normal development at age 4 years was reduced by more than 50% in those with at least one glucose concentration less than 30 mg/dl in the first 72 h of life [25▪▪]. It is interesting to note that no other neonatal morbidities (e.g., Apgar scores, asphyxia, septicemia, mechanical ventilation, or hyperbilirubinemia) were associated with developmental delay [25▪▪]. Therefore, only hypoglycemia in this group of moderately preterm infants was associated with parent-reported developmental delay at preschool age. A glucose value of less than 30 mg/dl was common (8.1%) and had an increased risk of developing developmental delay from between 9.1 and 20% [24]. The lack of physician-mediated neuropsychological testing is a weakness of this study and the absence of linkage to other morbidities contrasts with most other data sets.

Although there is no debate that recurrent severe hypoglycemia can cause neonatal brain injury [26], recent systematic reviews suggest a paucity of high-quality evidence to determine the relationship between early glucose concentrations and outcome, particularly in late preterm and term newborns with risk factors, which are the only infants included in the AAP guideline, producing four risk categories [27]. A recent study from Arkansas suggests an association between transient newborn hypoglycemia and fourth-grade achievement test proficiency [25▪▪]. This cohort had nearly 1400 largely late preterm and term infants, all of whom had glucose screening (within the first 3 h of life) and identified infants who had a glucose level below 35, 40, or 45 mg/dl, followed by a second value above those cutoffs. They reported on the relationship between a single initial low-glucose concentration and subsequent academic performance [25▪▪]. The glucose testing was done by the standard glucose oxidase method. Using data collected from fourth-grade school examinations from across the state of Arkansas, they found that a single episode of hypoglycemia as defined by a level less than 40 mg/dl soon after birth followed by a second level above that cutoff was associated with a 50% reduction in the odds of achieving proficiency in literacy and numeracy at age 10 years [25▪▪]. Similar findings for less than 35 mg/dl and for less than 45 mg/dl were also shown. In total, 10% of the cohort experienced a glucose level less than 40 mg/dl. The population included all infants born at the study center over a 12-month period not only those considered to be at risk. Study weaknesses included there being little information about how the hypoglycemia was managed and no information about the rate of breastfeeding, which may be important confounders [28▪]. We also do not know if the exposure group only had the one episode of hypoglycemia as no values beyond a second were reported and the possibility of residual confounding remains in the study despite extensive adjustment for perinatal and socioeconomic factors [28▪]. There is no reason yet to assume that the link between transitional neonatal hypoglycemia and subsequent poor academic performance is causal. It is possible that the brief period of hypoglycemia is a marker for something else. It could even be a marker for events occurring during intrauterine development.

Current guidelines recommend screening only for newborns that are symptomatic or at risk of developing hypoglycemia. However, the study noted above suggests that early transient newborn hypoglycemia may be associated with poorer academic achievement at age 10 years. Do we now have to contemplate universal glucose screening of all neonates? Screening is only justified when you can impact outcome with the result of the screen. In the study quoted above, the brief period of 'hypoglycemia' was diagnosed at 90 min of age, but the actual result was obtained almost 30 min after that. The second measurement showing resolution above the threshold was available some 70 min after the first or at approximately 3 h of age. It is unlikely that any intervention after the clinician knows the results can shorten the

exposure to the brief period of 'hypoglycemia' as defined by the levels they chose.

Recently, a study from the Children with Hypoglycemia and Their Later Development followed a large prospective cohort of term and late-preterm neonates at risk for hypoglycemia [29▪▪]. This provides the follow-up data for the 514 babies that we reviewed earlier that reported the number of infants diagnosed with hypoglycemia among the four risk groups when a level of less than 47 mg/dl was used [19]. The protocol aimed at maintaining the plasma glucose more than 47 mg/dl during the first 48 h of life [29▪▪]. They examined the association of hypoglycemia with neurodevelopmental outcome at 2 years. Overall, 53% were diagnosed with hypoglycemia and nearly 25% had levels below 47 mg /dl, only appreciated by the use of subcutaneous glucose sensors to detect periods of hypoglycemia. These were not detected by intermittent sampling [29▪▪]. Even with aggressive treatment using the dextrose gel, 25% of the infants experienced at least 5 h of glucose levels less than 47 mg/dl. They found that hypoglycemia was not associated with an increased risk of the primary outcomes of neurosensory impairment [29▪▪]. Risks were not increased even in those that were unrecognized as having hypoglycemia (interstitial monitoring only). The lowest blood glucose concentration, number of hypoglycemic episodes, and negative interstitial increment (area above the interstitial glucose concentration curve and <47 mg/dl) also did not predict outcome [30]. In fact, an unexpected observation in this study was that higher glucose levels after treatment for glucose less than 47 mg/dl tended to be associated with neurosensory impairment [29▪▪]. They do acknowledge that unknown confounders cannot be ruled out to explain that observation. Nonetheless, this finding is worrisome in that higher levels of glucose (54–72 mg/dl) might be harmful and adds to the debate about how best to treat newborns with transient hypoglycemia [30].

