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An Emerging Evidence Base for the Management of Neonatal Hypoglycaemia

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Abstract

Neonatal hypoglycaemia is common, and screening and treatment of babies considered at risk is widespread, despite there being little reliable evidence upon which to base management decisions. Although there is now evidence about which babies are at greatest risk, the threshold for diagnosis, best approach to treatment and later outcomes all remain uncertain. Recent studies suggest that treatment with dextrose gel is safe and effective and may help support breast feeding. Thresholds for intervention require a wide margin of safety in light of information that babies with glycaemic instability and with low glucose concentrations may be associated with a higher risk of later higher order cognitive and learning problems. Randomised trials are urgently needed to inform optimal thresholds for intervention and appropriate treatment strategies.

Keywords

Hypoglycaemia; neonatal; congenital hyperinsulinism; preterm; infant of diabetic mother; screening tests; breast feeding

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Conflict of Interest

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1. Introduction

Hypoglycaemia is the commonest metabolic disorder of the newborn, and perhaps the only readily preventable cause of neonatal brain injury. Despite this, management of neonatal hypoglycaemia has for decades been based on extremely limited evidence. This article outlines some current dilemmas in clinical management and describes some recent research that is beginning to indicate the potential for a more evidence-based approach to the diagnosis and treatment of neonatal hypoglycaemia.

2. Pathophysiology

Before birth the fetus receives a continuous intravenous supply of glucose, which crosses the placenta by carrier-mediated facilitated diffusion from the maternal circulation. During labour and delivery the secretion of stress hormones such as glucocorticoids and catecholamines causes a rise in fetal blood glucose concentrations, so that cord blood glucose concentrations are often high[1, 2].

Once the umbilical cord is cut, the exogenous supply of glucose ceases, and blood glucose concentrations fall. This fall in blood glucose results in a decrease in insulin secretion and increase in counter-regulator hormones such as glucagon, catecholamines and glucocorticoids. Together, these changes initiate fetal endogenous glucose production via glycogenolysis and gluconeogenesis, with a resultant stabilisation of blood glucose concentrations, although adult concentrations are not reached until approximately 72 hours of age[2, 3].

Failure of this sequence of physiological changes can lead to hypoglycaemia, which is most common in the first few hours after birth. In the majority of babies this hypoglycaemia is transient, recovering over a few hours to days, and is usually termed transitional hypoglycaemia. In a smaller number of babies the hypoglycaemia persists for days to weeks, and a few of these will turn out to have persistent neonatal hyperinsulinism and require additional interventions. There is some evidence that even transitional hypoglycaemia is likely to be due to relative hyperinsulinaemia[4].

Although management of hypoglycaemia is largely focussed on managing blood glucose concentrations, it is important to remember that the real objective is to ameliorate the risk of brain injury. Glucose is the major fuel for the brain, and for a neonate with a relatively large brain, almost all of the estimated total body glucose consumption can be accounted for by the brain. Since brain glucose uptake is directly proportional to circulating concentrations, in the absence of alternative brain fuels, any reduction in blood glucose concentrations results in a reduction in available brain oxidative substrates. Persistent hyperinsulinaemia is therefore important, because it may limit the production of alternative cerebral fuels such as ketones that may be otherwise neuroprotective during hypoglycaemia.

3. Definition

The difficulty in agreeing a definition for neonatal hypoglycaemia is related to the continued uncertainty as to what is a normal blood glucose concentration and what may cause damage.

Methods to define neonatal hypoglycaemia have included statistical[5], metabolic[3], neurophysical[6] and neurodevelopmental[7–9]. However, each of these methods is problematic. There are few studies of normal babies from which to extrapolate statistical definitions, especially in low risk exclusively breast fed babies[2]. Further, even if healthy term babies sometimes have low glucose concentrations during transition, it does not follow that their references ranges should be normative for infants at risk of impaired metabolic adaptation, many of whom have other risk factors for adverse development.

