Amanda Ogilvy-Stuart and
Paula Midgley

Practical Neonatal Endocrinology

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Practical Neonatal Endocrinology

This is a handbook of neonatal endocrinology. Our aim is to aid those caring for newborn babies in the diagnosis and management of suspected endocrine pathology. Interpretation of endocrine function in the newborn period can be difficult, because of the transition following hormonal influences of the mother and placenta. The situation is even more complex in infants born prematurely.

The unique format is clinically orientated from presentation, diagnosis, and management, including immediate, medium and long term. It clearly explains and describes how and when the samples should be taken, order of priority, sample volume required, length of time one can expect before results are available and normal values. This book gives guidance as to what to tell parents, providing addresses of support groups. This is very much a practical 'hands-on, how-to' approach with flow charts. It also provides a formulary and investigation methodology section and a brief description of physiology.

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Practical Neonatal Endocrinology

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Introduction

Endocrine disease in the neonate is uncommon, but may be life threatening or have profound long-term consequences if not promptly recognized and treated. In addition, interpretation of endocrine function in the newborn period can be difficult, because of the transition following the hormonal influences of the mother and placenta. The situation is even more complex in infants born prematurely.

The aim of this handbook is to aid those caring for newborn babies in the diagnosis and management of suspected endocrine pathology. A number of flow charts are provided to clarify the diagnostic process. This book is designed to guide clinicians in the diagnostic process, but an endocrine specialist should be involved at an early stage, where an endocrine abnormality is strongly suspected.

We have given a guide to how and when samples should be taken, and provided a guide as to sample volumes, length of time one can expect before the results are available and normative values. However, these will vary between hospitals, methodology used, and whether samples need to be sent elsewhere for analysis. We have also provided a formulary of drugs used in neonatal endocrinology.

Amanda Ogilvy-Stuart

Paula Midgley

Hyperglycaemia

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

FURTHER READING

Hawdon JM, Aynsley-Green A. Disorders of blood glucose homeostasis in the neonate. In *Textbook of Neonatology*, third edition, Eds. Rennie JM, Roberton NRC. Churchill Livingstone, pp. 939–956.

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Hypoglycaemia

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:

- *Neuroglycopaenic 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 uridyl transferase	Reducing substances
GH	β-OH butyrate		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 neuroglycopaenia. 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 $\geqslant$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.

Immediate

This depends on condition of baby:

- *Asymptomatic*, otherwise well infants, should initially be fed at an increased volume of milk or fed more frequently, and only if hypoglycaemia persists should an infusion of glucose be started.
- *Symptomatic* babies able to tolerate enteral feeds may just require an increase in volume or frequency of milk feeds but if hypoglycaemia persists despite feeding, or the baby is unable to tolerate feeds, start an IV infusion of glucose at an appropriate rate (at least 5 mg/kg/min of glucose, which is equivalent to 72 mL/kg/day of 10% dextrose).
- *Severe* hypoglycaemia should be treated with a slow bolus of 2 mL/kg of 10% dextrose before commencing the infusion. Bolus doses of concentrated glucose should be avoided as they cause insulin release and rebound hypoglycaemia.

If there is no venous access, intramuscular (IM) or subcutaneous glucagon 100–200 μg/kg/dose may be used to 'buy time' if an infusion is difficult to site. Forty per cent glucose gel (*hypostop*) is absorbed from the buccal mucosa and may also be used (small amount approximately 1 mL/kg is squeezed from the tube into the inside cheek or buccal mucosa of the baby).

The dextrose infusion rate should be increased if hypoglycaemia is not controlled. There is a risk of fluid overload with large volumes of 10% dextrose. If hypoglycaemia is difficult to control on reasonable volumes of fluid, or fluid restriction is required for other reasons, insert a central line and give higher concentrations of glucose in a smaller volume.

Persisting glucose infusion rates >8 mg/kg/min suggest hyperinsulinism (see Chapter 3).

There are more calories in 1 mL of milk than 1 mL 10% dextrose, and enteral feeding will establish normal hormonal regulation of glucose and should not be discouraged. Breast milk-fed babies have better ketogenic responses compared with formula-fed babies. Once the blood glucose level is normal, feeds can be increased and the infusion tailed off.

Medium term

Once blood sugars are stable, IV infusions should gradually be reduced as enteral milk feeds are increased.

Long term

With the common causes of neonatal hypoglycaemia (prematurity, SGA, birth depression, sepsis), the low glucose levels are usually short lived and require no long-term monitoring.

The rare metabolic and endocrine causes may require further investigation, treatment, genetic counselling, and follow-up.

What to tell parents

In vulnerable babies, explain why blood sugar monitoring is important. If treatment is required, explain this is likely to be for a short period until enteral feeds tolerated, and/or underlying cause treated. If persisting hypoglycaemia, explain importance of investigations and update with results. The need to keep the baby normoglycaemic because of potential effects on the brain should be discussed. Further information will depend on subsequent diagnoses. If the hypoglycaemia is severe or prolonged, the baby will need neurodevelopmental follow-up.

Interpretation of results

For interpretation of results refer to Figure 2.1.

GLUCOSE: PHYSIOLOGY

In the fetus blood glucose levels are determined by the placenta – the fetal levels reflecting maternal levels with no endogenous glucose production. Gluconeogenic enzyme levels are low or absent. Adipose tissue accumulates in the last trimester and glycogen stores are laid down in the last month of gestation.

With clamping of the umbilical cord, placental glucose supply is abruptly interrupted and glucose levels fall over the first 2–4 h of life before glucose homoeostatic enzymes, hormones and their receptors become fully functional, and feeding is established. Counter-regulatory hormones rapidly become active – with high adrenaline, glucagon and GH levels and a fall in insulin levels. This induces glycogenolysis, gluconeogenesis, and lipolysis. In healthy, full-term infants the early low blood sugar is countered by a rapid rise in fatty acids and ketone bodies, providing alternative metabolic fuels.

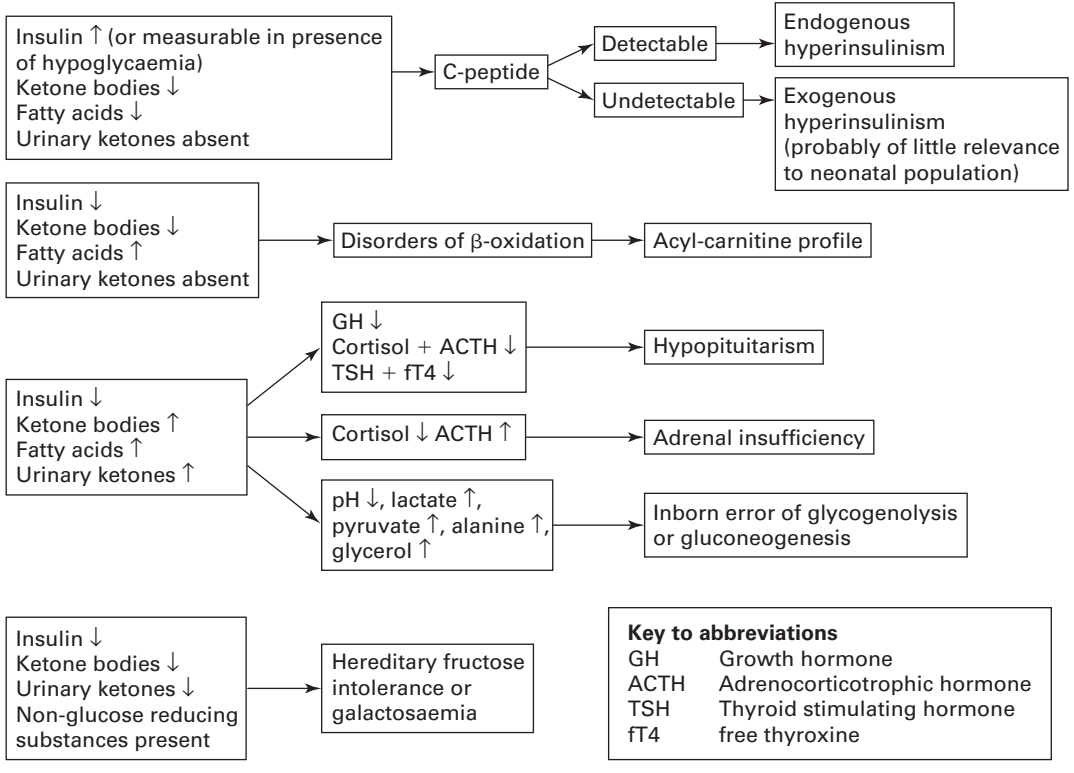

Figure 2.1 Interpretation of results

By 4–6 h glucose levels stabilize although glycogen stores become rapidly depleted.

In contrast to term babies, SGA and preterm babies have poor ketogenic responses and enhanced glycolysis. In addition, insulin secretion may be inappropriately high and not suppressed by low blood sugar levels. Immaturity of the normal homoeostatic mechanisms may therefore result in hypoglycaemia in these two groups of babies.

Hypoglycaemia will also arise if there is insulin excess or a deficiency or insufficiency in one of the counter-regulatory hormones (glucagon, adrenaline, cortisol, and GH) that may occur in endocrine pathology. If there is an inborn error of metabolism resulting in a block in the breakdown of glycogen or gluconeogenic pathways, or a block in one of the pathways involved in the provision of substrate for these pathways, hypoglycaemia will ensue with fasting.

Investigation of hypoglycaemia therefore involves exclusion of endocrine or metabolic disease and exclusion of pathologies causing excess utilization (such as congenital heart disease, hypothermia, and sepsis).

The glucose requirements of a newborn baby are 5–8 mg/kg/min and fall during childhood to adult values of 1–2 mg/kg/min.

Hypoglycaemia has both acute and long-term consequences. Infants with asymptomatic hypoglycaemia may have neurocognitive defects at the time of hypoglycaemia, including impaired auditory and sensory evoked responses. Long-term consequences of hypoglycaemia include decreased head size, lowered intelligent quotient (IQ), and specific regional brain abnormalities seen with magnetic resonance imaging (MRI). Many of the aetiologies of hypoglycaemia may have the same consequences, making the causal distinction difficult.

Hyperglycaemia results in an hyperosmolar state which not only causes an osmotic diuresis (thereby worsening the hyperosmolar state) but also increases the risk of intraventricular haemorrhage. There may also be an increased risk of sepsis.

Glycogen synthesis and breakdown involve separate pathways. Although glycogen is found in many tissues, only liver glycogen can be broken down to free glucose into the circulation because of the absence of glucose-6-phosphatase in other tissues.

Glycolysis is the metabolism of glucose to pyruvate. Pyruvate can then be converted to lactate or to acetyl coenzyme A (acetyl CoA) (which is oxidized in the tricarboxylic acid cycle). Acetyl CoA is the substrate for

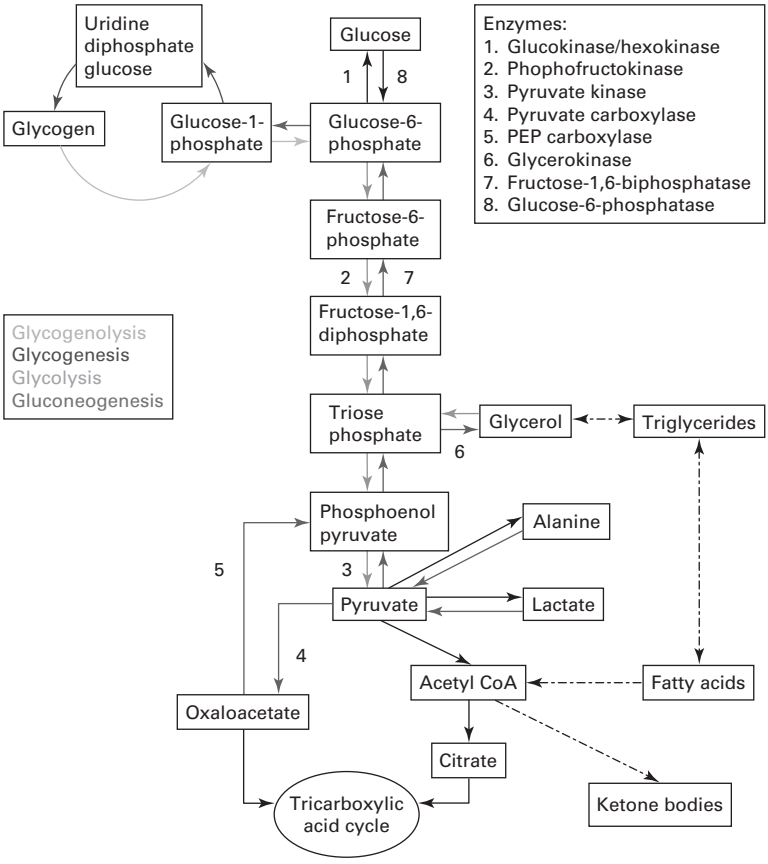

Figure 2.2 Pathways involved in glycogen synthesis and breakdown, glycolysis, and gluconeogenesis

the synthesis of fatty acids which can then be stored as triglycerides (lipogenesis).

Gluconeogenesis is the process in which amino acids, glycerol, and lactate are converted to glucose. Lactate is produced from glycolysis, amino acids from protein breakdown, and glycerol from lipolysis in the adipocyte (Figure 2.2).

USEFUL LINKS

Management of hyperinsulinism: Chapter 3.

SUPPORT GROUPS

Beckwith–Wiedemann Support Network: www.beckwith-wiedemann.org
Beckwith–Wiedemann Support Group: www.bws-support.org.uk

FURTHER READING

Lee PJ, Leonard JV. Hypoglycaemia. In *Clinical Paediatric Endocrinology*, third edition, Ed. Brook CGD. pp. 677–693.

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Management of hyperinsulinism

Clinical presentation

- Incidental finding of hypoglycaemia on blood glucose testing.
- Large birth weight.
- Features of Beckwith–Weideman syndrome (large tongue, ear lobe creases, exomphalos, visceromegaly).
- Small-for-gestational-age (SGA, due to dysregulation).
- Rhesus disease (largely historical since the introduction of anti-D immunization and intrauterine transfusions; hyperinsulinism was presumed to be due to protein from the breakdown of red blood cells stimulating insulin release in utero).

Symptoms include:

- Jitteriness and hypoglycaemic convulsions, but symptoms may be absent.

