Blood glucose levels in infancy – clinical significance and accurate measurement

A low blood glucose in a newborn baby is not an uncommon finding, but some controversy remains regarding the definition and clinical significance of neonatal hypoglycaemia. This article describes how application of data from clinical research studies assists our understanding of neonatal metabolic adaptation, and which babies are at risk of the sequelae of hypoglycaemia. In addition the more rare, but more significant, occurrence of hypoglycaemia in older infants is discussed. The mechanisms of development of hyperglycaemia in infants are also described. Finally, the requirement for accurate measurement of blood glucose levels is reinforced.

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Keywords

hypoglycaemia; hyperglycaemia; metabolic adaptation; ketone bodies; blood glucose measurement

Key points

Hawdon J.M. (2005) Blood glucose levels in infancy – clinical significance and accurate measurement. *Infant* 1(1): 24-27.

1. Healthy term babies adapt to the physiological fall in blood glucose concentration.
2. However, preterm or sick babies may fail in this adaptation and hypoglycaemia should be detected and treated.
3. In older infants, hypoglycaemia is more commonly a marker for serious underlying disorders so that in addition to treating hypoglycaemia the underlying disorder should be investigated.
4. Hyperglycaemia is not physiological at any age and the underlying cause should be investigated and treated.

The clinical significance of low and high blood glucose levels

Traditionally, a baby who has lower than normal blood glucose levels has been considered to have hypoglycaemia. Hypoglycaemia in infancy has been recognised for many years, and is more commonly described in the neonatal period[1,2]. At the same time, there has been much controversy regarding the definition of the condition and its clinical significance[3,4]. It is well known that severe and prolonged hypoglycaemia may cause brain injury. Anxieties regarding the effects of neonatal hypoglycaemia on the brain were heightened by papers that had studied particular patient groups, eg preterm babies[5,6]. These anxieties resulted in what may have been over-aggressive management of some babies, resulting in separation of babies from their mothers and the consequent impact on the establishment of breast feeding. Subsequent work has demonstrated that most infants are protected from the neurological effects of hypoglycaemia by mounting protective responses, eg increased availability of alternative fuels to glucose for the brain. The most abundant alternative fuels, especially in the early neonatal period, are ketone bodies, produced by the oxidation of fatty acids[4,5].

Hypoglycaemia is a less common occurrence in the older infant and as such usually has a pathological underlying cause and must be taken seriously. There have been fewer studies of the effects of hypoglycaemia on the brain in older infants, and whether there are protective responses, such as the increased availability of alternative fuels. It has been suggested that some cases of sudden infant death are the result of severe hypoglycaemia resulting from inborn errors of metabolism, but this is likely to be an extremely rare cause of this tragic event[7].

FIGURE 1 Babies with co-existing complications must have blood glucose levels monitored.

Until the advent of neonatal intensive care, hyperglycaemia was a rare phenomenon. However, it is now commonly seen in the increasing numbers of extremely low-birthweight infants who are cared for in our neonatal units. In addition, a small number of infants present with classical diabetes mellitus, or have transient hyperglycaemia in response to stress when very unwell. In the neonate it is rare for hyperglycaemia to be associated with osmolar diuresis, ketosis or hyperosmolar brain injury, but infants presenting with classical diabetes mellitus may become dehydrated and hyperosmolar.

The following groups of babies are at

risk of having blood glucose levels which are too high or too low, and must have blood glucose levels monitored especially when there are abnormal clinical signs:

1. *Babies cared for on neonatal units or paediatric wards who have known co-existing clinical complications* such as extreme prematurity, previous hypoxia-ischaemia, infection – low blood glucose concentrations indicate that energy provision (intravenous or enteral) should be increased and monitoring should be continued to assess the effects of changes in management (**FIGURE 1**). High blood glucose concentration may arise from injudicious high glucose infusion rates which must be adjusted, or may be an early marker of infection, uncontrolled pain or other stress which causes metabolic disturbance and thus should alert attending staff to carry out further investigations.

2. *A baby (neonate or infant) presenting unexpectedly with any acute illness,* especially with abnormal neurological signs – measurement of blood glucose concentration is important to identify hypoglycaemia as either the cause or an association of the collapse, and to guide subsequent intravenous fluid management. Unexpected hypoglycaemia should alert clinicians to an inborn error of metabolism or endocrine disorder (see below) and appropriate blood and urine samples should be taken immediately, as it is often difficult to diagnose metabolic conditions in such infants at times when they are unstressed and normoglycaemic. Finally, high blood glucose concentrations are commonly associated with the stress response in older infants, or may represent the onset of classical diabetes mellitus presenting with typical clinical signs in infancy.