3.1 The 2.6 mM Threshold

One definition in common use is < 2.6 mM, which arose primarily from reports by Lucas *et al.* and Koh *et al.* in the 1980s. Koh *et al.* determined that in babies (n = 5) and children (n = 12) monitored during spontaneous and induced hypoglycaemia, abnormal sensory evoked potentials occurred only in those with blood glucose concentrations < 2.6 mM[6]. However, the onset of abnormal sensory evoked potentials occurred over a range of blood glucose concentrations (0.7 to 2.5 mM), suggesting that different individuals may have different levels of susceptibility. In six participants, sensory evoked potentials returned to normal following correction of hypoglycaemia, but the remaining four babies had delayed recovery (one hour to 16 days). The authors recognised that the abnormalities in evoked potential had not been shown to cause permanent damage, but surmised that they would not be of benefit, and advised that blood glucose concentrations be maintained above 2.6 mM.

In the same year, Lucas *et al.* demonstrated an association between repeated episodes of hypoglycaemia and reduced scores on the Bayley Infant Scales of Development at 18 months' corrected age[7]. He studied preterm babies (<1850 g) admitted to neonatal intensive care who had intermittent blood glucose concentration measurements. Bayley scores were regressed on days of hypoglycaemia, using blood glucose concentration cut-offs varying from 0.4 to 4 mM, and a significant association was seen using a cut-off of < 2.5 mM. Lucas *et al.* therefore selected 2.6 mM as the cut off, and showed that hypoglycaemia on three or more days was significantly related to mental and motor developmental scores. Therefore, the authors advised that blood glucose concentrations be maintained above 2.6 mM[7]. A subsequent follow-up study demonstrated that the neurodevelopmental impairment persisted, with reduced scores for arithmetic and motor function[8].

Following publication of these two key studies, < 2.6 mM has remained a common, though debated, definition of neonatal hypoglycaemia worldwide.

3.2 Different Operational Thresholds

There is uncertainty about whether it is necessary to correct low blood glucose concentrations in babies who have brief, early (1 to 2 hours of age) low blood glucose concentrations and who are asymptomatic[10]. This uncertainty is due to the fall in blood glucose concentrations after birth which is commonly considered to be a normal physiological response[1, 11]. Therefore, different thresholds for intervention are often recommended for different postnatal ages.

Cornblath *et al.* suggested 'operational thresholds' in 2000 and advised clinical intervention in 'symptomatic' babies for blood glucose concentration < 2.5 mM[11]. For babies with risk

factors they suggested monitoring of blood glucose concentration, and close surveillance if < 2.0 mM, with intervention if there is no increase post-feed, if abnormal clinical signs develop or if < 1.4 mM. The same thresholds were advised for preterm and term infants. The authors acknowledge the empirical, expert-opinion basis of these thresholds, but justified them with a desire to provide operational thresholds high enough to provide a margin of safety and be applicable to a wide range of clinical aetiologies.

A review of the evidence was undertaken in a workshop for the National Institute for Child Health and Human Development in 2009[10]. Recognising the lack of evidence, the workshop panel advised that repeated and prolonged very low plasma glucose concentrations should be investigated and treated, but did not specify blood or plasma glucose concentration thresholds or duration.

The American Academy of Pediatrics' current guide for management of newborns at risk born at ≥ 34 weeks' gestation includes an algorithm with suggested thresholds for intervention[3]. The advised thresholds depend upon postnatal age and range from 1.4 to 2.2 mM in the first four hours, 1.9 to 2.5 mM from four to 24 hours and 2.5 mM for babies > 24 hours old. In babies with clinical signs, the advised threshold for intervention is a blood glucose concentration of 2.2 mM. The authors acknowledge that this guidance is also pragmatic rather than evidence based.

The most recent advice from the American Pediatric Endocrine Society for babies at risk of hypoglycaemia who are feeding normally within the first 48 hours after birth is that a 'safe target' is > 2.8 mM and that this should be increased to > 3.3 mM for babies who require interventions beyond normal feeds[4]. The committee justified these thresholds as a balance of the risk of intervention against a 'period of brief undertreatment' based on the threshold for neuroglycopenic symptoms of 3 mM in older children and adults. A recent comment comparing the differing guidelines noted that the safest approach might be a compromise of using the lower thresholds recommended by the American Academy of Pediatrics, but with awareness of the need to exclude a diagnosis of persistent hypoglycaemia when hypoglycaemia continues beyond 48 hours. This approach might reduce unnecessary screening, and therefore unnecessary treatment while still identifying persistent/non-transitional hypoglycaemia.