Investigations

For samples during hypoglycaemia:

- See Chapter 2, Table of Samples to be taken during hypoglycaemia (p. 9, Table 2.1).
- It is essential to include a sample for ammonia during hypoglycaemia on at least one occasion, to identify infants with activating glutamate dehydrogenase (GLUD1) mutations (see below).

Diagnosis

Diagnosis is based on the insulin level at the time of hypoglycaemia (when insulin production should be completely suppressed), and/or a glucose requirement $\geqslant$8 mg/kg/min. Ketone body and free fatty acid production should also be low, which may support the diagnosis, particularly in the situation where no insulin result is available.

Hyperinsulinism is the commonest pathological cause of neonatal hypoglycaemia and is usually transient (and less severe), but can be persistent (persistent hypoglycaemic hyperinsulinaemia of infancy (PHHI)) and more difficult to manage.

Approach to the problem

For all infants

Calculate glucose intake in mg/kg/min (see Appendix 1) each day in order to monitor the trend in glucose requirement (if declining the hyperinsulinism may be transient). Due to the inability to utilize alternative sources of energy (e.g. ketones) in hyperinsulinism, blood glucose should be maintained $\geqslant$3.5 mmol/L.

For severe hyperinsulinism

Site a central line (e.g. long silastic) for glucose infusion. This should be done at an early stage. Glucagon 100–200 μg/kg/dose intramuscularly (IM) or subcutaneously (SC) can be used for emergencies (i.e. if the drip has tissued) but will cause rebound increase in insulin secretion thereafter. Buccal hypostop (1 mL/kg/dose) will also allow time for venous access to be obtained.

If the *blood glucose requirement* is >12 mg/kg/min, drugs may be needed to suppress insulin secretion. If the blood glucose is persistently in the 15–20 mg/kg/min range, the infant will almost definitely need drug therapy and specialist endocrine advice should be sought at an early stage (Figure 3.1).

If the infant is tolerating oral feeds (but be aware that the protein load of milk may stimulate insulin secretion), use *diazoxide* (5–20 mg/kg/day divided into three doses, e.g. start at 5–10 mg/kg/day and work up) *always* with *chlorothiazide* (3.5–5 mg/kg 12 hourly). Chlorothiazide helps counteract the fluid retention caused by diazoxide and also has additional effects on suppression of insulin secretion. Avoid excessive fluid intake during diazoxide therapy. Diazoxide can also be given intravenously (IV) (but an alternative diuretic will be required as chlorothiazide is not available IV).

Blood pressure (BP) must be monitored (intermittently will do) on diazoxide therapy. Side effects include fluid retention, hypertrichosis (chronic

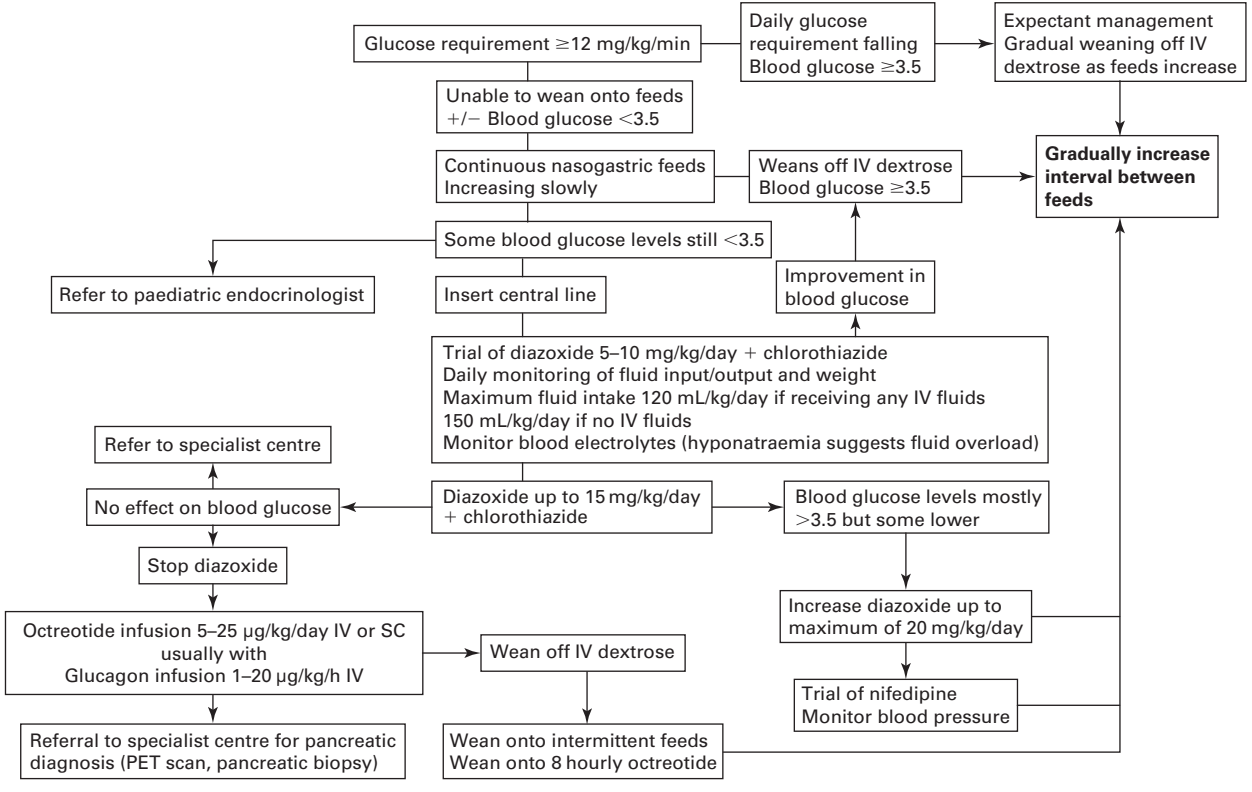

Figure 3.1 Suggested guide for management of persistent hyperinsulinism

use), hyperuricaemia, hypotension, rarely leucopenia, thrombocytopenia. Fluid retention can be serious, and infants on diazoxide should have their weight and electrolytes monitored daily initially to identify/prevent this problem. If on any IV fluids, then the total fluid intake should be restricted to 120 mL/kg/day (a central line allows the administration of higher concentrations of dextrose to maintain blood glucose). Milk feed volume should not exceed 150 mL/kg/day. If there is no response to diazoxide 15 mg/kg/day, pushing the dose up further is not likely to have any effect. About one-third of cases of severe hyperinsulinism will be diazoxide sensitive, and it is the two-thirds that are not, that particularly require highly specialized assessment.

If there is no response to diazoxide/chlorothiazide then these drugs should be stopped and a trial of octreotide given (see below). If there is a response to diazoxide/chlorothiazide, but blood glucose is still a problem consider adding nifedipine, although the effects of nifedipine may be marginal. *Nifedipine* 0.25–2.5 mg/kg/day divided into 4 or 6 hourly regimen. Start at the *lowest dose* and work up as the BP tolerates. In practice, it is almost impossible to administer <1 mg. If there is no arterial line, then measure BP before and at 15-min intervals after each dose, continuing for at least 1 h.

If feeds are not tolerated, or the hypoglycaemia is not controlled by diazoxide/chlorothiazide, a trial of *somatostatin* (*octreotide*) 5–25 μg/kg/day as a continuous infusion either IV or SC (start on low dose as causes vasoconstriction in the gut) usually accompanied by IV *glucagon* infusion 1–20 μg/kg/h may be effective.

Somatostatin infusion must be under ECG monitoring. Somatostatin also suppresses growth hormone (GH), thyroid-stimulating hormone (TSH), adrenocorticotrophic hormone (ACTH), and can cause steatorrhoea, cholelithiasis, abdominal distension. Paradoxically, high doses can cause a fall in blood glucose.

Glucagon infusion can cause hypokalaemia, vomiting, and increased myocardial contractility.

In severe hyperinsulinism, the use of continuous nasogastric feeds provides more stability in insulin secretion than bolus feeds. Start with a low volume (1 mL/h) and build up gradually depending on the response in blood glucose. The protein content of total parenteral nutrition (TPN) also stimulates insulin secretion, and a protein-reduced preparation may be required if TPN is essential.

The infant may require surgery (removal of part of the pancreas) if he/she is unable to wean from IV dextrose onto feeds, and is either unresponsive to, or requiring a high dose (20 mg/kg/day) of diazoxide.

A significant number of cases (30–40%) are due to focal hyperplasia of the islet cells, where resection of the affected portion can be undertaken, which is important as there is a risk of pancreatic failure (diabetes, with or without exocrine deficiency) later in childhood following subtotal pancreatectomy.

Differentiation between diffuse and focal disease is difficult. Over the past few years selective pancreatic venous sampling has been used, but this has largely been replaced by a combination of laparoscopic biopsy of the pancreas and positron emission tomographical (PET) scanning. Pancreatic biopsy should only be performed in experienced centres, and at present PET scanning is only available via the Hospital for Sick Children, Great Ormond Street, London in the UK. The service may be developed in other centres in the UK in the future.

Management of the infant with less severe hyperinsulinism

Many infants can be managed with a background dextrose infusion, weaning slowly onto frequent feeds. The feed interval should be increased gradually, while blood glucose is being measured regularly before feeds. The infant should be able to go 4–6 h between feeds without becoming hypoglycaemic before being discharged home. Where this is difficult, the addition of cornstarch to the feeds can be helpful (slower burning carbohydrate). In this case, or where blood glucose levels have been borderline, or where drug treatment has been necessary, it is wise to teach the parents to monitor blood glucose at home.

For more severe hyperinsulinism the infant may require tube feeds in addition to drug treatment. It may be inadvisable to insert a gastrostomy tube (and risk adhesions) if subsequent pancreatic surgery is anticipated, but this may be necessary if the infant requires continuous feeds.

Discharge planning for persistent hyperinsulinism

Discharge planning should include instruction in the use of emergency IM glucagon, an emergency management letter, and a flow chart for the

parents for management of blood glucose levels (including use of hypostop) with emergency contact numbers. Diazoxide and chlorothiazide are prescribed on a named patient basis and both solutions are produced in the USA, therefore their supply has to be secured in advance.

What to tell parents

A simple explanation of the cause of the hypoglycaemia should be given.

The problem may be transient (weeks or months) or persistent. It is likely that the baby will be in hospital for a minimum of 10 days (transient hyperinsulinism) but this could easily be longer. It is vital that the blood sugar is normal (consistently for 3 days or more) before the infant can go home, and that it is clear how long the infant can manage between feeds without the blood sugar falling.

With persistent hyperinsulinism the duration of hospital stay depends on the severity, but if unresponsive to diazoxide it is likely to be 10–12 weeks, and surgery may be required. Warning of the side effects of treatment should be given, particularly the hypertrichosis caused by chronic diazoxide use which includes the encroachment of the hairline onto the face.

If the infant has persistent hyperinsulinism the family should be referred to a geneticist.

DEVELOPMENT AND FUNCTION OF THE PANCREAS

The principle endocrine function of the pancreas is the regulation of blood glucose. The islets of Langerhans are scattered throughout the pancreas and contain three-cell types:

- 60–80% β-cells which secrete insulin to reduce blood glucose;
- 15–20% α-cells which secrete glucagon to increase blood glucose;
- 5–10% δ-cells which release somatostatin.

There are also small numbers of cells releasing peptides which act on the gut.

The pancreas is formed by two separate embryonic rudiments which subsequently come together to form one organ. Differentiation and development of the islet cells is controlled by numerous transcription factors in organogenesis (e.g. HIX, PDX1, CDX1, NKx2.3, PAX4) and insulin gene expression (e.g. HNF1α, HNF4α, PDX1). PDX1 appears to be essential for the normal islet development and function. β-cells are detectable from 14-weeks gestation and insulin secretion by 18 weeks.

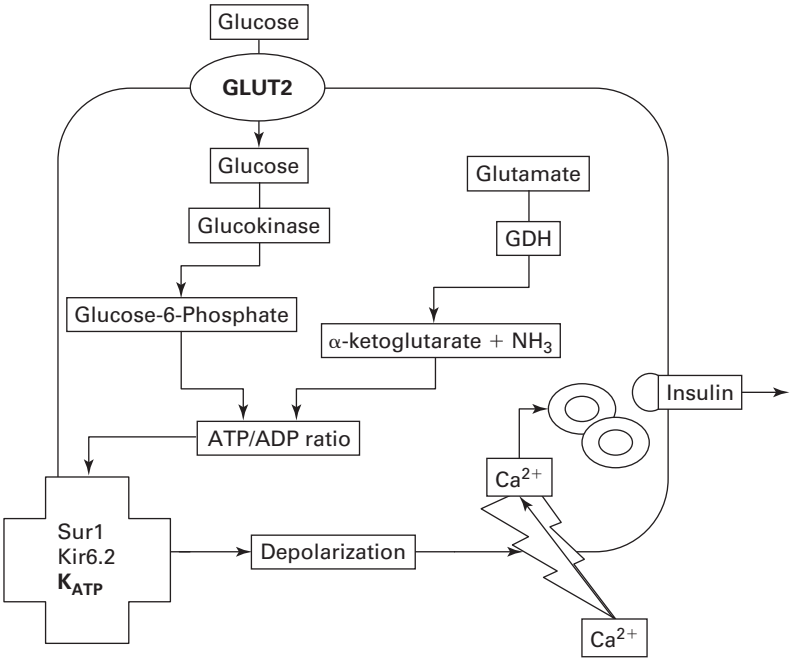

Figure 3.2 The β-cell.

Control of insulin secretion by the β-cell

At rest, the K_{ATP} channels on the β-cell are open. When blood glucose rises, it enters the cell through a membrane-bound glucose transporter (GLUT2). In the β-cell glucose is phosphorylated by glucokinase, which leads to an increase in ATP/ADP ratio. As ATP rises, the K_{ATP} channel closes causing depolarization of the cell, which in turn opens voltage-dependent calcium channels, resulting in an influx of calcium. High calcium in the cytosol stimulates exocytosis of insulin from secretory granules (Figure 3.2).