3. *Newborn babies of diabetic mothers when there has been poor diabetic control in pregnancy* – these babies may have high insulin levels persisting in the first few days after birth which will result in hypoglycaemia with, in addition, impaired protective alternative fuel responses.

4. *Neonates of macrosomic appearance* – in the absence of diabetes in pregnancy. These babies may have intrinsic pancreatic dysfunction causing hyperinsulinism and usually present with clinical signs of hypoglycaemia as alternative fuel production is also impaired.

5. *Moderately preterm or growth retarded neonates* – blood glucose monitoring is carried out alongside the support and optimisation of breast feeding. Many of the babies in this group will mount protective responses and will tolerate low-normal blood glucose levels. Therefore, there must be experienced clinical assessment as well as glucose monitoring, to indicate when additional measures, such as tube feeds with breast milk (preferably) or formula (if necessary) are required to maintain energy levels. This is far preferable to a blanket policy of formula supplementation of breast feeds in this group.

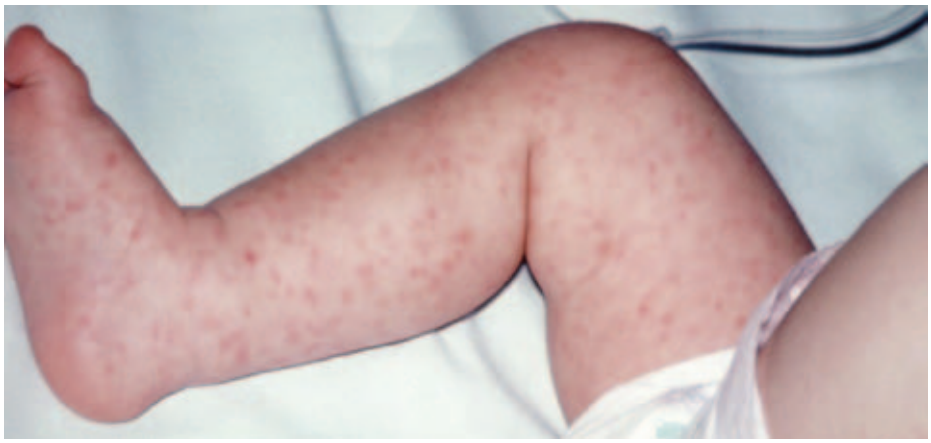

FIGURE 2 Infants with septicaemia are at risk of hypoglycaemia and hyperglycaemia. Photograph courtesy of Meningitis Research Foundation.

In summary, the accurate measurement of blood glucose concentration is essential for the prevention of severe and prolonged hypoglycaemia and hyperglycaemia in at risk groups, for the diagnosis of underlying disorders in sick infants, and in guiding feeding and fluid prescriptions for small, vulnerable or sick infants.

Pathophysiology of hypoglycaemia and hyperglycaemia

The preceding section highlighting 'at risk' infants refers to some of the underlying causes of blood glucose disturbances. This section now provides more detail regarding underlying mechanisms of hypoglycaemia and hyperglycaemia.

Hypoglycaemia

Insufficient glucose supply with failure of alternative fuel production

- Very preterm or very sick (eg septicaemia, hypoxia-ischaemia) neonates due to immaturity and dysfunction of enzyme systems and exhaustion of fuel stores (eg liver glycogen and fat in adipose tissue). Hypoglycaemia may also be found in older infants who are severely unwell (eg septicaemia) and should always be ruled out, but is less common as counter-regulation is more robust in the older, previously well infant. The older infant who is metabolically stressed is more likely to present with hyperglycaemia (see below) (**FIGURE 2**).
- Rarely, moderately preterm neonates (34-36 weeks' gestation) or those who have experienced intrauterine growth retardation may exhaust their counter-regulatory response if milk intake is insufficient, and present with significant hypoglycaemia.
- Inborn errors of metabolism – defects of fatty acid oxidation are the most common inborn errors of metabolism to present with hypoglycaemia in infancy. The severity of this group of conditions is heightened by the failure of alternative fuel (ketone body) production. Other conditions that may present with hypoglycaemia in infancy are glycogen storage disorders and fructose-1, 6-biphosphatase deficiency. These disorders usually require to be 'unmasked' by the baby entering a catabolic state. Therefore they most commonly present in the neonatal period, or during intercurrent illness, or when the baby commences sleeping through the night. Details of investigations for these conditions are to be found in standard neonatal and paediatric textbooks.
- Endocrine disorders – infants are dependent on counter-regulatory hormones to mount the metabolic responses to hypoglycaemia. The most common endocrine deficiency that presents with hypoglycaemia in infancy is adrenal insufficiency which may arise from primary adrenal dysfunction (eg congenital adrenal hyperplasia), or as a result of abnormal control of adrenal function by the pituitary, as in pituitary insufficiency. Again, it is often only possible to confirm this diagnosis on samples taken during hypoglycaemia or other stress.