Given the very limited evidence upon which all of these recommendations are based, outcomes of a randomised controlled trial comparing two thresholds for intervention (2.0 or 2.6 mM) in at risk babies will provide welcome additional data. Preliminary results reported no significant difference in neurodevelopmental outcome at age 18 months[12].

3.3 Relationship to Thresholds in Older Children and Adults

The current intervention thresholds suggested for neonates are lower than those used in older children and adults. In teenagers and adults with diabetes, the American Diabetes Association and The Endocrine Society recommend using 3.9 mM as the definition for hypoglycaemia. The use of 3.9 mM allows for a larger margin of safety as reduced awareness of hypoglycaemia may occur in older children and adults with recurrent hypoglycaemia. Given their proportionately larger demand for glucose by the brain, there

seems no reason to assume that a lower threshold for intervention is likely to be appropriate in neonates.

4. Screening for Neonatal Hypoglycaemia

As symptoms are non-specific and neonatal hypoglycaemia may be harmful even if the baby is asymptomatic[7], it is common practice in developed countries to screen babies known to be at risk of hypoglycaemia. However, this approach currently does not meet several of the accepted criteria for a screening programme. Specifically, the natural history is incompletely understood, there is a lack of a defined target population and there is no scientific evidence of screening programme effectiveness. Despite this absence of this evidence, the target population is generally accepted to be babies of diabetic mothers, babies born preterm, or of small or large birthweight[13]. The initial screening test is usually done at one to two hours after birth, followed by regular blood glucose measurements over the next 12 to 48 hours until the baby is consistently euglycaemic. The screening samples are usually taken before the baby is fed, as the baby may be fed differently if the glucose is low, e.g., formula feed. However, there is no evidence that the blood glucose concentration in newborn babies is lowest before a feed, or that the timing of the blood glucose measurement has an impact on neurodevelopmental outcome.

It has become common practice in many centres for hypoglycaemia screening to be done using point of care testing (POCT) rather than by sending blood samples to the laboratory[14]. There are several reasons for this: the result is available immediately, so a baby with hypoglycaemia can be treated promptly; laboratory analysis is expensive, while POCT is cheap; POCT is commonly used on the post-natal wards to measure blood glucose concentrations of diabetic mothers, so is readily available and midwives are familiar with its use, and POCT requires a smaller blood sample volume. However, most POCT instruments do not use the gold standard of enzymatic analysis, and the results are inaccurate compared to analysis using a glucose oxidase method. It is difficult to find another example in modern medicine of a screening test that is intended to prevent permanent brain damage but in which it is considered acceptable to use an inaccurate test to inform management. The alternative to non-enzymatic POCT is the use of cot-side enzymatic-based tests, e.g., i-STAT® (Abbott Laboratories, Abbott Park, Illinois, USA) or EPOC (Alere™, Massachusetts, USA), which use the gold standard glucose oxidase reaction, produce reliable results, are portable and the result is available immediately. Consumables are more expensive than for standard POCT. However, the cost is considerably less than the cost of long-term neurodevelopmental impairment.

Use of any POCT, either enzymatic or non-enzymatic, also means that glucose concentrations are analysed in blood rather than plasma. Although the initial reports of neonatal hypoglycaemia were based on blood glucose analysis, subsequent research was mainly done using plasma glucose concentrations[7, 10] until recently[15]. Unfortunately, blood and plasma measurements cannot be used interchangeably as blood glucose concentrations are 10% to 18% higher than plasma concentrations. This difference depends on the haematocrit, which is variable in newborn babies, so it is not accurate to calculate the plasma concentration from analysis on a blood sample in an individual baby. Future research on

neonatal hypoglycaemia needs to report consistently using either blood or plasma concentrations and the results need to be applicable to standard clinical practice. It is of limited use to have a definition of hypoglycaemia based on plasma concentrations if clinicians are routinely measuring and acting upon blood glucose concentrations.

5. Incidence

The incidence of neonatal hypoglycaemia varies depending on the proportion of babies at risk in the population tested; the screening guideline used; the threshold for defining hypoglycaemia, and the analysis method. The incidence of hypoglycaemia (defined as < 45mg/dl or 2.5 mM) in a whole population cohort where all babies were screened using laboratory testing of plasma, was 19%[16]. However, in a population of at-risk babies screened using the glucose oxidase method on whole blood the incidence of hypoglycaemia (defined as < 2.6mM) was 51%[13], and was a similar among the different risk factor groups.