Hyperinsulinism

The majority of cases of PHHI are of autosomal recessive inheritance, involving genes located on chromosome 11p15.1, where the SUR (β-cell sulphonylurea receptor) gene, and Kir6.2 (β-cell K+ inward rectifier channel) gene are situated. Both genes encode components of ATP-sensitive potassium channels (K_{ATP}) on the β-cell, and mutations have a variable

effect on channel activity. Mutations inactivating the K_{ATP} channels leave the voltage-dependent calcium channels open continuously, resulting in continuous insulin release. Diazoxide opens normal K_{ATP} channels, and therefore is ineffective in these mutations. Octreotide (long-acting somatostatin analogue) reduces calcium influx, and has a direct effect on insulin secretory granules. Interestingly, activating Kir6.2 mutations are associated with neonatal diabetes.

Some cases of hyperinsulinism are associated with a mild asymptomatic hyperammonaemia. These are due to activating mutations of glutamate dehydrogenase. Episodes of hypoglycaemia are more severe after increased protein intake. (However, hypoglycaemia in response to protein is also common in other forms of diazoxide-resistant PHHI.)

Mutations involving glucokinase result in a reduced threshold for insulin secretion, i.e. the blood glucose has to fall to a lower level than normal before insulin secretion is switched off. Hypoglycaemia is usually milder. Inheritance is autosomal dominant.

In Beckwith–Wiedemann syndrome hyperinsulinism is transient and responds to diazoxide.

The majority of cases of congenital hyperinsulinism are due to diffuse disease, where all the β-cells are hyperactive and hypertrophic. However, 30–40% of cases are due to focal adenomatous hyperplasia of the β-cells (inherited through loss of maternally expressed or imprinted genes). Clinical presentation of diffuse and focal disease is identical (although there is a slight increase in prematurity in diffuse), but differentiation between the two types is important as focal lesions can be excised discretely, avoiding the long-term complications of subtotal (95%) pancreatectomy. Unfortunately there is no easy diagnostic test that can distinguish between the two forms. Routine imaging (USS, CT, MRI) is useless. Pancreatic venous sampling has been performed to map the site of the lesions using the concentrations of insulin in the head, body, and tail of the pancreas, but has largely been superceded by ^{18}Fluoro-dopa PET scanning and pancreatic biopsy. PET scanning can delineate a focus or foci, and is sometimes performed with simultaneous CT or MRI to enhance anatomical localization. PET scanning can also identify an ectopic pancreatic focus. There are currently about 10 centres worldwide performing PET scanning. Laparoscopic biopsy of the tail of the pancreas provides histological information, but can be difficult to interpret, particularly in diffuse disease. If focal disease is identified then the focus is removed surgically. With diffuse disease, practice

varies worldwide, but the general trend is towards conservative management, on the basis that diffuse disease may burn itself out over time (although this may take 5 years or longer). Children are maintained on SC octreotide (by continuous infusion pump or 8 hourly injections). Interestingly, even children who have not had a pancreatic resection occasionally go on to develop diabetes, suggesting either an excessive apoptotic process in the β-cells, and/or that the β-cells remain 'blind' to glucose.

USEFUL LINKS

Hypoglycaemia: Chapter 2.
Formulary: Appendix 5.

FURTHER READING

Arch Dis Child Fetal Neonatol Ed 2000; 82: F79–F97 provides a series of related articles.

Hussain K. Congenital hyperinsulinism. *Semin Fetal Neonatal Med* 2005 August; 10: 369–376.

Hardy O, Wanner L, O'Rourke S, et al. Focal lesions in congenital hyperinsulinism localized using [18F]-fluorodopa PET scan. *Horm Res* 2005; 64 (Suppl 1): P3-1262, p. 366.

Blankenstein O, Monhnike W, Fuechtner F, Mohnike K, Grueters A. Combined 18Fluoro-L-Dopa-PET/CT as a tool for localization diagnostic in patients with congenital hyperinsulinism. *Horm Res* 2005; 64 (Suppl 1): P3-1260, p. 365.

Hussain K, Smith V, Pierro A. The laparoscopic approach to the management of congenital hyperinsulinism of infancy. *Horm Res* 2005; 64 (Suppl 1): P3-1263, p. 366.

Walker R, Jack M, Greer R, Brown D, Bowling F, Cowley D, Bell J, Cotterill A. Role of histology in planning definitive surgery in patients with hyperinsulinism of infancy. *Horm Res* 2005; 64 (Suppl 1): P3-1264, pp. 366–367.

Hypoglycaemia in infant of a diabetic mother

Clinical presentation

- Hypoglycaemia in infants of diabetic mothers should be anticipated and all infants should have early and regular glucose measurements until these are stable.
- Hypoglycaemia may be asymptomatic or symptomatic.

Approach to the problem

- Expectant management in all infants of diabetic mothers.
- Early enteral feeds.
- Regular (1–2 hourly) blood sugar measurements for first 12 h.

Differential diagnosis

Other causes of hypoglycaemia (see Chapter 2).

Investigations

- Blood glucose level.
- Other investigations for hypoglycaemia are not usually required unless hypoglycaemia is persistent.
- Calcium and magnesium levels are required in symptomatic babies as symptoms overlap.

- Haematocrit should be assessed if the baby appears plethoric or blood sugar is difficult to control (dilutional exchange transfusion may be required if the baby is polycythaemic).

Management

Immediate

- *If able to tolerate enteral feeds*, increase the volume and frequency of the feeds.
- *If unable to tolerate feeds*, commence an intravenous (IV) infusion and titrate the quantity of glucose to maintain the blood glucose concentration >2.6 mmol/L. Use a higher concentration of glucose via a central line (silastic long-line or umbilical venous catheter) rather than excess volumes of 10% dextrose as the latter is likely to result in fluid overload and hyponatraemia.
- If IV access is difficult, intramuscular glucagon (100–200 μg/kg/dose) or buccal hypostop (40% glucose polymer, 1 mL/kg) may restore euglycaemia and buy time to achieve vascular access.
- Hypoglycaemia usually resolves within 24 h, but may last for several days.

Anticipate other complications associated with maternal diabetes:

- Increase in congenital abnormalities:
  - *Cardiovascular system*: cardiomyopathy with intraventricular hypertrophy, ventricular septal defect, and transposition of the great arteries.
  - *Central nervous malformations*: caudal regression, anencephaly, and spina bifida.
  - *Gastrointestinal*: small left colon syndrome, duodenal or anorectal atresia.
- Delivery complications secondary to macrosomia.
- Increased incidence in respiratory distress syndrome.
- Polycythaemia resulting in hyperviscosity.
- Hypocalcaemia and hypomagnesaemia.

Medium term

Once blood sugar levels are stable and the baby is able to tolerate enteral feeds, gradually reduce the IV glucose.

Long term

There is no need for longer follow-up unless the hypoglycaemia is severe and prolonged which might cause brain injury. In this situation, neurodevelopmental follow-up should be undertaken.

What to tell parents

Simple explanation of pathophysiology and likely time scale of hypoglycaemia are required. The importance of the baby remaining in hospital until the blood sugars are normal should be stressed.

USEFUL LINKS

Glucose physiology: Chapter 2.

SUPPORT GROUPS

Not applicable (N/A).

FURTHER READING

Hawdon JM, Aynsley-Green A. Disorders of blood glucose homeostasis in the neonate. In *Textbook of Neonatology*, third edition, Eds. Rennie JM, Roberton NRC, Churchill Livingstone. pp. 939–956.

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Ward Platt M, Deshpande S. Metabolic adaptation at birth. *Semin Fetal Neonatal Med* 2005; 10: 341–350.

Deshpande S, Ward Platt M. The investigation and management of neonatal hypoglycaemia. *Semin Fetal Neonatal Med* 2005; 10: 351–361.

Dysmorphic features

Clinical presentation

Dysmorphic features may point to an underlying endocrine abnormality.

Approach to the problem

Examination for

- Midline defects, e.g. central cleft palate and/or lip, hypotelorism or hypertelorism.
- Features of recognizable syndrome, e.g. Beckwith–Wiedemann syndrome (macroglossia, ear lobe creases, exomphalos), Smith–Lemli–Opitz (microcephaly, second- and third-toe syndactyly, see below), Robinow syndrome.

Other physical features to look for

- Symmetrical growth retardation.
- Micropenis (hypopituitarism, dysmorphic syndrome, see below).
- Large-for-gestational-age, exomphalos, ear lobe creases (Beckwith–Wiedemann syndrome).

Other symptoms/signs

- Hypoglycaemia (*hormone insufficiency*: e.g. cortisol, growth hormone (GH); *hormone excess*: i.e. insulin; metabolic abnormality).
- Hypothermia (hypopituitarism; sepsis, which can be secondary to an underlying metabolic problem).
- Prolonged jaundice (hypopituitarism).
- Tetany or seizures (hypocalcaemia).

History of

- Consanguinity suggestive of an autosomal recessive problem.
- Neonatal death suggestive of inherited disorder, e.g. metabolic disorder previously presenting as *Escherichia coli* septicaemia.

Facial appearance of parents (i.e. facial features may be normal for the family).

Differential diagnosis

- Underlying genetic defect
- Hypopituitarism with or without septo-optic dysplasia (SOD), optic nerve hypoplasia (ONH)
- Hypoadrenalism
- Hypocalcaemia (hypoparathyroidism, e.g. DiGeorge syndrome)
- Metabolic disorder

Identify those with implication for:

- urgent management (Beckwith–Wiedemann, SOD, inborn errors of metabolism);
- hormone balance in the newborn period (infants with Down's syndrome have an increased incidence of hypothyroidism).

Always consider hypopituitarism in the infant with undermasculinized genitalia, particularly when associated with hypoglycaemia and/or hypotension.

Investigations

Investigations (in the following order of priority):

- Blood glucose (with hypoglycaemia screen if low, see Chapter 2).
- Acid–base balance.
- Investigations should be performed for suspected hypopituitarism (see Chapter 7). These include:
  - blood electrolytes
  - osmolality
  - hormone measurements
  - urine output and concentration
  - imaging (head ultrasound scan (USS) for midline defects such as absent corpus callosum, absent septum pellucidum)
  - ophthalmological opinion as detailed in Chapters 7 and 16.
- Blood karyotype. (*Note*: infants with XXY karyotype can present with ambiguous genitalia.)
- Metabolic screen
  - plasma and urine amino acids
  - urine organic acids
  - plasma ammonia.
- Blood calcium and phosphate (and parathyroid hormone (PTH) if indicated, see Chapter 20).

- Blood cholesterol (low, with increased precursors in Smith–Lemli–Opitz syndrome).
- Genetics opinion.
- Dysmorphology database, e.g. OMIM (Online Mendelian Inheritance in Man).
- Blood for genetic analysis for specific syndromes (e.g. Beckwith–Wiedemann mutation), which may also require blood samples from both the parents.

Management

Immediate

- Resuscitation.
- Maintenance of normoglycaemia (see Chapter 2).
- Fluid balance (see Chapter 15).

Medium term

- Consider steroid therapy while awaiting a definitive diagnosis of hypopituitarism, once blood samples for cortisol, adrenocorticotrophin (ACTH), and GH have been obtained.

Long term

- Counselling/prognosis depends on diagnosis.
- Hypopituitarism (see Chapter 7), Beckwith–Wiedemann syndrome (see Chapter 3).

Note: It is essential to seek confirmation of a diagnosis of Beckwith–Wiedemann syndrome, even if hyperinsulinism is not a problem, because of the implications for Wilms' tumour screening in childhood.

Rare causes of facial dysmorphism, and/or genital anomalies or hormone abnormalities

22q11 deletion syndrome.

This includes DiGeorge syndrome, Shprintzen or velocardiofacial syndrome and conotruncal anomaly face syndrome. The acronym CATCH-22 encompasses the phenotypic spectrum: *C*ardiac anomaly, *A*bnormal facies,

*T*hymic aplasia, *C*left palate, *H*ypocalcaemia, deletion on chromosome *22q*. Characterised by hypocalcaemia due to parathyroid hypoplasia, susceptibility to infection secondary to thymic hypoplasia (T-cell deficit), and outflow tract defects of the heart (tetralogy of Fallot, interrupted aortic arch, truncus arteriosus, right aortic arch and aberrant right subclavian artery). Ears are low set and deficient in the vertical diameter with abnormal folding of the pinna. Telecanthus with short palpebral fissures, upward and downward slanting eyes have been described as well as short philtrum and relatively small mouth. There may be micrognathia. Short stature and mild to moderate learning difficulties are common. Hypothyroidism, cleft lip and deafness are rare. Hypocalcaemia typically resolves in early childhood, although parathyroid dysfunction may detectable on testing in later life. The condition is due to a disturbance of cervical neural crest migration into the derivatives of the pharyngeal arches and pouches. Most cases result from a deletion of chromosome 22q11.2. The heterogeneity of the condition and the association of at least 2 chromosomal locations suggests that several genes are involved in control of migration of neural crest cells.

Antley-Bixler syndrome

Features include craniosynostosis resulting in trapezoidocephaly, midface hypoplasia, proptosis, choanal stenosis or atresia, humeroradial synostosis, bowing of the femora and ulnas, long bone fractures, long slender fingers with camptodactyly, and cardiac and renal malformations. The Antley-Bixler syndrome can be caused by mutations in fibroblast growth factor receptor 2 gene (FGFR2). About 50% of reported cases have been associated with ambiguous genitalia and adrenal dysfunction, but it is now thought that these may represent a distinct disorder caused by mutations in the cytochrome P450 oxidoreductase (POR) gene. In POR deficiency females may be virilized, and males undervirilized, and cortisol synthesis is impaired.

Beckwith-Wiedemann syndrome

Features include earlobe creases, macroglossia, exomphalos, visceromegaly, hyperinsulinism. Infants are usually large for gestational age, with a large placenta and long umbilical cord. Polyhydramnios may also be present. Beckwith-Wiedemann syndrome is caused by a mutation in the chromosome

11p15.5 region, with imprinting. Prediction of hyperinsulinism and prevention of hypoglycaemia in the newborn can prevent neurological damage. Hyperinsulinism is transient, and responds to diazoxide. Renal USS screening is indicated in childhood for the detection of Wilms' tumour. Increased incidence of adrenal carcinoma, nephroblastoma, hepatoblastoma, and rhabdomyosarcoma.

Denys Drash syndrome

Features include genital ambiguity, congenital nephropathy and Wilms' tumour and is caused by mutations in the Wilms' tumor suppressor (WT1) gene. Diagnosis is made by finding proteinuria and renal impairment and determining the WT1 mutation.