CONCLUSION

The main goal of the PES recommendation is to heighten the awareness to rule out persistent hypoglycemic syndromes when it comes to infants with low levels of glucose that persist. It is critical to identify those with persistent hypoglycemic syndromes to prevent serious neurologic injury [4▪▪]. It is possible that low-glucose levels seen in the first 48 h may herald metabolic disorders. Therefore we must follow these infants after 48 h and carefully monitor them for development of any clinical signs and make sure they achieve glucose more than 70 mg/dl after the first days of life that is maintained through several feed-fast cycles. We agree with the authors of this study that a 6-h fast prior to discharge is worthwhile for some neonates who are at increased of a persistent hypoglycemic syndrome [5▪▪]. Discharge from the nursery should not occur until these diagnoses are ruled out.

The current practice for managing low-glucose levels in the first 48 h of life is based largely on expert opinion, and there is no agreement on whether or not transitional neonatal hypoglycemia in otherwise healthy newborns is a normal physiological variation or whether it is a marker of inadequate metabolic adaptation and, in some cases, associated with neuroglycopenia [4▪▪,28▪]. We know that a low-blood glucose can cause seizures [1], and that it can cause permanent brain damage [26,31]. However, in the study by McKinley *et al.* [29▪▪] higher glucose levels after treatment were associated with neurosensory impairment, especially cognitive delay. Those who spent a larger proportion of the time outside the central range of 54–72 mg/dl in the first 48 h of life had worse outcomes [29▪▪]. This suggests that the rapid correction of glucose less than 47 mg/dl to a higher blood glucose concentration may be associated with a poorer outcome [29▪▪].

It becomes clear that a glucose threshold of 47 mg/dl is not a 'magic' number for treating neonatal hypoglycemia. The data on undetected 'hypoglycemia' with the interstitial monitoring also suggest that we need a considerable margin of safety in setting such a threshold, but unfortunately we cannot agree on where that should be. The report on outcome using the less than 47 mg/dl as a treatment threshold is at least reassuring in the sense that the protocol had many similarities to recommendations in the AAP Committee on Fetus and the Newborn report in 2011 and was recently ratified again [6]. The lower levels from the AAP document, along with enhanced vigilance to identify persistent hypoglycemia syndromes after 48 h, might be the best compromise to prevent overscreening, and thus overtreatment, while still committing to diagnosing persistent hypoglycemia after the transitional period before discharge from the hospital.

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Conflicts of interest

There are no conflicts of interest.

REFERENCES AND RECOMMENDED READING

Papers of particular interest, published within the annual period of review, have been highlighted as:

- ■ of special interest
- ■■ of outstanding interest

1. Cornblath M, Odell GB, Levin E. Symptomatic neonatal hypoglycemia associated toxemia of pregnancy. J Pediatr 1959; 55:545–562.
2. ■ Adamkin DH. Metabolic screening and postnatal glucose homeostasis in the newborn. Pediatr Clin North Am 2015; 62:385–409.

Review of AAP versus PES recommendations.

3. ■ Simmons R, Stanley C. Neonatal hypoglycemia studies: is there a sweet story of success yet? N Engl J Med 2015; 373:16.

Editorial discussing whether a single low early glucose level may impact outcome.

4. ■■ Stanley C, Rozance P, Thornton MB, *et al.* Re-evaluating transitional neonatal hypoglycemia: mechanism and implications for management. J Pediatr 2015; 166:1–6.

Review of the physiology of transitional hypoglycemia.

5. ■■ Thornton PS, Stanley CA, DeLeon DD, *et al.* Recommendations from the Pediatric Endocrine Society for Evaluation and Management of Persistent Hypoglycemia in Neonates, Infants, and Children. J Pediatr 2015; 167:238–245.

Set of recommendations from PES.