6. Treatment

The overall aim of treatment for neonatal hypoglycaemia is to improve the blood glucose concentration, thereby providing adequate cerebral fuel and decreasing the risk of brain damage.

Given the uncertainties regarding the appropriate thresholds for intervention, the most common treatment for asymptomatic hypoglycaemia is to increase the frequency of feeding. If feeding does not improve the glucose concentration, then admission to the newborn intensive care unit is normally required for treatment with intravenous dextrose. The ideal treatment for hypoglycaemia would support the establishment of breast feeding while avoiding admission to an intensive care unit.

6.1 Feeding

The advantages of breast-feeding are well recognised for both mother and baby. Unfortunately, hypoglycaemia is most common in the first 48 hours, at a time when breast-feeding is being established, the volume of breast milk is low and the milk content is high in protein but considerably lower in carbohydrate and fat than in mature milk. A hypoglycaemic baby also can often require considerable encouragement to feed, and a diagnosis of hypoglycaemia can cause anxiety for mothers, all of which can result in difficulties with early breast-feeding.

Breast fed babies have been shown to have higher blood concentrations of ketones during the first week than formula fed babies, and therefore it has been speculated that ketones may provide relative neuroprotection to breast fed babies. However, the concentrations of ketones are extremely low during the first 48 hours after birth in hypoglycaemic babies, and are unlikely to be neuroprotective at this time[17].

There are few reports about breast-feeding as a treatment for hypoglycaemia. However, midwifery assessment of pre-feed alertness and quality of the feed are not good predictors of the change in blood glucose concentrations after a breast feed in hypoglycaemic babies[18].

This suggests that, contrary to common clinical practice, clinical assessment of a breast feed should not be used to determine whether or when to measure blood glucose concentrations.

6.2 Expressed breast milk

Many hospitals encourage antenatal expression of breast milk, largely on the assumption that feeding expressed breast milk to babies at risk will help improve blood glucose concentrations or treat hypoglycaemia, although there is no evidence that this actually occurs. Indeed, our data suggest that expressed breast milk is almost always of very small volume and has little effect on blood glucose concentrations[18]. Preliminary findings from the Diabetes and Antenatal Milk Expressing (DAME) randomised trial show that advising women with diabetes to antenatally express breast milk from 36 weeks' gestation did not alter the incidence of neonatal hypoglycaemia, requirement for intravenous dextrose or admission to the neonatal unit, but did reduce the use of formula[19]. Based on current evidence, the practice of antenatal breast milk expressing cannot be recommended for management of neonatal hypoglycaemia.

6.3 Infant formula

Infant formula is the most commonly used treatment for neonatal hypoglycemia[14]. The carbohydrate content of formula is significantly higher than breast milk, and formula is relatively inexpensive and easy to administer. However, feeding with infant formula risks disrupting the establishment and duration of breast-feeding, alters the neonatal microbiome, and increases the risk of infections and allergies. Whether these disadvantages outweigh the disadvantages of neonatal unit admission and intravenous dextrose is a matter of often strongly held opinion but little evidence.

6.4 Dextrose gel

Dextrose gel 200 mg/kg massaged into the buccal mucosa before a feed has been shown to be effective in improving blood glucose concentrations in hypoglycaemic late preterm and term babies in the first 48 hours after birth[15]. Furthermore, compared with placebo gel, dextrose gel reduced admission to newborn intensive care for the management of hypoglycaemia, improved breast-feeding outcomes at two weeks, and was well tolerated, acceptable to staff and parents, and inexpensive. Recurrent and rebound episodes of hypoglycaemia were uncommon and there was no hyperglycaemia. At follow-up at 2 years of age, dextrose gel appeared safe, with no effects on neurosensory impairment, processing difficulties, or developmental and growth outcomes[20].

Dextrose gel in conjunction with breast-feeding provides an attractive non-invasive alternative to infant formula and is increasingly being used as first-line treatment for neonatal hypoglycemia[21].