Ectrodactyly, ectodermal dysplasia, and cleft lip/palate syndrome (EEC)

Features include ectrodactyly of hands and feet, ectodermal dysplasia with severe keratitis, and cleft lip/palate. In the absence of cleft lip/palate, EEC patients have a characteristic facial morphology with maxillary hypoplasia, short philtrum, and broad nasal tip. Choanal atresia has been reported. EEC can be associated with GH deficiency and/or genital anomalies secondary to developmental defects of the hypothalamus.

Fanconi anaemia

This is a disorder affecting all bone marrow elements and associated with cardiac, renal, and limb malformations (radial aplasia, hypoplastic or bifid thumb), as well as skin pigmentary changes (café-au-lait spots). All marrow elements are usually affected, resulting in anaemia, leucopenia, and thrombocytopenia, although haematological abnormalities may not be manifest in the neonatal period. 60% have congenital malformations. Genital anomalies are common in males, and there may be hypergonadotrophic hypogonadism.

Frasier syndrome

This syndrome is characterized by streak gonads, genital ambiguity, and renal failure and is caused by mutation in the WT1 gene, but appears to be a separate entity from Denys Drash syndrome.

Hypoparathyroidism–retardation–dysmorphism syndrome (HRD) (Sanjad-Sakati)

Features include congenital hypoparathyroidism associated with dysmorphism, growth retardation and developmental delay. Congenital hypoparathyroidism in association with growth and mental retardation and seizures has been reported from the Middle East in children of consanguineous parents. Facial features include deep-set eyes, depressed nasal bridge with beaked nose, long philtrum, thin upper lip, micrognathia, and large floppy earlobes. Medullary stenosis and other skeletal defects may be present. Reduced numbers of T-cell subsets have been reported. The hypocalcaemia is associated with hyperphosphataemia and low concentrations of immunoreactive parathyroid hormone. The syndrome is not associated with congenital heart disease.

IMAGe association

Features include *I*ntrauterine growth retardation, *M*etaphyseal dysplasia, *A*drenal hypoplasia congenita, and *Ge*nital anomalies. Patients present shortly after birth with growth retardation and severe adrenal insufficiency, mild dysmorphic features, bilateral cryptorchidism, micropenis, and hypogonadotrophic hypogonadism. Skeletal surveys show metaphyseal dysplasia with or without epiphyseal dysplasia. Patients have documented or suspected hypercalciuria and/or hypercalcaemia, which may result in nephrocalcinosis, or visceral calcification.

Kallman syndrome

Characteristic features are hypogonadotrophic hypogonadism and anosmia. It can be associated with small penis, cryptorchidism (and absent postnatal rise in LH and testosterone, with blunted response to gonadotrophin-releasing hormone (GnRH) and human chorionic gonadotrophin (hCG)). Anosmia may be elicited in family history. Choanal atresia and cleft lip or palate have also been reported. Kallmann syndrome may represent the least severe form of the holoprosencephaly-hypopituitarism complex.

Laurence-Moon-Biedl syndrome

Features include polydactyly, obesity, retinitis pigmentosa, renal anomalies, mental retardation with progressive ataxia and spastic diplegia. These patients have hypogonadism. Inheritance is autosomal recessive.

Meacham syndrome

Patients have sex reversal with cardiac, pulmonary and diaphragmatic defects. XY males have undervirilization of the external genitalia, retention of Müllerian structures and double vagina. Other features are diaphragmatic hernia with hypoplastic or dysplastic lungs, and complex congenital heart disease. It is now thought that this syndrome may be associated with WT1 mutations.

Müllerian derivatives, persistence of, with lymphangiectasia and postaxial polydactyly (Urioste syndrome)

Features include prenatal growth deficiency, hypertrophied alveolar ridges, redundant nuchal skin, and postaxial polydactyly. XY karyotype with cryptorchidism, some with small penis, and internal Müllerian duct remnants. Other features include renal anomalies, lymphangiectasia, protein losing enteropathy and an early death.

Pallister–Hall syndrome

This is a neonatally lethal malformation syndrome of hypothalamic hamartoblastoma causing hypopituitarism, postaxial polydactyly, and imperforate anus. Some have laryngeal cleft, bifid epiglottis, abnormal lung lobation, renal agenesis or dysplasia, short 4th metacarpals, nail dysplasia, multiple buccal frenulae, hypoadrenalism, microphallus, congenital heart defect, and intrauterine growth retardation. Dysmorphic facial features are described but phenotype appears to be variable.

Prader Willi syndrome

Babies present in the neonatal period with central hypotonia and feeding difficulties with failure to thrive. There may have been reduced fetal movements.

After infancy there is insatiable appetite and obesity. Other features include mental retardation, short stature and in males, small genitalia. 75% of patients have deletion 15q11-13 and 24% have maternal uniparental disomy of the proximal arm of chromosome 15.

Robinow syndrome

Features include costovertebral anomalies with mesomelia, brachydactyly, bifid thumbs with abnormal orientation. There are characteristic facial features including large mouth and tongue, frontal bossing, wide downslanting palpebral fissures, hypertelorism with depressed nasal bridge, small low-set ears, gingival hypertrophy. Patients may have cleft lip/palate (not midline). Genital anomalies include hypoplastic genitalia, hypospadias or cryptorchidism. Intelligence may be normal. Inheritance can be autosomal recessive or dominant. The autosomal recessive form of Robinow syndrome is caused by homozygous mutations in the ROR2 gene (ROR2 gene on chromosme 9q22 affecting cartilage and bone formation). Heterozygous mutations in the same gene cause autosomal dominant brachydactyly B. Adult males show partial primary hypogonadism, whereas gonadal function and fertility in females seems to be normal which may explain a lack of male-to-male transmission in the dominant form. The recessive Robinow syndrome tends to be more severe.

Short rib-polydactyly syndrome Type II

Also known as Majewski syndrome. There is polydactyly with neonatal chondrodystrophy type II. Malformations include median cleft lip, pre- and postaxial polysyndactyly, short ribs and limbs, genital abnormalities, and anomalies of epiglottis and viscera. Other reported features are hydrops, malformation of the larynx, pulmonary hypoplasia, glomerular and renal tubular cysts or polycystic kidneys, ambiguous genitalia. Death occurs perinatally.

Smith–Lemli–Opitz syndrome

This syndrome is also known as lethal acrodysgenetic syndrome. It is caused by mutations in the sterol delta-7-reductase gene, which maps to 11q12–q13. There is a clinical and biochemical spectrum of severity. Features include small for gestational age (SGA), microcephaly, epicanthic folds, ptosis, broad

nasal tip with anteverted nostrils, micrognathia, slanted or low-set ears. There may be postaxial polydactyly, 80% have syndactyly of 2nd and 3rd toes. There may be cataracts, cleft palate, congenital heart disease, pulmonary abnormalities, hypospadias or cryptorchidism or sex reversal (i.e. XY with female phenotype). Infants may be hypotonic, and have a distinctive shrill cry. Plasma cholesterol is low and 7-dehydrocholesterol elevated.

Williams syndrome

Features include elfin facies with hypercalcaemia, supravalvular aortic stenosis (SVAS), multiple peripheral pulmonary arterial stenoses. Other features include mild to moderate mental retardation with disproportionately strong language skills, and dental malformations. 95–98% of individuals have a deletion on band 7q11.23 encompassing the elastin gene. Most cases are sporadic, but some autosomal dominant.

Wilms' Tumour WT1 'WAGR' syndrome

This syndrome is characterised by susceptibility to Wilms' tumour, aniridia, genitourinary abnormalities, and mental retardation. Hemihypertrophy is also a feature. Gonadoblastoma occurs as part of the complex. A constitutional deletion on chromosome 11p13 affects several contiguous genes, resulting in a constellation of defects.

USEFUL LINKS

Management of hyperinsulinism: Chapter 3.
Hypopituitarism: Chapter 7.
Hypercalcaemia: Chapter 19.
Hypocalcaemia: Chapter 20.
Ambiguous genitalia: Chapter 8.
Cryptorchidism: Chapter 9.

SUPPORT GROUPS

Beckwith-Wiedemann Support Network: www. beckwith-wiedemann.org
Beckwith-Wiedemann Support Group: www.bws_support.org.uk

Contact a Family (UK): www.cafamily.org.uk
Laurence-Moon-Bardet-Biedl Society: www.lmbbs.org.uk
Max appeal: www.maxappeal.org.uk
National Organization for Rare Disorders (US): www.rarediseases.org
Prader-Willi Syndrome Association (UK): www.pwsa.co.uk
The 22q11 Group: www.vcfs.net
The Pituitary Foundation: www.pituitary.org.uk
Unique – The Rare Chromosome Disorder Support Group: www.rarechromo.org
Velo-Cardio-Facial Syndrome Education Foundation: www.vcfsef.org

Micropenis

Clinical presentation

Micropenis:
- Incidental finding on newborn examination.
- Finding on examination of an hypoglycaemic baby.

Definition

Penile size: measured from the pubic tubercle to tip of the stretched penis in a term baby is usually >3 cm. Micropenis is a measurement <2.2–2.5 cm (varies with ethnicity).

In the preterm baby the normal penile length (cm) is 2.27 + 0.16 GA, where GA is the gestational age in weeks.

Approach to the problem

History:
- Family history of ambiguous genitalia.
- Ethnic origin.

Examination:
- *Dysmorphism*.
- *Midline defects*: hypertelorism, cleft palate.
- *Ophthalmic examination*: Optic nerve hypoplasia/septo-optic dysplasia.
- Symptoms/signs hypothalamic–pituitary hormone deficiencies (see Chapter 7).

Differential diagnosis

- Normal variant.
- Anterior pituitary hormone deficiency.

- Ambiguous genitalia (see Chapter 8).
- Syndromes, such as CHARGE association, Prader–Willi syndrome.

Investigations

- Investigate as for hypopituitarism (see Chapter 7).
- It is essential to do pre-feed blood sugars until normal and stable.
- Temperature.
- Ultrasound of head for midline defects.
- Anterior pituitary hormone levels:
  - Adrenocorticotrophic hormone (ACTH) and cortisol.
  - Growth hormone (GH) (insulin-like growth factor (IGF-I), insulin-like growth factor binding protein-3 (IGFBP3)).
  - Luteinizing hormone (LH) and follicle stimulating hormone (FSH).
  - Thyroid-stimulating hormone (TSH) and free thyroxine (fT4).
- Magentic resonance imaging (MRI) of the head.
- Karyotype.
- Genetics opinion.
- Investigate as for ambiguous genitalia if appropriate (see Chapter 8).

Management

Immediate

- Correct hypoglycaemia.
- Contact paediatric endocrinologist.
- Consider steroid replacement therapy if ill while awaiting results.
- Consider GH therapy if hypoglycaemia is refractory.
- Baby should remain in hospital long enough to establish feeds and secure blood glucose measurements.

Medium term

- Referral to a paediatric surgeon and endocrinologist, if appropriate.
- Severe micropenis, may need to consider gender of rearing.
- Consider treatment with intramuscular testosterone (25 mg testosterone once per month for 3 months) or topical dihydrotestosterone gel (0.2–0.3 mg/kg once daily for 3–4 months) in an attempt to enlarge the penis.

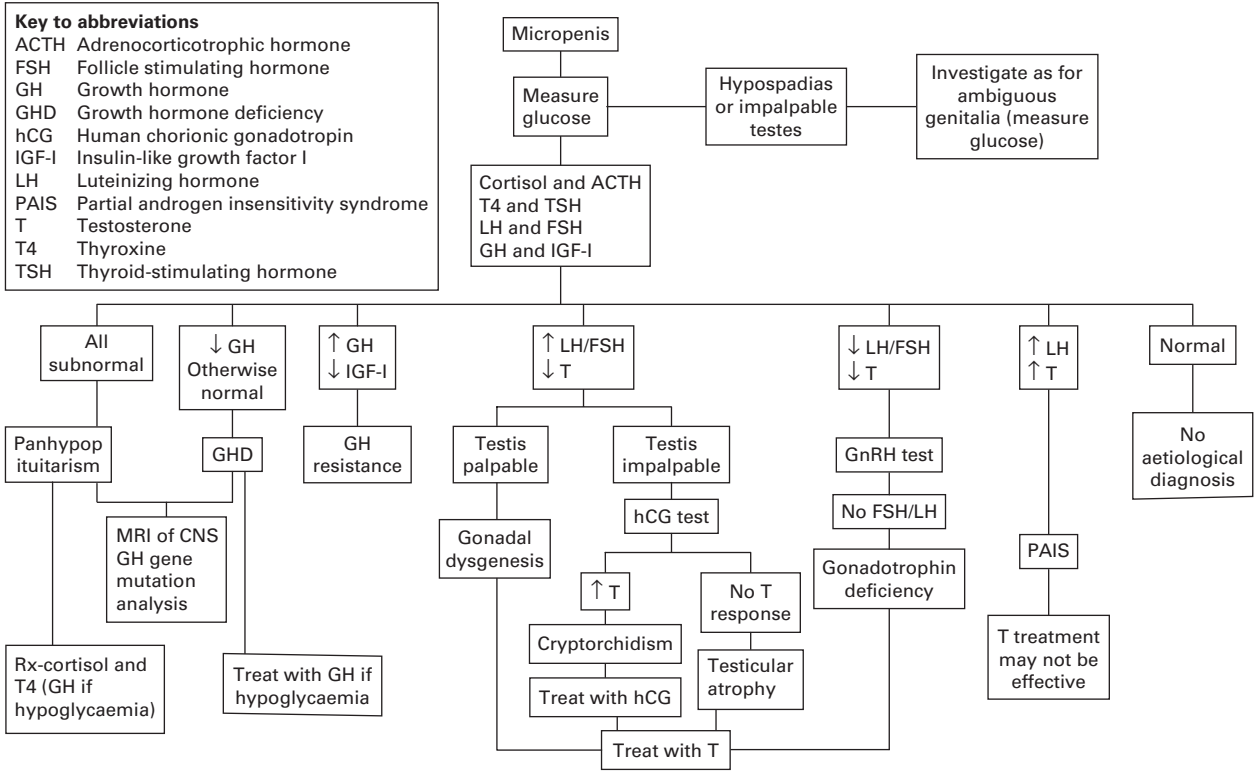

Figure 6.1 Flow chart: micropenis

Long term

Management depends on diagnosis and degree of micropenis.