6. Adamkin DH. Committee on Fetus and Newborn, clinical report-postnatal glucose homeostasis in late-term and preterm infants. Pediatrics 2011; 127:575.
7. Srinvasan G, Pildes RS, Cattamanchi G. Plasma glucose values in normal neonates: a new look. J Pediatr 1986; 109:114–117.
8. Marconi AM, Paolini C, Buscaglia M, *et al.* The impact of gestational age and fetal growth on the maternal-fetal glucose concentration difference. Obstet gynecol 1996; 87:937–942.
9. Hawdon JM, Ward Platt MP, Aynsley-Green A. Patterns of metabolic adaptation for preterm and term infants in the first neonatal week. Arch Dis Child 1992; 67:357–365.
10. Desmond MM, Hild JR, Gast JH. The glycemic response of the newborn infant to epinephrine administration: a preliminary report. J Pediatr 1950; 37:341–350.
11. Stanley CA, Anday EK, Baker L, Delivoria-Papadopolous M. Metabolic fuel and hormone responses to fasting in newborn infants. Pediatrics 1979; 64:613–619.
12. Hawdon JM, Weddell A, Aynsley-Green A, Ward Platt MP. Hormonal and metabolic response to hypoglycemia in small for gestational age infants. Arch Dis Child 1993; 68:269–273.
13. Wight NE. Hypoglycemia in breastfed neonates. Breastfeed Med 2006; 1:253–262.
14. Heck LJ, Erenberg A. Serum glucose levels in term neonates during the first 48 h of life. J Pediatr 1987; 110:119–122.
15. Adamkin DH. Update on neonatal hypoglycemia. Arch Perinat Med 2005; 11:13–15.
16. Rozance P, Hay NW. Neonatal hypoglycemia answers but more questions. J Pediatr 2012; 16:775–776.
17. Collins JE, Leonard JV, Teale D, *et al.* Hyperinsulinaemic hypoglycemia in small for dates babies. Arch Dis Child 1990; 65:1118–1120.
18. Hoe FM, Thornton PS, Wanner LA, *et al.* Clinical features and insulin regulation in infants with a syndrome of prolonged neonatal hyperinsulinism. J Pediatr 2006; 148:207–212.
19. Harris DL, Weston P, Harding JE. Incidence of neonatal hypoglycemia in babies identified as at risk. J Pediatr 2012; 161:787–791.
20. Lucas A, Morley R, Cole TJ. Adverse neurodevelopmental outcome of moderate neonatal hypoglycemia. BMJ 1988; 297:1304–1308.
21. Lucas A, Morley R, Cole TJ. Randomized trial of early diet in preterm babies and later intelligence quotient. BMJ 1998; 318:195.
22. Lucas A, Morley R. Outcome of neonatal hypoglycemia [letter]. BMJ 1999; 318:195.
23. Tin W, Brunskill G, Kelly T, Fritz S. 15 year follow-up of recurrent 'hypoglycemia: in preterm infants'. Pediatrics 2012; 130:1497–1503.
24. Kerstjens JM, Bocca-Tjeertes IF, de Winter AF, *et al.* Neonatal morbidities and developmental delay in moderately preterm-born children. Pediatrics 2012; 130:e265–e272.
25. ■■ Kaiser JR, Bai S, Gibson N, *et al.* Association between transient newborn hypoglycemia and fourth-grade achievement test proficiency: a population-based study. JAMA Pediatr 2015; 169:913–921.

Transient neonatal hypoglycemia affects cognitive outcomes 10 years later.

26. Burns CM, Rutherford MA, Boardman JP, Cowan FM. Patterns of cerebral injury and neurodevelopmental outcomes after symptomatic neonatal hypoglycemia. Pediatrics 2008; 122:65–74.
27. Boluyt N, van Kempen A, Offringa M. Neurodevelopment after neonatal hypoglycemia. Pediatrics 2006; 117:2231–2243.
28. ■ McKinley CJ, Harding JE. Revisiting transitional hypoglycemia: only time will tell. JAMA Pediatrics 2015; 169:892–894.

Editorial addressing transitional neonatal hypoglycemia and cognitive outcome.

29. ■■ McKinley CJD, Alsweiller JM, Ansell JM, *et al.* Neonatal glycemia and neurodevelopmental outcomes at 2 years. N Engl J Med 2015; 373:1507–1518.

Neurodevelopmental outcomes normal at 2 years of age despite newborn glucose levels $<$ 47 mg/dl for extended periods of time.

30. Simmons RS, Stanley C. Neonatal hypoglycemia studies: is there a sweet story of success yet? N Engl J Med 2015; 373:1567–1569.
31. Anderson JM, Milner RDG, Strich SJ. Effects of neonatal hypoglycaemia on the nervous system: a pathological study. J Neurol Neurosurg Psychiatry 1967; 30:195–310.