6.5 Intravenous dextrose

Babies who remain hypoglycaemic after initial treatment, or whose blood glucose concentrations are very low, are often admitted to the neonatal unit for treatment with intravenous dextrose. Once again, there is limited evidence to underpin current clinical practice in these babies. In hypoglycaemic babies given a 200 mg/kg intravenous bolus of

10% dextrose followed by a continuous infusion of 8 mg/kg.min, the blood glucose concentration was restored within one minute[22]. There was considerable variation between babies and within differing at risk groups in magnitude of the change in blood glucose concentration, although the reason for this individual variation was unclear.

Although rapid restoration of blood glucose concentrations has been seen as the primary objective of treatment, it recently has been reported that a rapid increase in blood glucose concentration following hypoglycaemia in the first 12 hours after birth was associated with worse neurosensory outcome at 2 years of age[9] (see below). Further investigation is required regarding the rate and magnitude of change in blood glucose concentration in relation to neurological outcome.

7. Outcomes

There is no doubt that severe, persistent hypoglycaemia can cause seizures and brain injury in newborns. The long-term significance of early, asymptomatic or transitional low glucose concentrations remains contentious. Recent population-based studies have reignited debate that exposure to even brief, mild to moderate asymptomatic hypoglycaemia may permanently impair brain development and later learning[16]. However, progress in our understanding of the long-term effects of neonatal hypoglycaemia has been limited by a paucity of high quality prospective studies that are adequately powered, involve detailed assessment of glycaemia and later neurocognitive function, and have appropriate controls and adequate adjustment for confounding factors.

A systematic review of the neurodevelopmental effects of neonatal hypoglycaemia, published in 2006, identified just two studies of sufficient methodological quality for quantitative analysis, despite research spanning over 40 years[23]. One of these studies involved 75 large-for-gestational age term infants, and no differences were seen in cognitive development or behaviour at 4 years of age between infants who did and did not develop hypoglycaemia on day one (<2.2 mM 1h after birth or <2.5 mM thereafter), though scores were generally lower in the hypoglycaemic group. The other study by Lucas *et al.* referred to above found that in low birthweight infants (<1850 g), moderate hypoglycaemia (<2.6 mM), if persistent (≥5 days), was associated with decrease cognitive and motor scores at 18 months of age by nearly one standard deviation, and poorer arithmetic scores at 8 years of age[7, 8]. Apart from the CHYLD Study[9], we are aware of only one other subsequent study[24] that meets the methodological criteria recommended by Boluyt *et al.*[23]. This study attempted to reproduce the earlier findings of Lucas in preterm babies, but could not confirm an association between recurrent, moderate hypoglycaemia and cognitive function or impairment at 2 and 15 years of age, though cognitive scores were relatively low in both the exposure and control groups[24].

Considering repeated calls for further research about the potential impact of neonatal hypoglycaemia on development[10], it is surprising that so few prospective studies have been performed. There are several possible reasons for this. First, recruitment of cohorts around the time of birth is challenging and access to accurate glucose testing is not universal. Second, longitudinal assessment of neuropsychological function is expensive, requires

specialised teams of assessors and cohorts need to be large to detect or exclude clinically important differences. Third, the preponderance of epidemiological rather than outcomes-based approaches to defining hypoglycaemic thresholds in the literature has led to uncritical acceptance that low glucose concentrations in the early newborn period are simply part of normal physiological variation. Frequently cited reference studies may have been biased by management practices no longer considered standard, such as maternal dextrose infusion during labour and delayed introduction of feeding[1].

With this background, we established the CHYLD Study to prospectively evaluate the long-term effects of neonatal hypoglycaemia in term and late preterm infants born at risk, and to relate the frequency, severity and duration of low glucose concentrations to neuropsychological function in early childhood and beyond[9]. In recognition of the fact that cognitive development in early childhood is complex and that higher order functions, which form the foundations for later learning, do not emerge until late in the pre-school years, we assessed children at 2 and 4.5 years. Two-year outcomes have been reported[9] and 4.5-year data are currently under analysis. Because the effects of hypoglycaemia on the neonatal brain may be broader than traditionally defined, CHYLD assessments employed a multi-disciplinary approach involving a paediatrician, developmental psychologist, and optometrist, using standardised tests of cognition, language, behaviour, vision and motor skills, combined with novel tests of executive function and visual perception (global motion coherence).