What to tell parents

Initially explain concerns regarding penile size and possible associated hormone deficiency and hence need for further observation and investigation.

USEFUL LINKS

Ambiguous genitalia: Chapter 8.
Physiology of the gonads: Chapter 10.

SUPPORT GROUPS

Depending on diagnosis:
UK Intersex association: www.ukia.co.uk
Androgen insensitivity: www.medhelp.org/www/ais

FURTHER READING

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Ludwig G. Micropenis and apparent micropenis – a diagnostic and therapeutic challenge. *Andrologia* 1999; 31 (Suppl 1): 27–30 (review).

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Hypopituitarism

Clinical presentation

- Usually symptomatic hypoglycaemia which may result in convulsions.
- Asymptomatic hypoglycaemia and prolonged jaundice.
- Dysmorphic baby with midline anomalies.
- Micropenis.

Congenital hypopituitarism is uncommon and may not present in the neonatal period.

It results from a deficiency of any or all of the hormones secreted by the pituitary gland:

- **Anterior pituitary hormones**
  - Adrenocorticotrophic hormone (ACTH).
  - Thyroid-stimulating hormone (TSH).
  - Luteinizing hormone (LH) and follicle stimulating hormone (FSH).
  - Growth hormone (GH).
  - Prolactin.
- **Posterior pituitary hormone**
  - Antidiuretic hormone (ADH).

There may be an isolated hormone deficiency (GH deficiency is the most common) or combined pituitary hormone deficiencies.

Approach to the problem

History: Perinatal complications (breech delivery, Caesarean section, prolonged or precipitous delivery, intrapartum distress, and a low APGAR score) are common.

- Anterior hypopituitarism:
  - Symptoms and signs of hypoglycaemia (see Chapter 2).
  - Other symptoms and signs include micropenis (see Chapter 6), hypothermia, conjugated hyperbilirubinaemia.

  - Dysmorphic features such as midline defects and craniofacial anomalies (see Chapter 5).
  - Ophthalmic examination may reveal optic nerve hypoplasia/dysplasia.
  - Most have a birth length and weight below the mean (although usually within normal centiles).
  - Some have severe growth failure, even at birth.
  - Although some children may grow normally in early childhood, in others growth failure is more immediate.
- Posterior hypopituitarism:
  - May present with polyhydramnios.
  - After birth, there may be signs of dehydration: excessive weight loss, irritability, fever, hypernatraemia, convulsions, or coma.
  - Breast-fed babies may present later with failure to thrive, anorexia, vomiting, fever, constipation, or developmental delay.

Differential diagnosis

- Other causes of hypoglycaemia (see Chapter 2).

Causes of congenital hypopituitarism

- Hypothalamic:
  - Hypothalamic dysplasia.
  - Hypothalamic hormone deficiency(s): corticotrophin-releasing hormone (CRH), growth-hormone-releasing-hormone (GHRH), gonadotrophin-releasing hormone (GnRH), thyrotrophin-releasing hormone (TRH).
- Anterior pituitary:
  - Dysplasia.
  - Anterior pituitary hormone deficiency(s): GH, TSH, ACTH, FSH, LH.
- Posterior pituitary:
  - Familial (X-linked or autosomal dominant).
  - Idiopathic.
  - Secondary to: trauma/asphyxia, intraventricular haemorrhage, disseminated intravascular coagulation (DIC), inflammation (e.g. meningitis), and maternal drugs (e.g. lithium).
- Associated with other congenital anomalies:
  - Anencephaly/holoprosencephaly.
  - Agenesis of the corpus callosum.

- Persistent septum pellucidum.
- Familial pituitary hypoplasia.
- Septo-optic dysplasia.
- Central cleft lip and/or palate.
- Congenital rubella, congenital toxoplasmosis.
- Wolfram syndrome.

Investigations

- Blood sugar.
- Levels of GH, cortisol, ACTH, TSH, and free thyroxine (fT4) should be measured in *any* baby with severe or symptomatic hypoglycaemia, as part of a hypoglycaemia screen (Chapter 2).
- Other hormone measurements.
  - Insulin-like growth factor-1 (IGF-1).
  - Insulin-like growth factor binding protein-3 (IGFBP3).
  - LH and FSH.
- The biochemical diagnosis of hormone deficiencies needs to be interpreted with respect to normal neonatal values (see Normal ranges, Appendix 3).
- Tests of pituitary function (see Tests section, Appendix 2):
  - Measurement of cortisol, ACTH, and GH at the time of stress (e.g. difficult insertion of cannula) can be extremely helpful, and if found to be high, formal pituitary function testing may not be required.
  - Further tests should be performed under the guidance of an endocrinologist.
  - An insulin tolerance test is not appropriate because the clinical signs of severe hypoglycaemia are not always apparent in this age group.
  - A glucagon stimulation test will assess both GH and adrenal axes, but late hypoglycaemia may be profound, and should be anticipated. If it occurs, treatment with hydrocortisone as well as dextrose may be appropriate.
  - An ACTH stimulation test has the advantage of being safe, but is an indirect indicator of pituitary ACTH status. A CRH test measuring cortisol *and* ACTH response may be more appropriate.
  - TRH to stimulate TSH and prolactin may be used, but probably will not add much to baseline measurements of TSH, fT4.
  - Prolactin is not usually helpful as it is often high in the early neonatal period.

  - Other hypothalamic-releasing hormone tests (CRH to stimulate ACTH, GHRH to stimulate GH, and GnRH to stimulate LH and FSH) are rarely required, although the latter may be helpful for later management of puberty and fertility. An absent response suggests pituitary defect whereas a partial or delayed response suggests a hypothalamic defect, but these are not diagnostic.
  - The diagnosis of ADH deficiency is made by monitoring weight, reviewing fluid balance records, and measuring both urine and plasma osmolalities (i.e. polyuria with dilute urine (low osmolality) and a high plasma osmolality).
- Cranial ultrasound scan with or without MRI scan to pick up associated structural anomalies of the brain, hypothalamic–pituitary axis, and the optic nerves (the hypothalamus and pituitary gland will *not* be visible on ultrasound scan). In particular:
  - A small or absent anterior pituitary, attenuated or absent pituitary stalk, and an ectopic posterior pituitary are all seen in hypopituitarism.
  - Associated abnormalities include optic nerve hypoplasia, absent septum pellucidum, and Arnold–Chiari I malformation.
  - Trauma to the pituitary stalk results in hypoplasia of the anterior pituitary, and with regeneration of the distal axon of the hypothalamus, an ectopic, superior pituitary gland. Such children are more likely to have multiple pituitary hormone deficiencies rather than isolated GH deficiency.
- Genetic analysis:
  - *PIT1* and *PROP1* mutations should be considered in patients with multiple pituitary hormone deficiencies, a family history of hypopituitarism or consanguinity, or decreased responses to hypothalamic releasing hormones. The relevant gene analysis should then be undertaken. (*Note*: *PIT1* and *PROP1* mutations rarely present in the neonatal period.)
  - *HESX1* gene mutational analysis may be considered for those with septo-optic dysplasia.
  - Isolated GH deficiency may be caused by GH1 gene mutation.

Management

Immediate

Correct hypoglycaemia (see Chapter 2).

Replacement treatment with corticosteroid, thyroxine and vasopressin (DDAVP), if deficient, will be required (see Appendix 5):

- Hydrocortisone 8–10 mg/m^2/day divided into two or three doses under specialist advice. Pre-prepared solutions are unreliable, but a tablet can be crushed and dissolved in water (e.g. 10 mg hydrocortisone in 1 mL of water). Alternatively 2.5 mg 'Corlan' tablets can be halved to give 1.25 mg hydrocortisone.
- Thyroxine 10–15 μg/kg/day.
- In those with ADH deficiency excessive fluid loss is reversed with vasopressin or DDAVP, but care needs to be taken that fluid overload does not occur (see Chapters 15 and 17).
  - Vasopressin is given as a continuous intravenous (IV) infusion. The half-life is approximately 30 min with an initial duration of action of 2–3 h. Start at 1 mU/kg/h (=0.001 U/kg/h). The usual dose range is 0.5–2.0 mU/kg/h. The solution can be diluted in normal saline.
  - DDAVP may be given as an intranasal solution (0.25 μg 12 h, increased gradually until a satisfactory response is achieved; the usual maximum is 5–20 μg 12 h) or by IV or subcutaneous (SC) injection (0.02 μg 12 h increasing gradually until a satisfactory response is achieved). Both injection solution and intranasal solution may be diluted 1:10 with 0.9% sodium chloride immediately before use.
- With persistent hypoglycaemia and GH deficiency, GH replacement may be needed. GH 0.2 mg SC (this is the lowest practical dose with current delivery devices).

Medium term

- Babies with abnormalities of the optic nerves require ophthalmic referral.
- Parents need to be taught glucose monitoring before discharge home and management of hypoglycaemia (e.g. with buccal hypostop).
- Steroid card/bracelet should be issued.
- Parents will require support at home, with several home visits particularly in the first month by a paediatric endocrine nurse (or similar) under the guidance of the paediatric endocrinologist.
- Parents need clear instructions about what to do in case of illness. In the short term any illness should lead the parents to seek medical advice, particularly if the infant is vomiting, or refusing feeds. Thereafter parents should be advised to double hydrocortisone if the child is slightly unwell

(e.g. upper respiratory tract infection), and treble the dose if febrile. Parents must be given hydrocortisone intramuscular (IM) injection to take home at the time of discharge from the neonatal unit having been instructed in the practicalities of giving it.
- The baby should have open access for assessment or admission to paediatric wards.
- Micropenis may require testosterone injections (25 mg once a month for 3 months) or use of dihydrotestosterone gel (0.2–0.3 mg/kg topically once daily for 3–4 months), which is most likely to be effective in the first 6 months of life.

Long term

- Unlike anterior pituitary hormone deficiencies, which tend to be permanent (and hence require life-long hormone replacement), the posterior pituitary may recover (and hence DDAVP/vasopressin may not be required long term).
- As growth failure may be early and be severe in those with GH deficiency, GH therapy should be considered early. Administration is difficult as delivery devices are designed for larger children, but it is practical to give a dose of 0.2 mg/day.
- Genetic counselling may be required for inherited causes of hypopituitarism.

What to tell parents

An explanation for the presenting symptom(s) is required and need for further investigations. Further discussions depend on results of these investigations. Long-term hormone replacement therapy, management of intercurrent infections (see above) and importance of glucose monitoring needs to be discussed. Child minders need to be informed about the risk of adrenal insufficiency during an intercurrent illness. Babies with anomalies of the optic nerve may have reduced visual acuity or be blind. Implications of associated anomalies, particularly the brain will require discussion.

USEFUL LINKS

Hypoglycaemia: Chapter 2.
Micropenis: Chapter 6.

Normal ranges: Appendix 3.
Dynamic tests: Chapter 2.
Hyponatraemia: Chapter 15.
Hypernatraemia: Chapter 17.
Formulary: Appendix 5.

SUPPORT GROUPS

The pituitary Foundation: www.pituitary.org.uk
Serono booklet: Emergency Information Pack for Children with Cortisol and GH Deficiencies and those Experiencing Recurrent Hypoglycaemia: www.bsped.org.uk/patients/serono/05_EmergencyInformationPack.pdf

Ambiguous genitalia (male): XY disorders of sex development

8

Clinical presentation

Ambiguous genitalia noted at birth or on newborn examination, or suspected from antenatal ultrasound scans.

Approach to the problem

History:

- Is there a family history of ambiguous genitalia?
- Enquiry into maternal health (including presence of virilization) and drugs taken during pregnancy.
- History of previous stillbirths or neonatal death?

Examination:

- General examination
  - Look for other dysmorphic features or midline defects.
  - State of hydration.
  - Blood pressure.
- Genitalia
  - Are the gonads palpable? If *yes* they are likely to be testes or ovotestes. They may be normal or dysgenetic.
  - Assess the degree of virilization. This is graded by either Prader stage (Figure 8.1) or external masculinization score (Table 8.1).
  - Measure the length of the phallus (stretched length from pubic tubercle to tip of penis). Normal penile length at term is about 3 cm. Micropenis is a length <2–2.5 cm depending on ethnic origin.
  - Note presence of chordee.
  - Note the position of the urethral opening.
  - Is there a vaginal opening?

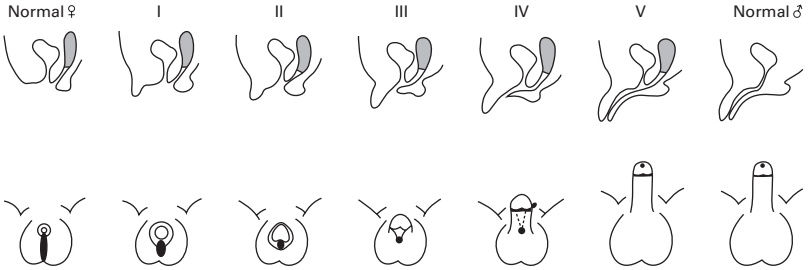

Figure 8.1 Differential virilization of the external genitalia using the staging system of Prader, from normal female (left) to normal male (right). Sagittal (upper panel) and perineal (lower panel) are views shown

Table 8.1 External masculinization score

3	Yes	No	Normal			
2			Glandular			
				Scotum	Scotum	1.5
1			Penile	Inguinal	Inguinal	1
				Abdominal	Abdominal	0.5
0	No	Yes	Perineal	Absent	Absent	0
	Scrotal fusion	Micro phallus	Urethral meatus	Right gonad	Left gonad	

- Note the appearance of labioscrotal folds and the presence of rugosity.
- Note the pigmentation of genital skin (occurs with excessive adrenocorticotrophic hormone (ACTH) and opiomelanocortin in congenital adrenal hyperplasia).
- Determine the baby's gestation (in preterm girls, the clitoris and labia minora are relatively prominent; and in boys, testes are usually undescended until 34 weeks).

Differential diagnosis

For virilized female see Chapter 10. Causes of an undervirilized male:

- Gonadal dysgenesis/malfunction
- Biosynthetic defect
- End-organ unresponsiveness
- Syndromes (Smith–Lemli–Opitz, Denys–Drash, etc.).

