

Hyperglycaemia

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■ Clinical presentation

- Hyperglycaemia is usually picked up incidentally on routine blood glucose assessment or in response to finding glycosuria.
- It may be noted as part of the workup of a sick baby.

■ Definition of hyperglycaemia

The upper end of the 'normal' range for blood sugar has not been clearly defined in neonatal practice, although levels of >7 mmol/L are unusual in healthy term babies. Most neonatologists would treat by reducing sugar intake or with insulin if the blood sugar is >10 – 12 mmol/L, especially if there is significant glycosuria causing an osmotic diuresis, particularly in sick preterm babies. However, tighter glucose control in intensive care patients may be more appropriate.

■ Approach to the problem

Hyperglycaemia usually occurs in very preterm or small-for-gestational age (SGA) babies due to impaired insulin secretion and/or insulin resistance as well as immaturity of the liver enzymes involved in glucose metabolism (dysregulation of glucose homeostasis).

If hyperglycaemia occurs out of context (such as a previously healthy appropriate-for-gestational-age, enterally fed infant), the cause needs to be identified.

■ Differential diagnosis

Commonly

- Iatrogenic from excessive intravenous glucose delivery
- Impaired glucose homeostasis in preterm/SGA baby
- Sepsis
- Stress
- Drugs particularly corticosteroids

Rarely

- Transient neonatal diabetes
- Permanent neonatal diabetes
- Pancreatic agenesis

■ Investigations

- Measure the true blood glucose to confirm the diagnosis.
- Calculate the glucose infusion rate (see Appendix 1) to exclude excessive glucose delivery.

If hyperglycaemia is persistent exclude neonatal diabetes and measure:

- *In blood concomitant*
 - Glucose
 - Insulin
 - C-peptide
 - Ketone bodies
- *In urine*
 - Ketones

Genetic investigations

- Uniparental disomy of chromosome 6 has been found in some cases of transient neonatal diabetes.
- Activating mutations in the gene encoding the ATP-sensitive potassium-channel subunit Kir6.2 may cause permanent neonatal diabetes and may also be associated with developmental delay, muscle weakness, and epilepsy.
- Permanent neonatal diabetes has also been shown to result from complete deficiency of glucokinase activity.

- Mutations in the human IPF1 gene (also known as IDX1, STF1, and PDX1) have been found in patients with pancreatic agenesis.

■ Management

Immediate

- Treat underlying cause (sepsis, etc.).
- Reduce glucose infusion rate (if high) and/or calorie intake to 5 mg/kg/min (equivalent to 3 mL/kg/h of 10% dextrose, fetal glucose production rate), but not below 3 mg/kg/min of glucose or 45 kcal/kg/day.
- Some very premature babies develop hyperglycaemia and an osmotic diuresis with normal infusions of glucose. This can be treated by reducing the glucose input or giving an insulin infusion.
- Treatment with insulin should be considered when the blood sugar is >10 mmol/L or there is an osmotic diuresis, which is uncommon in full-term neonates.
- Suggested starting treatment dose of insulin is 0.05 unit/kg/h. This may need to be altered depending on response.
- When using insulin it is *essential* to have accurate blood sugar measurements to identify and avoid hypoglycaemia.

Medium term

- Hyperglycaemia secondary to dysregulation in preterm babies resulting from delayed maturation of hepatic enzymes may persist at least until the time of discharge. However, in the majority of babies, insulin therapy can be discontinued after a few days once hormonal maturation and maturation of the liver have occurred.
- If hyperglycaemia persists, consider neonatal diabetes (rare, incidence 1 in 400,000). Treatment with insulin may be temporary (months) or permanent. Insulin may be given as subcutaneous intermittent injections or via an insulin pump, but should only be undertaken under the supervision of a paediatric diabetologist. Subcutaneous injections can be difficult technically because of small body size in relation to insulin delivery devices and lack of subcutaneous tissue. There is a risk of iatrogenic hypoglycaemia.
- Babies diagnosed with neonatal diabetes will require urgent referral to a paediatric diabetologist and geneticist.

- As those with a KIR6.2 mutation may respond to sulphonylureas, and therefore not require longterm insulin therapy, early genetic analysis is important. Arrangements for KIR6.2 mutation testing can be found on the diabetesgenes.org website. Test results take about 6 weeks.

Long term

- Permanent neonatal diabetes will require lifelong insulin therapy.
- Transient neonatal diabetes may re-emerge as type II diabetes in adolescence.