At 2 years of age, we found no differences between at-risk children who were and were not exposed to neonatal hypoglycaemia[9]. Further, infants with more severe or prolonged hypoglycaemia did not have worse outcome, and we could not establish a lower threshold at which risks increased, possibly because infants were carefully screened and treated to maintain blood glucose concentrations ≥2.6 mM. However, we have cautioned against any reduction in operational thresholds because the overall rate of impairment was high (38%) and masked continuous interstitial monitoring showed that episodes of low glucose concentration were very common. For example, among infants with normal intermittent blood glucose screening (no blood glucose measurements <2.6 mM), 25% had ≥1 episode of low interstitial glucose (<2.6 mM), and one quarter of those treated for hypoglycaemia spent ≥5 hours <2.6 mM. Importantly, initial findings at 4.5 years suggest that neonatal hypoglycaemia is associated with impaired emerging higher neurocognitive function, including executive function and visual-motor integration [25].

8. Current controversies

Neonatal hypoglycaemia is commonly conceptualised as a blood glucose concentration or period of time below some minimum threshold. However, in the CHYLD 2-year study the factor that was most predictive of outcome in the first 48 hours after birth was glucose instability, defined as the proportion of measurements or duration of time outside a central range of 3 to 4 mM[9]. While hypoglycaemia *per se* did not increase the risk of adverse outcome at 2 years, infants with hypoglycaemia had less stable glucose concentrations in the first 48 hours, and infants in the highest quintiles for instability had a 2 to 3 fold increased risk of neurosensory impairment. Further, among infants with hypoglycaemia, those who

developed impairment at 2 years had a steeper rise in glucose concentrations following dextrose treatment[9].

Thus, hypoglycaemia may be a marker of wider perturbations in metabolic adaptation, perhaps due to suboptimal intrauterine conditions or peripartum stress. If this hypothesis is true, treatments that aim to rapidly correct low blood glucose concentrations may be either beneficial or potentially harmful, depending on the underlying metabolic milieu. Animal studies have demonstrated that higher glucose concentrations during recover from hypoglycaemia worsen neuronal injury, possibly due to generation of reactive oxygen species and changes in cerebral perfusion. Moreover, in intensive care patients, the combination of hypoglycaemia and high glucose variability is strongly associated with mortality. Thus, the manner in which hypoglycaemia is treated, and subsequent stability of blood glucose concentrations, may also be important in newborns.

When planning interventions to prevent or treat neonatal hypoglycaemia there are other potential iatrogenic effects to consider. For example, pain-induced stress in newborns, such as that associated with heel lancing for blood sampling, has been associated with impaired cortical maturation at school age. At-risk infants frequently receive supplementary formula feeds and those who develop hypoglycaemia are often admitted to neonatal care units, separating mother and baby. Both of these interventions have been associated with reduced breast-feeding rates.

These are important factors to bear in mind when deciding which infants to screen for hypoglycaemia. Most current guidelines recommend only screening infants with established risk factors. However, in a recent large linkage study in which unselected newborns underwent routine blood glucose screening shortly after birth, a brief single episode of hypoglycaemia was associated with approximately a 50% reduction in the chance of achieving proficiency in literacy and numeracy at 10 years of age[16]. This raises the question of whether screening should be universal. However, as we have argued elsewhere[9], it is by no means clear that exposed infants in this study simply had transient hypoglycaemia, nor that the association was causal. Further, it is unlikely that intervention would have shortened the period of hypoglycaemia, and for the reasons listed above, it needs to be proven that additional intervention would not do more harm than good.

9. Conclusions and Future Research

It is clear that earlier calls for further research[10] remain relevant. Longitudinal studies are needed to describe the normal range of changes in blood glucose concentrations in breast fed babies in current practice conditions. Continuous glucose monitoring would be useful in such studies to ensure episodic hypoglycaemia is not missed, and to help inform rational strategies for blood glucose screening. Carefully designed randomised trials are needed to determine whether treatment at different thresholds results in altered neurodevelopmental outcomes. Such studies need to be adequately powered and include follow-up at least to school age to detect clinically meaningful effects on learning and behaviour. Randomised trials are also required to assess the effects of different treatment approaches, and

particularly the rate of increase of blood glucose concentrations after hypoglycaemia, on later outcomes.

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