Investigations

- FISH or PCR for Y and X chromosomes (result takes 24–48 hours) – this does not give a definitive diagnosis.
- Blood karyotype (results in 3–5 days).
- Bone marrow aspirate performed by a skilled haematologist can give the result the same day, but there may not be sufficient cells for analysis and so should only be considered if the diagnosis is urgent and FISH/PCR is unavailable.
- Blood electrolytes.
- Blood sugar (hypoglycaemia may suggest cortisol deficiency secondary to hypothalamic–pituitary or adrenocortical insufficiency).

If a male/mosaic karyotype is confirmed, further investigations are directed at determining anatomy of internal genitalia and establishing whether testicular tissue is capable of producing androgens:

- Testosterone and human chorionic gonadotrophin (hCG) test (see Appendix 2).
- Luteinizing hormone (LH) and follicle stimulating hormone (FSH) (gonadotrophin-releasing hormone, GnRH test (see Appendix 2) adds little to basal levels).
- Synacthen test (see Appendix 2).
- Urine steroid profile.
- Urinalysis for proteinuria (to exclude associated renal anomaly, e.g. Denys–Drash/Frasier syndrome).

If female karyotype refer to Chapter 10.

Determining internal anatomy:

- Degree of virilization of internal anatomy is defined by Prader stages I–V (Figure 8.1). The presence of Müllerian structures (uterus with Fallopian tubes) will inform the diagnosis (see flow diagram, Figure 8.2).
- Ultrasound scan by a specialist radiologist to determine the anatomy of urogenital sinus/vagina/uterus/renal anomalies.
- Urogenital sinogram (X-ray with contrast in urogenital sinus).
- Examination under anaesthesia/cystography with or without laparoscopy with or without biopsies of gonads and skin (the latter may be deferred until reconstructive surgery in later childhood)
- MRI scan of the pelvis.

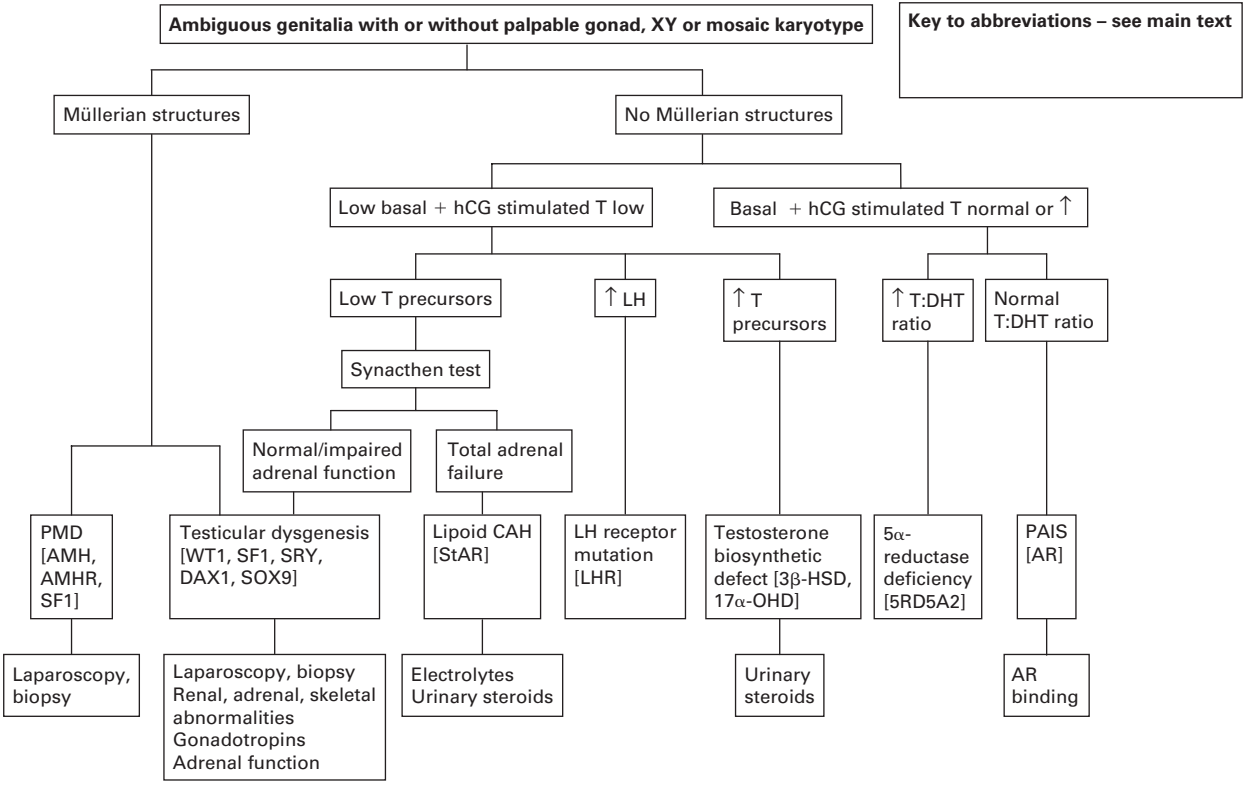

Figure 8.2 Ambiguous genitalia with or without palpable gonad, XY or mosaic karyotype

All the above investigations should be guided by a paediatric endocrinologist in conjunction with a paediatric surgeon but management also requires the involvement of:

- Geneticist
- Radiologist
- Psychologist
- Specialist laboratories.

Interpretation of results

The flow diagram (Figure 8.2) will assist in interpretation of the results.
The abbreviations used in the flow diagram are as follows:

hCG: human chorionic gonadotrophin
LH: luteinizing hormone
T: testosterone
CAH: congenital adrenal hyperplasia
PMD: persistent Müllerian duct syndrome
LHR: luteinizing hormone receptor
AMH: anti-Müllerian hormone
AMHR: anti-Müllerian hormone receptor
StAR: steroidogenic acute regulatory protein
DHT: dihydrotestosterone
SLO: Smith–Lemli–Opitz
3β-HSD: 3β-hydroxysteroid dehydrogenase deficiency
17α-OHD: 17α-hydroxylase deficiency
AR: androgen receptor

The genes in the flow diagram include:

- SF1
- DAX1
- WT1
- SRY
- SOX9
- 5RD5A2.

Gonadal dysgenesis/malfunction

Testicular dysgenesis:

- Karyotype 46XY or mosaic (e.g. 45X/46XY).
- Low basal and low hCG-stimulated testosterone.

- Elevated basal gonadotrophins.
- Possible presence of Müllerian structures (usually hypoplastic) due to inadequate secretion of AMH from dysgenetic testis.

Biosynthetic defect

Testosterone biosynthetic defect

Includes steroidogenic acute regulatory protein (StAR) defect, Smith–Lemli–Opitz syndrome, 3β-hydroxysteroid dehydrogenase deficiency (3β-HSD), 17α-hydroxylase deficiency (17α-OHD):

- Karyotype 46XY.
- Low basal and low hCG-stimulated testosterone.
- Increased testosterone precursors (androstenedione and DHEAS) on hCG test.
- In lipoid CAH (caused by an abnormality in the StAR protein), adrenal failure is confirmed on Synacthen test, electrolytes, and urinary steroids.

5α-reductase deficiency

- Karyotype 46XY.
- Normal or increased basal and peak testosterone on hCG test.
- Increased testosterone: DHT ratio.
- Diagnosis is confirmed by screening for mutations in the 5α-reductase type II gene (5RD5A2) in blood.

Leydig cell hypoplasia (inactivating mutation of LH receptor)

- Karyotype 46XY.
- Low basal and hCG-stimulated testosterone.
- Increased LH level.

End-organ unresponsiveness

Partial androgen insensitivity (caused by a mutation in the androgen receptor):

- Karyotype 46XY.
- Normal or increased basal and peak testosterone on hCG test.
- Normal testosterone:DHT ratio.
- Diagnosis is suggested by demonstrating an abnormality in androgen binding in genital skin fibroblasts or a mutation in the androgen receptor

gene. The genital skin fibroblasts are usually obtained at surgery in early childhood and the result may not be available for many months after this because of the complexity of the studies performed.

Complete androgen insensitivity does not present in the neonatal period as these children have a normal female phenotype.

Syndromes

Smith–Lemli–Opitz syndrome

In this syndrome there are multiple congenital anomalies and mental retardation.

- Physical features include microcephaly, micrognathia, broad nasal tip with anteverted nostrils, ptosis, epicanthal folds, strabismus, broad maxillary alveolar ridges, slanted or low-set ears, syndactyly of second and third toes, hypospadias or cryptorchidism in males and, occasionally, complete sex-reversal.
- Caused by point mutations affecting 7-dehydrocholesterol reductase (hence may be grouped as biosynthetic defect).
- Diagnosis made by finding hypocholesterolaemia and elevated 7-dehydrocholesterol levels.

Denys–Drash syndrome

Features include genital ambiguity, congenital nephropathy and Wilms' tumour:

- Caused by mutations in the Wilms' tumor suppressor (*WT1*) gene.
- Diagnosis is made by finding proteinuria and renal impairment and determining the *WT1* mutation.

Management

Immediate

- *Reassurance of parents*. It is paramount that clear explanations and investigations are commenced promptly, and that *no attempt is made to guess the sex of the baby*. Extreme sensitivity is required. Advise the parents not to name their baby, and be careful to whom they wish to tell, as they may wish to keep the issue confidential until gender has been assigned.
- Ensure registration of birth is not undertaken until sex of rearing determined (if necessary this can be postponed beyond the requisite 21 days

in Scotland and 42 days in England and Wales, by applying to the registry office)
- A cot card that is not pink or blue should be used.
- Laboratories have mechanisms to handle samples where gender cannot be assigned.
- Ideally the baby should be managed in a tertiary centre by a multidisciplinary team including a paediatric endocrinologist, a paediatric surgeon, clinical psychologist, geneticist, experienced radiologists and the facilities of specialist laboratories.

Determine sex of rearing depends on:
- Genital appearance.
- Biochemistry.
- Karyotype.
- Opinion of parents and all professionals involved.

Hospital management

- Investigate as above.
- Disorders of testosterone biosynthesis with concomitant corticosteroid or mineralosteroid deficiency may require appropriate steroid replacement therapy (see Chapter 10).
- Before assigning sex of rearing, it may be appropriate to assess the effect of intramuscular (IM) testosterone (25 mg IM monthly for 3 months) or topical dihydrotestosterone cream (0.2–0.3 mg/kg once daily for 3–4 months) on penile growth to help anticipate the response in puberty.
- Before discharge, appropriate follow-up with endocrinologist, paediatric surgeon, psychologist and geneticist should be arranged.

Home management

- Depends on cause.
- Adrenal steroid replacement may need to be continued.

What to tell parents

- Child is healthy (if appropriate).
- Simple explanation as to why the genitalia are ambiguous.
- Reassurance child will be male or female (not a bit of both).

- Further information depends on subsequent investigations.
- Discussion on fertility.
- The terms 'ambiguous genitalia' and 'intersex' are regarded as pejorative to many families and are being replaced by 'disorders of sex development'. Hence male undervirilization will be termed 'XY DSD' and true hermaphrodism 'ovotesticular DSD'.

USEFUL LINKS

Gonadal physiology: Chapter 10.
Figure on gonadal development: Chapter 10, Figure 10.2.
Synacthen test: Appendix 2.
hCG test: Appendix 2.
Normal ranges gonadotrophins and androgens: Appendix 3.
Cryptorchidism: Chapter 9.
Cryptorchidism flow chart: Chapter 9, Figure 9.1.
Micropenis: Chapter 6.
Micropenis flow chart: Chapter 6, Figure 6.1.
Formulary: Appendix 5.
Dysmorphic features: Chapter 5.

SUPPORT GROUPS

Most support groups depend on a diagnosis, which may not be available to the parents at this stage (or ever). An alternative would be to put the parents in contact with a family who have had a child with a similar anatomical problem.
UK Intersex association: www.ukia.co.uk
A www.medhelp.org/www/ais
CAH: www.cah.org.uk
Klinefelters: www.ksa-uk.co.uk
Hypogonadotrophic hypogonadism (Kallman syndrome): www.hypohh.net
Anorchidism support group: freespace.virgin.net/asg.uk
Hypospadias support group: www.hypospadias.co.uk
Scottish genital anomaly network: www.sgan.nhsscotland.com

FURTHER READING

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Warne GL, Hughes IA. The clinical management of ambiguous genitalia. In *Clinical Paediatric Endocrinology*, third edition, Ed. Brook CGD. Blackwell. pp. 53–68.

Cryptorchidism

Clinical presentation

- Cryptorchidism is incomplete testicular descent.
- The condition may be unilateral or bilateral.
- Testes may be palpable, impalpable or ectopic.
- The position of testis may be abdominal, inguinal, prescrotal, or gliding.

Approach to the problem

History

- As for ambiguous genitalia (see Chapter 8).
- Family history of undescended testes.

Examination:

- General physical examination. Look for signs of syndromes that may be associated with cryptorchidism:
  - *Prader–Willi syndrome*: A chromosomal microdeletion/disomy disorder arising from deletion or disruption of genes in the proximal arm of chromosome 15 or maternal disomy of the proximal arm of chromosome 15. Features include reduced fetal movements, hypotonia in infancy, obesity, mental retardation, short stature, hypogonadotrophic hypogonadism, strabismus, and small hands and feet.
  - *Kallmann syndrome*: Sporadic, autosomal dominant, autosomal recessive or X-linked recessive condition with isolated gonadotrophin deficiency, and anosmia or severe hyposmia. Some have mutations in the *KAL* gene and loss-of-function mutations of the gene encoding fibroblast growth factor receptor 1 (FGFR1) have been described.
  - *Laurence–Moon–Biedl syndrome*: Autosomal recessive condition, with hypogonadism, polydactyly, retinitis pigmentosa, renal anomalies, obesity, and mental retardation with progressive ataxia and spastic paraplegia.