■ What to tell parents

In most cases, hyperglycaemia will be secondary to prematurity/SGA, hence an explanation for the use of insulin is immaturity of the normal mechanisms that usually keep the glucose level stable. This is likely to last just a few days, by which time the baby's hormone regulation and liver maturity will allow insulin to be discontinued. In some babies, high sugar levels can last for a few weeks.

If the baby does have neonatal diabetes, the temporary or permanent nature of the disease needs to be discussed. Parents will require training in insulin administration, glucose monitoring, and management of hypoglycaemia. Appropriate back-up from diabetes nurse specialist and diabetologists will need to be in place before discharge home.

USEFUL LINKS

Glucose physiology: p. 12.
 Intermediary metabolism: p. 15.
 Calculation of glucose infusion rate: Appendix 1.
diabetesgenes.org website

SUPPORT GROUPS

For the patient with diabetes:
 Diabetes UK: diabetes.org.uk
 ChildrenWithDiabetes (US): www.childrenwithdiabetes.com

Cambridge University Press
978-0-521-83849-8 - Practical Neonatal Endocrinology
Amanda Ogilvy-Stuart and Paula Midgley
Excerpt
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FURTHER READING

- Hawdon JM, Aynsley-Green A. Disorders of blood glucose homeostasis in the neonate. In *Textbook of Neonatology*, third edition, Eds. Rennie JM, Robertson NRC. Churchill Livingstone, pp. 939–956.
- Polak M, Shield J. Neonatal and very-early-onset diabetes mellitus. *Semin Neonatol* 2004; 9: 59–65 (review).
- Hume R, Burchell A, Williams FL, Koh DK. Glucose homeostasis in the newborn. *Early Hum Dev* 2005; 81: 95–101.
- Hey E. Hyperglycaemia and the very preterm baby. *Semin Fetal Neonatal Med* 2005; 10: 377–387.

Cambridge University Press
978-0-521-83849-8 - Practical Neonatal Endocrinology
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Hypoglycaemia

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■ Clinical presentation

Hypoglycaemia may be picked up incidentally in an asymptomatic baby.

Blood glucose should be measured regularly in vulnerable babies (see below).

Symptoms are non-specific:

- *Neuroglycopenic symptoms* of hypoglycaemia include apnoea, hypotonia, jittering, irritability, lethargy, abnormal cry, feeding problems, convulsions, and coma.
- *Autonomic symptoms* (pallor, sweating, tachypnoea) are generally not prominent in the newborn.
- Macrosomia may be present in infants of diabetic mothers.
- Macrosomia in the absence of a history of maternal diabetes suggests hyperinsulinism.
- Macrosomia with magroglossia, organomegaly, exomphalos, or ear lobe creases suggests Beckwith–Wiedemann syndrome (approximately 80% demonstrate genotypic abnormalities of the distal region of chromosome 11p).
- Midline defects, micropenis, and jaundice suggest hypopituitarism (see Chapter 7).
- Babies can have low blood glucose levels and be completely asymptomatic.

■ Approach to the problem

- *Asymptomatic* healthy term babies of normal birth weight (9th to 91st centiles) do *not* require blood sugar measurements.
- *Symptomatic* hypoglycaemia in a term baby is *always* pathological until proved otherwise.

Babies at risk of hypoglycaemia

- *Preterm or intrauterine growth retardation*: lack of glycogen stores, immature enzymes involved in glucose homoeostasis, inappropriately high insulin levels.
- *History of birth depression*: lack of glycogen stores due to utilization.
- *Infants of diabetic mothers, large-for-dates babies, babies with Beckwith–Wiedemann syndrome, babies with rhesus disease*: excessive insulin secretion.
- *Polycythaemia*: excessive metabolism of glucose by erythrocytes.
- *Congenital heart disease, sepsis, hypothermia*: excessive glucose demands.
- *Metabolic disorders*:
 - *Insufficient glucose production* by blocking glucose release or synthesis, or blocking or inhibiting gluconeogenesis including glycogen storage disease, glycogen synthase deficiency, fructose-1,6-diphosphatase deficiency, phosphoenol pyruvate deficiency, pyruvate carboxylase deficiency, galactosaemia, hereditary fructose intolerance, maple syrup urine disease. Children may become adapted to their hypoglycaemia because of its chronicity. Lactate levels are often high.
 - *Defects in glucose utilization* (Krebs cycle defects, respiratory chain defects) are rare but interfere with the ability to appropriately generate ATP from glucose oxidation. Lactate levels are high.
 - *Defects in alternative fuel production* (carnitine acyl transferase deficiency, hepatic hydroxymethyl glutaryl coenzyme A (HMG CoA) lyase deficiency, long- and medium-chain acyl-coenzyme A (acyl-CoA) dehydrogenase deficiency, variably in short-chain acyl-CoA dehydrogenase deficiency) interfere with the use of fat as energy supply so the body is dependent on glucose only. This becomes a problem during periods of prolonged fasting. Ketone levels are low.
 - *Galactosaemia*.
- *Endocrine abnormalities*: imbalance between insulin and counterbalancing hormones (growth hormone (GH) and cortisol). These babies usually present with prolonged jaundice caused by giant cell hepatitis. Micropenis may be apparent (see Chapter 6).
- *Hyperinsulinism*: persistent hypoglycaemic hyperinsulinaemia of infancy (PHHI) (see Chapter 3).
- *Maternal or neonatal β -adrenergic blocker use*.