Excessive glucose utilisation

■ The baby of a diabetic mother after poor diabetic control in pregnancy. Fortunately it is now rare for such babies to be severely affected as improved maternal management prevents the fetus (and therefore neonate) becoming hyperinsulinaemic. If hyperinsulinism does occur, the babies are invariably of macrosomic appearance and the circulating insulin levels fall within a few days of birth, the condition is self limiting. However, hyperinsulinism causes both hypoglycaemia and failure to produce alternative fuels. Therefore, the baby is completely dependent upon glucose and glucose requirements are high. There is a consensus view that babies who present with significant hyperinsulinism should receive milk intake or glucose infusion adequate to maintain blood glucose levels above 3mmol/L[4].

■ Neonatal hyperinsulinism. This may arise from diffuse pancreatic dysfunction (previously termed nesidioblastosis), or a localised insulinoma so that excessive quantities of insulin are secreted, even when blood glucose levels are low. Hyperinsulinism is also associated with some congenital syndromes eg Beckwith Weidemann syndrome. Hyperinsulinism in these conditions is usually more prolonged and severe than in the infant of the diabetic mother and requires treatment in specialist centres. If diagnosed and treated promptly and adequately, hypoglycaemic brain injury may be avoided[8].

■ Accidental or non-accidental administration of insulin or oral hypoglycaemic agents. This must be considered if a baby presents with severe and unexplained hypoglycaemia, and if suspected, appropriate child protection processes must be employed.

Hyperglycaemia

■ Insulin insufficiency. It is rare for classical diabetes mellitus to present in the under-5 age group, and therefore this very rarely presents in infancy[9]. When diabetes mellitus occurs in the neonatal period, usually as a result of underlying genetic abnormalities, this may be transient (with increased risk of later type 2 diabetes) or permanent[10].

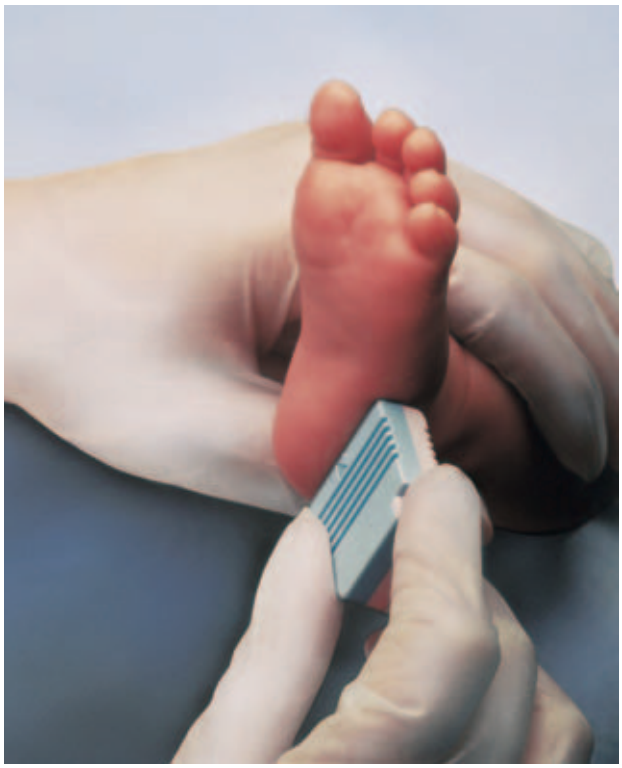

FIGURE 3 Collecting blood using a heel incision device. Photograph courtesy of LDH UK Ltd.

■ Insulin resistance. This occurs as a result of the endocrine stress response, for example during severe illness or surgery, especially if without adequate analgesia, or as a result of trauma, including submersion[11-16]. High circulating levels of cortisol and catecholamines (adrenaline and noradrenaline) have the reverse action to insulin, rendering the baby insulin resistant and catabolic, and in addition the latter directly suppress insulin release. High glucose levels may be the earliest indication of deterioration in a baby's condition and are associated with a worse prognosis[14,15].

■ Excessive glucose administration. The extremely preterm neonate is very sensitive to excessive glucose administration, especially if glucose infusion rates exceed 10mg/kg/min (equivalent to >144 ml 10% dextrose/kg/day) or are increased rapidly to this level. There is also a risk in older infants that injudicious glucose administration will result in inefficient glucose utilisation, hyperglycaemia and hyperosmolar states[17,18].