- Determine gestation (testes are not normally descended until about 34 weeks gestation).
- Genitalia
  - Look for evidence of hypospadias or other features of ambiguity.
  - Hypospadias coexisting with undescended testis is commonly associated with intersex states especially mixed gonadal dysgenesis and true hermaphroditism and requires investigation as for ambiguous genitalia (see Chapter 8) including urgent referral to a paediatric endocrinologist.
- Testicular examination
  - Use a two-handed technique.
  - One hand should start at the hip and gently sweep along the inguinal canal. An undescended or ectopic inguinal testis will be felt to 'pop' under the examiner's fingers during this manoeuvre. A low ectopic or retractile testis will be felt by the opposite hand as it is 'milked' into the scrotum. An ectopic testis will spring out of the scrotum as soon as it is released. A retractile testis will remain momentarily in the scrotum until further stimulation causes a cremasteric reflex.
  - Note position, consistency and size of the undescended testis in relation to the opposite testis.
  - Non-testicular tissue, such as gubernaculum or dissociated epididymis and vas deferens may feel like an atrophic testis and may coexist with an intra-abdominal testis and hence requires paediatric surgical referral.
  - Differentiation of a retractile testis from a true undescended testis is sometimes difficult.
  - If in doubt refer to a paediatric surgeon.

Differential diagnosis

- Ambiguous genitalia (see Chapter 8).
- Syndromes including Prader–Willi, Kallmann's or Laurence–Moon–Biedl.

Investigations

Bilateral impalpable testes in an otherwise 'normal boy' may be a severely virilized girl hence urgent karyotype is required:

- If female karyotype is confirmed, proceed as in Chapter 10 on female ambiguous genitalia.

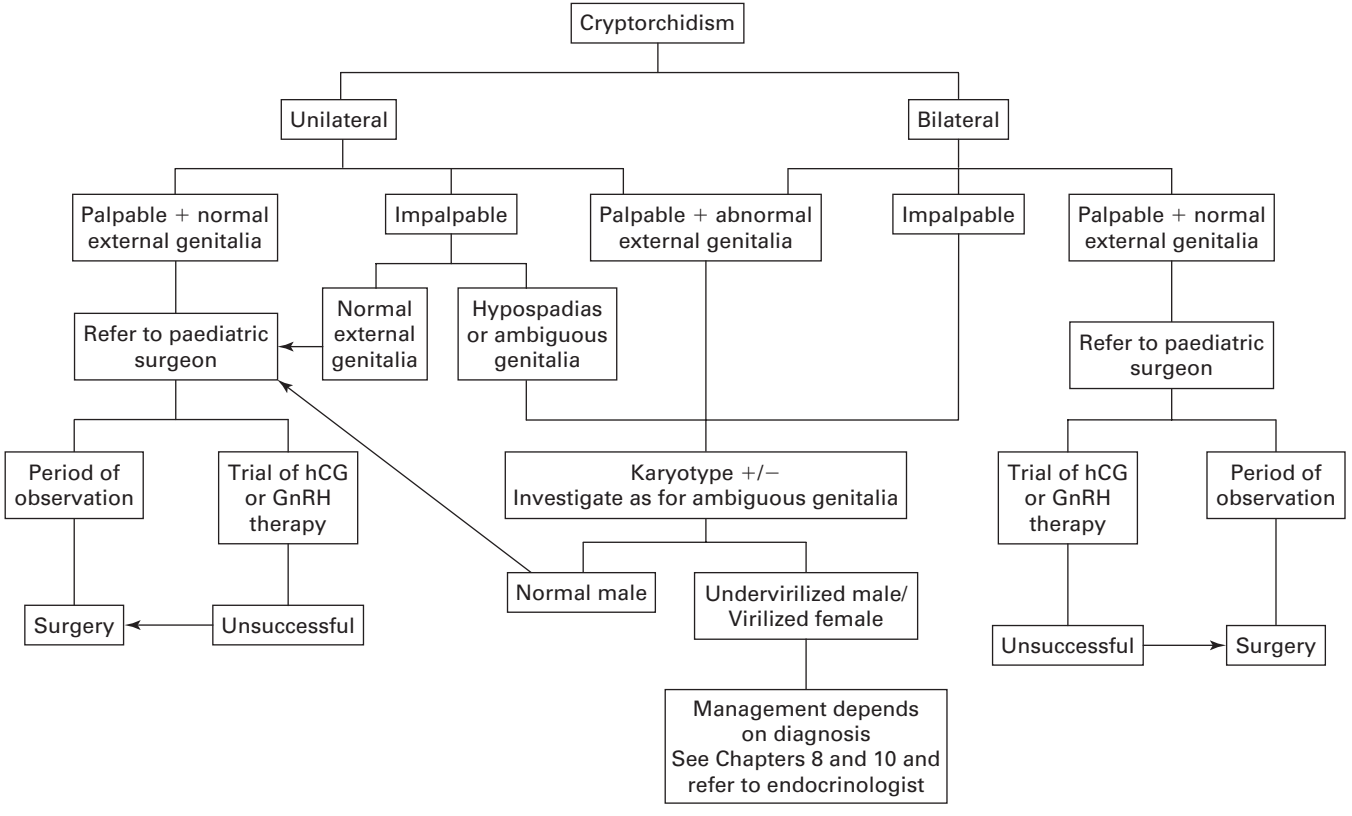

Figure 9.1 Flow chart: Cryptorchidism

- If male karyotype is confirmed proceed as in Chapter 8 on ambiguous genitalia with male karyotype.

If one or more testis is palpable and the genitalia also appear ambiguous, investigate as in chapter on ambiguous genitalia (see Chapter 8).

If one or both testes are palpable and the genitalia are normal male, refer to a paediatric surgeon:

- Exclude causes of ambiguous genitalia if necessary (see Chapter 8).
- The testosterone response to human chorionic gonadotrophin (hCG) will determine whether there are functioning Leydig cells present.
- Anti-Müllerian hormone (AMH) and inhibin B are secreted by the Sertoli cells. Inhibin B is detectable for the first 6 months. AMH levels are high in boys postnatally for several years. Although not routinely available in the UK, AMH may be a more sensitive marker for the presence of testicular tissue than testosterone and inhibin B predicts the testosterone response to hCG.
- Elevated gonadotrophin levels are consistent with primary gonadal failure.
- Radiological imaging is generally not reliable. Although ultrasound may help identify a testis located in the inguinal canal, it is of limited use for intra-abdominal testes. MRI and CT scan may be useful for identifying intra-abdominal testes but in babies there is high false-negative rate. Imaging may however be useful in identifying female internal genitalia.

Management

Immediate

If appropriate, exclude causes of genital ambiguity that require immediate steroid with or without other hormone replacement therapy.

Medium term

Refer to paediatric surgeon. Many testes will descend normally in the first few months of life (prevalence approximately 3% at birth at term and 1% at 1 year).

Treatment for cryptorchidism can be hormonal, surgical, or a combination of the two. Hormonal treatment has usually been IM hCG or intranasal gonadotrophin-releasing hormone (GnRH). There are a large number of

different protocols for both. This is not usually commenced in the neonatal period but hCG injections may be used in the first 6 months of life.

Orchidopexy is usually performed in the first year of life.

Long term

A paediatric endocrinologist and/or paediatric surgeon should be involved in the management.

Fertility is reduced in men who had cryptorchidism. Infertility may be increased six-fold in those with bilateral cryptorchidism and possibly up to two-fold in those with unilateral cryptorchidism compared with the general population.

Testicular cancer rates are increased in those with a past history of cryptorchidism with a relative risk of developing testicular cancer of 5–10 and may occur in the testis which was not maldescended.

What to tell parents

If uncomplicated (i.e. if not part of an intersex problem): Cryptorchidism is a common problem which can be corrected with surgery or hormone therapy. Cryptorchidism refers to a developmental condition in which one or both testicles fail to descend into the scrotum. Many will descend normally in the first few months of life. Testes begin to descend into the scrotum at about 34 weeks gestation and 95% of newborn males have fully descended testicles at birth. If the testes have not descended by 6 months of life, it is unlikely that they will do so. The condition occurs in about 1 out of every 50–200 male births. The cause is unknown but may relate to a hormone imbalance just before and after birth.

Surgery or hormone therapy is recommended to maximize the child's chances for fertility, improve his physical appearance, and decrease the chance of injury to the testes. Since there is a slight risk of later malignancy associated with undescended testes successful hormone therapy or surgical placement into the scrotum offers the opportunity for examination of the testis. Surgery should be done early in childhood because of the changes that occur in undescended testicles due to higher body temperature when not in the scrotum. Treatment may decrease the chance of malignancy and increase the chance for fertility.

Surgery is usually performed at about 1 year of age, although may be successful later in childhood.

The surgical operation for undescended testes is called an orchidopexy, and usually performed as a day-case procedure.

USEFUL LINKS

Ambiguous genitalia: Chapter 8.

SUPPORT GROUPS

Anorchidism support group: http://freespace.virgin.net/asg.uk/
Institute of child health fact sheet: www.gosh.nhs.uk/factsheets/families/F040036/index.html
Hypogonadotrophic hypogonadism (Kallmann syndrome): www.hypohh.net
Laurence–Moon–Bardet–Biedl Society: www.lmbbs.org.uk
Prader–Willi Association (UK) http://pwsa.co.uk
Prader–Willi Association (USA) http://www.pwsausa.org

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Swerdlow AJ, Higgins CD, Pike MC. Risk of testicular cancer in cohort of boys with cryptorchidism. *Br Med J* 1997; 314: 1507–1511.

Ambiguous genitalia (female): XX disorders of sex development

Virilization in females

- Congenital adrenal hyperplasia (CAH):
  - 21-hydroxylase deficiency (21-OHD) (rarely 11β-hydroxylase deficiency (11β-OHD) and 3β-hydroxysteroid dehydrogenase (3β-HSD) deficiency, P450 oxidoreductase deficiency).
- Fetal exposure to maternal androgens (maternal ovarian or adrenal tumour).
- Fetal exposure to maternal drugs: testosterone, aminoglutethamide, historically progestins for recurrent miscarriage.
- Placental aromatase deficiency. Very rare. Maternal oestrogen levels may be low antenatally.

Clinical presentation of CAH

- Ambiguous genitalia in females (21-OHD) or males (3β-HSD deficiency).
- Pigmentation of the genitalia (suggestive of excess adrenocorticotrophic hormone (ACTH) production).
- Salt-losing crisis.

Rarer causes of CAH

11β-OHD can cause marked virilization in females due to excess testosterone production. Deoxycorticosterone (DOC) is also produced in excess and acts as a mineralocorticoid to cause hypertension, however, this almost never occurs in the neonatal period. 11β-OHD may be misdiagnosed as 21-OHD because of elevated level of 17α-hydroxyprogesterone (17α-OHP),

hence the importance of performing a urine steroid profile, and measuring plasma 11-DOC.

3β-HSD deficiency presents with adrenal failure and severe salt loss due to aldosterone deficiency. It can present with undermasculinization in the male and virilization in the female. It is associated with a high mortality in infancy.

Mutations in the gene encoding the intracellular cholesterol transport protein steroidogenic acute-regulatory protein (StAR) can also cause CAH, as can P450 oxidoreductase deficiency which causes genital ambiguity in males, and mild virilization in females, and the biochemical features of both 21-OHD and 17α-OHD (see Chapter 12).

Over 90% of cases of CAH are due to 21-OHD, which can be identified most quickly by raised plasma 17α-OHP. Infants with this condition usually make sufficient cortisol for needs unless stressed, and this should allow time to collect diagnostic samples before starting steroid treatment.

Investigations

- Karyotype: Blood/FISH/PCR (see Chapter 8):
  - Electrolytes.
  - Blood sugar (hypoglycaemia may suggest cortisol deficiency secondary to hypothalamic–pituitary or adrenocortical insufficiency).
- Pelvic USS
  - Should show normal uterus and ovaries.
  - Requires an expert operator, and so results can be misleading (e.g. structures not seen).
- Plasma 17α-OHP (take sample **before** any steroid given)
  - Optimal timing is 48 h of life to allow clearance of placental production, subsidence of the postnatal surge in the infant, and for accumulation postnatally in affected infants.
  - This is a test which may need to be sent to a specialist laboratory (likely to take days/up to a week) (see Appendix 4).
- Urine steroid profile (collect sample **before** any steroid given)
  - 15–20 mL collection, universal container, optimal to start collecting on or after day 3 but start sooner if treatment becomes urgent (i.e. unwell and requiring hydrocortisone therapy).
  - Essential to confirm the exact site of the block/diagnosis.
  - The sample will be sent to specialist laboratory, and the turnaround time is likely to be at least a week (the physical processing of the sample

takes 2–3 days). It is also an expensive test, and so should be reserved for infants in whom there is a strong suspicion of CAH.

- Blood for genetic analysis (CYP21) from infant and both parents.

Other investigations

- Blood dehydroepiandrosterone sulphate (DHEAS), androstenedione, testosterone (specific assay for neonates, see Appendices 3 & 4), and DOC are useful in determining the site of the block in the steroid pathway (Figure 10.1).
- A Synacthen test (measuring 17α-OHP, and urinary steroids) may be useful when initial tests give equivocal results (Appendix 2).

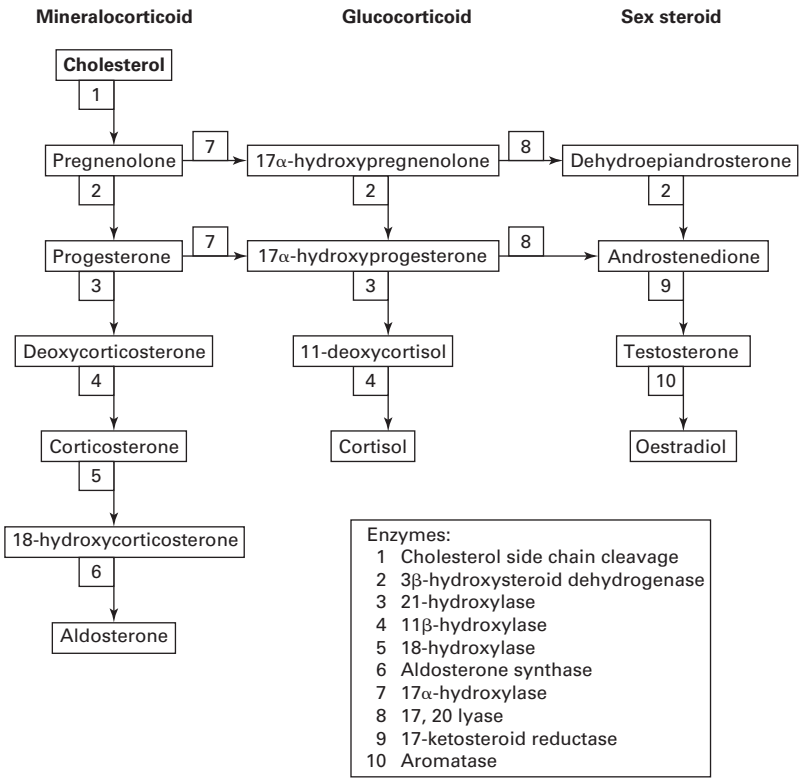

Figure 10.1 Adrenal steroid pathway

Management

Immediate

Refer to a paediatric endocrinologist.