■ Differential diagnosis

Sepsis, intraventricular haemorrhage, electrolyte abnormalities, or most neonatal illnesses, can present with symptoms or signs suggestive of hypoglycaemia.

■ Investigations

Calculate the glucose infusion rate in mg/kg/min (see Appendix 1) and ensure the baby is receiving at least 5 mg/kg/min.

Low blood sugar must be confirmed by a method that uses glucose oxidase or glucose-6-phosphate dehydrogenase. (BMstix are *not* acceptable – they are not accurate at low values especially using whole blood with a high haemoglobin concentration.)

Anticipated hypoglycaemia in a vulnerable baby which resolves within the first few days of life requires no further investigation.

Unexpected hypoglycaemia (e.g. symptomatic hypoglycaemia in a term baby), severe hypoglycaemia (<1 mmol/L), or persisting hypoglycaemia should be investigated with samples taken while the baby is hypoglycaemic (Table 2.1).

Table 2.1 Samples in order of importance to be taken *during* hypoglycaemia.

Blood samples			Urine
Hormones	Metabolites	Other	Metabolites
Insulin	Glucose	pH	Ketones
Cortisol	Free fatty acids	Galactose-1-phosphate	Reducing substances
GH	β-OH butyrate	uridyl transferase	Organic acids
ACTH	Lactate		Amino acids
*Thyroid-stimulating hormone	Amino acids		
	Pyruvate		
*Thyroxine	Acetoacetate		
C-peptide	Urate		
Glucagon	Lipids		
	Total and free carnitine		
	Acyl carnitine profile		
	Ammonia		

*Not necessary to take during hypoglycaemia.

Key: GH, growth hormone; ACTH, adrenocorticotrophic hormone; β-OH butyrate, β-hydroxybutyrate.

Definition of hypoglycaemia

The blood glucose concentration at which hypoglycaemia exists is not known and this may not reflect neuroglycopenia. In appropriate-for-gestational-age term babies, the ability to produce alternative fuels in the form of ketone bodies suggests glucose levels per se are not important. *Well* term, appropriate-for-gestational-age babies do *not* require glucose monitoring. Preterm babies and babies born small-for-gestational-age (SGA) are unable to produce alternative fuels appropriately, however, breast milk appears to produce a more exaggerated ketogenic response compared with formula feeds. The concentration of glucose that is 'safe' in these babies is unknown. Neurophysiological data and epidemiological data suggest that the blood sugar should be kept at least ≥ 2.6 mmol/L in vulnerable babies. With a lack of alternative metabolic fuels, a level of >3 mmol/L may be more appropriate.

■ Management

Prevention

Anticipate hypoglycaemia in vulnerable babies and measure blood sugar as soon as possible after birth, within 2–3 h of birth and before feeding, or at any time there are symptoms or signs of hypoglycaemia. Blood sugar should be reassessed within 30 min to 1 h after intervention (which should be prompt!). Normoglycaemic babies should be reassessed approximately 4–6 hourly before feeds until the blood sugars are stable with at least two normal measurements.

If appropriate, early milk feeds should be initiated in vulnerable babies. Milk stimulates gut hormones which may facilitate postnatal metabolic adaptation. Millilitre for millilitre, milk has a higher energy content than 10% dextrose. Breast milk induces a more rapid postnatal metabolic adaptation than formula feeds and is the milk of choice.

If early enteral feeding is not anticipated (e.g. a very preterm or a sick baby), an intravenous (IV) dextrose infusion will need to be commenced; 3 mL/kg/h (72 mL/kg/day) of 10% dextrose will provide 5 mg/kg/min. This is usually sufficient to prevent hypoglycaemia.