Definitions and accurate blood glucose measurement

Ideally, definition of hypoglycaemia and hyperglycaemia should include the following details – blood glucose concentration considered to be the minimum or maximum safe level, the length of time beyond which the abnormal blood glucose level is considered to be harmful, the presence of clinical signs or associated complications, the group of infants studied, and the consideration of protective responses. Most of these criteria have never been adequately addressed by previously published definitions, despite the extensive literature regarding the numerical definition of neonatal hypoglycaemia, which has been succinctly summarised by Halamek et al[19]:

"As of 1997 no consensus exists in the normal newborn nursery, NICU, or the courtroom as to the definition of hypoglycaemia in the neonate."

This paucity of data has resulted in a pragmatic approach to hypoglycaemia recently proposed by a group of clinicians that is based on thresholds for intervention rather than attempts to define hypoglycaemia as a single numerical term[4]. This group suggested that, for infants who are at risk of neurological sequelae by virtue of their inability to mount protective responses (see above), intervention to raise blood glucose should be considered if two consecutive blood glucose levels, in a baby with no abnormal clinical signs, are below 2mmol/L (measured using accurate device) or a single blood glucose level is below 1mmol/L. Regardless of the blood glucose concentration, neurological signs in association with low blood glucose levels should prompt investigations to establish a firm diagnosis of hypoglycaemia and its underlying cause, and the institution of urgent treatment. The group recommended maintenance of blood glucose levels above 3mmol/L if hyperinsulinism is suspected or identified.

Although there can be no single defining values for hypoglycaemia and hyperglycaemia, most clinicians caring for small, sick or unstable neonates aim to maintain blood glucose levels above 2-3mmol/L and below 10-15mmol/L. For older infants, where low blood glucose levels are more likely to have a more serious underlying cause, clinicians usually aim to maintain blood glucose levels above 3mmol/L.

Adhering to a range of optimal blood glucose values necessitates accuracy of monitoring as management may be

changed if blood glucose measurements are perceived to change by as little as 1mmol/L at either end of the optimal range. Inaccurate monitoring may also lead to over treatment or under treatment which may in turn harm the baby.

Differences in measurement arise when comparing plasma and whole blood measurements of glucose, even using accurate laboratory methods[20]. This difference is greater at high haematocrit (ie a greater practical issue in neonates when compared to older infants). However, as long as either plasma or blood values are consistently used for an individual subject and method of measurement is reported, the difference between plasma and whole blood measurements is of lesser clinical significance than the potential inaccuracies of measurement described below.

The gold standard, and a standard to which we should be aspiring in practical terms, is measurement of blood glucose concentration using an accurate laboratory method. This may be conveniently sited in a neonatal unit side laboratory, where it should undergo the same stringent quality control processes as blood gas analysers.

In reality, the most common method used for blood glucose monitoring has been by reagent strip at the cotside, using heelprick capillary blood samples (**FIGURE 3**). The perceived advantages of this method are cost, ease of use, accessibility and need for minimal training. The reagent strips are designed for the detection of hyperglycaemia in diabetic patients, for which purpose they are sufficiently accurate. However, it has been demonstrated, and the manufacturers themselves acknowledge, that reagent sticks have no role in the diagnosis of hypoglycaemia, because of inherent inaccuracies at low blood glucose concentrations[21,24]. These problems have been highlighted by the UK Department of Health[25] and American Academy of Pediatrics[26]. Attempts to introduce more accurate (and more expensive) methods of near-patient glucose monitoring, have proved equally disappointing in neonatal practice as they have not delivered the expected improvement in accuracy[27-29].

If samples are sent to hospital laboratories for accurate measurement to confirm cotside readings, there is the inevitable decline in glucose in a whole blood sample during transit and delay in reporting a result[29].

Summary

Hypoglycaemia and hyperglycaemia are clinical signs, not 'stand alone' diagnoses. It is clear that blood glucose control may be impaired for a variety of underlying reasons, and it is essential that the cause of hypoglycaemia or hyperglycaemia is considered and treated, rather than blindly treating the abnormal blood glucose value alone. In general terms, hypoglycaemia may be avoided and treated by identifying infants at risk and ensuring there is adequate exogenous energy provision. Occasionally additional treatments are required, especially if there is persistent hyperinsulinism. The mechanisms underlying hyperglycaemia are more complex and management of hyperglycaemia must be based upon the understanding of the underlying cause in each case.

Finally, babies at risk of disturbances of blood glucose control cannot be managed without access to accurate and reliable methods of measurement.

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