Once samples have been sent for diagnosis, and preferably once some support for diagnosis obtained (e.g. ambiguous genitalia with female karyotype, or raised 17α-OHP in either sex):

- Start hydrocortisone 3.75–5 mg/day, ideally divided into 3 doses. Pre-prepared oral solutions are dangerously unreliable, but crushed tablets can be used (e.g. 10 mg tablet dissolved in 1 mL water), or 2.5 mg 'corlan' pellets can be halved to give 1.25 mg hydrocortisone (e.g. 2.5 mg am, 1.25 mg afternoon, 1.25 mg nocte). If the baby is unwell, a higher dose (X2-3) should be used initially. Treatment should be under the advice of a paediatric endocrinologist.
- Assess blood electrolytes daily from day 3 for early identification of salt loss (likely to occur from day 4 onwards). Measurement of urine electrolytes is not an alternative. Trends are mostly easily viewed on a flow chart of blood results.
- The first sign of aldosterone deficiency will be a rise in plasma potassium, and this is likely to precede the fall in sodium.

If potassium rises (or sodium falls):

- Take a blood sample for *aldosterone* and *plasma renin activity* (see Appendix 4).
- Start 9α-fludrocortisone 25 μg b.d., increase to 50 μg b.d. if sodium remains low (can be increased in resistant cases, see Appendix 5).
- In addition it is essential to give salt supplements (5 mmol/kg/day), which is relatively easy if the infant is bottle-fed, but can be difficult (and even more essential) in breast-fed infants. Fludrocortisone will not be effective without sufficient salt replacement.
- If the infant is diagnosed once significant salt loss has occurred, e.g. male presenting with salt-losing crisis, then the salt deficit must also be replaced (see Chapter 13).

Some units start fludrocortisone on the assumption that the infant will be salt losing (as 70–80% will be). It may then be possible to use genetic testing to ascertain whether the infant has a mutation that is associated with salt loss.

Long term

Genetic analysis for identification of mutations of the 21-hydroxylase gene is informative for the index case, and for future antenatal diagnosis.

What to tell parents

CAH is a manageable condition, but it does require daily medication for life, and close monitoring, particularly in infancy and the preschool years (when mortality is increased). The treatment dose must be correct to optimize growth (too little treatment causes rapid growth but early fusion of epiphyses, too much steroid treatment can suppress growth, cause osteopaenia and increase risk of infection).

Salt supplementation needs to be given in infancy (at least until well established on solids), and can be difficult to administer in infants who are breast-fed.

Surgery: timing of surgery may depend on the severity of the anatomical defect, in particular the urogenital sinus. Clitoral reduction may still be performed in infancy/early childhood, but in the UK most extensive reconstructive (vaginal) surgery is left until adolescence. A paediatric surgeon with experience of genital reconstruction should be involved at the outset.

Many families find the terms 'ambiguous genitalia' and 'intersex' disturbing (particularly if they persist in the notes) and these terms are now being replaced by 'disorders of sex development (DSD)' of which CAH is XX, DSD.

Home management

The infant will already be under the care of a paediatric endocrinologist.

Hydrocortisone treatment is taken t.d.s., with fludrocortisone in the morning and evening. Parents need clear instructions about what to do in case of illness. In the short term, any illness should lead the parents to seek medical advice, particularly if the infant is vomiting, or refusing feeds, and there should be open access to the hospital. Thereafter parents should be advised to double hydrocortisone if the child is slightly unwell (e.g. upper respiratory tract infection), and treble the dose if febrile. Parents must be given hydrocortisone intramuscular (IM) injection to take home at the time

of discharge from the neonatal unit having been instructed in the practicalities of giving it (see Appendix 5). The family may require support at home especially in the first month of life. A steroid card should be issued.

Background

The 21-OHD is of autosomal recessive inheritance. The synthesis of 21-hydroxylase is controlled by two genes, the active CYP21B gene and the CYP21A pseudogene located on chromosome 6p21.3. Although more than 50 mutations have been described, only 10 types of mutation are common. Genotype and phenotype are sufficiently close to make molecular genetic analysis informative for clinical management, e.g. predicting residual enzyme activity, likelihood of salt loss, and severity of virilization. The classical form of 21-OHD presents in early life, but a milder 'non-classical' form presents later in childhood or in adult life.

In many countries, there is neonatal screening for 21-OHD (blood spot measurement of 17α-OHP), but not currently in the UK.

Antenatal treatment of 21-OHD

Following the birth of an affected infant, it is usual to undertake genetic studies of that infant and both parents. This information allows for antenatal diagnosis in a future pregnancy. It is possible to suppress excessive androgen production in an affected fetus by the administration of dexamethasone to the mother, and this has been shown to reduce virilization of affected girls. To be effective, dexamethasone has to be started by 7 weeks of gestation, and preferably before. Dexamethasone is continued until the sex of the fetus is known (only females need treatment), and diagnosis confirmed by genetic testing (chorionic villous sampling). Affected female fetuses are treated until term. The controversial issues of this treatment are that 7 out of 8 fetuses will receive dexamethasone unnecessarily (1:4 inheritance, but boys do not require treatment), and the long-term effects of fetal exposure to dexamethasone in early pregnancy are not yet known. More recently, PCR for Y DNA chromosomal material (from fetal cells) in maternal blood at 5–6 weeks gestation has been used to ascertain fetal sex prior to treatment in some countries, thus reducing the number of fetuses exposed to dexamethasone unnecessarily. This approach may become

available more widely in the future, but requires precise pregnancy planning and may not be reliable if Y fragments persist from a previous pregnancy, and so should still be regarded as an experimental technique. Maternal side effects on dexamethasone (weight gain, striae, hypertension) are prominent and may lead to discontinuation of treatment. Due to these issues, in several countries including the UK, use of antenatal dexamethasone is used either as part of a clinical study (in the UK this is through the *British Society for Paediatric Endocrinology and Diabetes*), or as a closely monitored process in large specialized centres.

USEFUL LINKS

Ambiguous genitalia: Chapter 8.
Adrenal insufficiency: Chapter 12.
Collapse: Chapter 13.
Synacthen test: Appendix 2.
Biochemistry samples: Appendix 4.
Formulary: Appendix 5.

SUPPORT GROUPS

CGF Information Leaflets (Serono) Series No. 6: Congenital Adrenal Hyperplasia
www.bsped.org.uk/patients/serono/06_CongenitalAdrenalHyperplasia.pdf
Congenital Adrenal Hyperplasia Support Group Web site: www.cah.org.uk

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■ PHYSIOLOGY OF GONADS

Genetic sex is determined from the moment of conception and determines the differentiation of the gonad. The differentiation of the gonad in turn determines the development of both the internal genital tracts and the external genitalia (via the production of hormones in the developing testis)

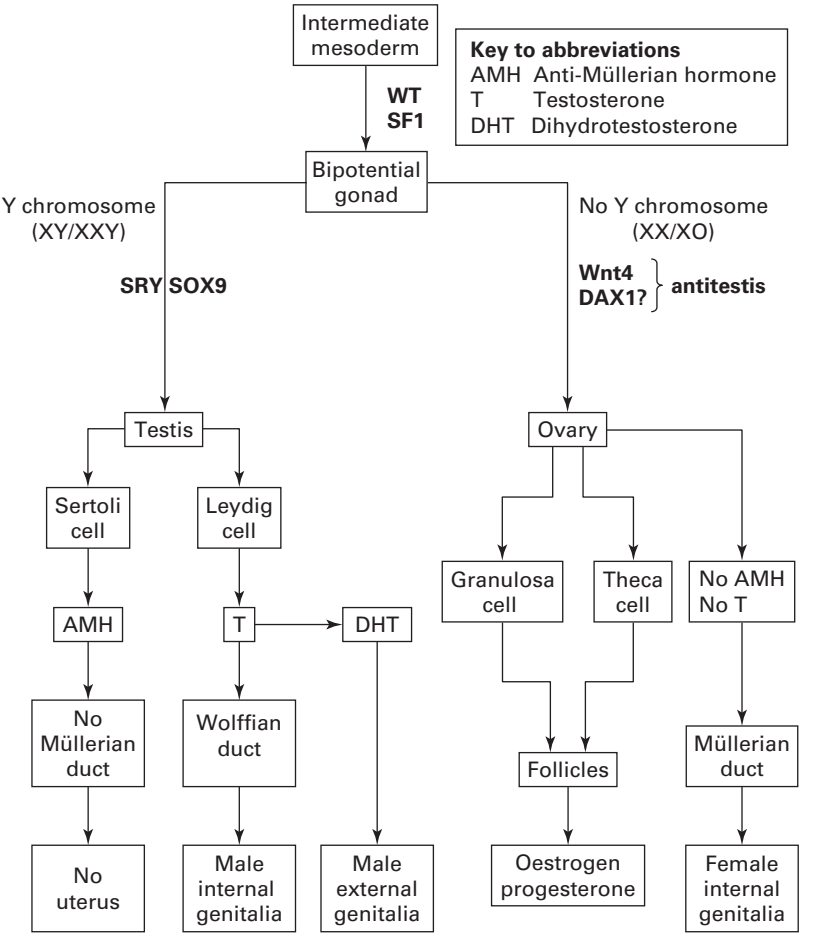

Figure 10.2 Development of the gonads, genital tracts and external genitalia

and thus *phenotypic sex*, which occurs later in development (from about 5 to 6 weeks of gestation). Both male and female genitalia differentiate from the same structures along the urogenital ridge. At about 4 weeks after fertilization, primordial germ cells migrate from the yolk sac wall to the urogenital ridge that develops from the mesonephros. The urogenital ridge also contains the cells that are the precursors for follicular or Sertoli cells and steroid-producing theca and Leydig cells. The *indifferent* gonads form on the genital ridges.

The development of the fetal adrenals and gonads occur in parallel, as before migration, the potential steroidogenic cells of both originate from

the mesonephros. There are many genes and transcription factors that are expressed in both tissues (e.g. SF1 and DAX1), and hence mutations in these genes may affect both adrenal and gonadal development. In addition, WT1 is expressed in the kidney and gonad, hence the association of Wilms' tumour and gonadal dysgenesis in Denys–Drash syndrome, for example.

The undifferentiated gonad is capable of developing into either an ovary or a testis. The theory that the *default* programme generates an ovary is probably not correct, although the exact role of *ovarian-determining* genes in humans is unclear at present. In contrast, testicular development is an active process, requiring expression of the primary-testis-determining gene SRY, and other testis-forming genes such as SOX9. Transcription factors such as SF1 and WT1 are also required for development of the undifferentiated gonad, as well as for the activation of the other male pathway genes required for testis development and the consequent development of male internal and external genitalia.

DAX1 and Wnt4 are two genes that may act to *antagonize* testis development. Overexpression of DAX1 (through duplication of Xp21) and Wnt4 (through duplication of 1p35), have been associated with impaired gonadal development and undervirilization in a small number of karyotypic 46 XY males.

Mutations or duplications in the various genes responsible for gonadal differentiation and the subsequent development of the internal and external genital phenotype genes may be responsible for gonadal dysgenesis and in some cases complete sex-reversal.

Wnt4 is also expressed in the Müllerian ducts and in the absence of anti-Müllerian hormone (AMH) and testosterone, Müllerian structures develop, while the Wolffian ducts involute. AMH promotes regression of Müllerian structures and as the only source of AMH in the fetus is the testes, the absence of a uterus in a baby with ambiguous genitalia is evidence that there has been functional testicular tissue (Sertoli cell) present. Testosterone produced from Leydig cells promotes differentiation of the Wolffian ducts and hence the internal male genitalia (vas deferens, epididymis, and seminal vesicles).

Testosterone is converted to dihydrotestosterone (DHT) by the enzyme 5α-reductase. DHT masculinizes the external genitalia from about 6 weeks gestation, and the degree of masculinization is determined by the amount of fetal androgen present (irrespective of source) and the ability of the tissues to respond to the androgens.

Defects in any part of this pathway (including gene mutations and chromosomal abnormalities (e.g. 46XY/46XX, 45,X/46XY), inappropriate hormone levels or end-organ unresponsiveness) may result in genital ambiguity, with undervirilization of an XY individual, virilization of an XX individual or the very rare true hermaphrodite (an individual with both ovarian tissue with primary follicles and testicular tissue with seminiferous tubules which may be in separate gonads or ovotestes). The term 'true hermaphrodite' is being replaced with 'ovotesticular disorder of sex development'.

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Pigmented scrotum

11

Clinical presentation

A pigmented scrotum is usually identified as an incidental finding on routine neonatal examination (Figure 11.1).

Approach to the problem

The usual reason for pigmentation of the scrotum is racial or familial. Note the family's racial origins, pigmentation being common in infants of Asian, African or Middle-Eastern origin. If none of these apply, are the family of dark colouring? (The Spanish Armada was responsible for adding to the British gene pool, particularly on the West Coast). Ask if scrotal pigmentation has been noted in a previous infant in the family.

Examination: Are the genitalia normal? Be sure the testes are palpable, i.e. the infant is male.

Differential diagnosis

- Normal variation.
- Congenital adrenal hyperplasia (CAH), (21-hydroxylase deficiency (21-OHD)).
- Other causes of excessive adrenocorticotrophic hormone (ACTH) stimulation, e.g. ACTH resistance (familial glucocorticoid deficiency, FGD) and adrenal hypoplasia congenita (AHC).

Investigations

If the pigmentation is clearly of racial origin, no investigations are required, unless there are other risk factors for CAH, e.g. parental consanguinity.

Investigations are not required on day 1, unless the testes are not palpable or the genitalia appear abnormal (in both cases refer to Ambiguous genitalia, Chapter 8).

On day 3 weigh the infant and take a blood sample for:

1 Electrolytes and urea (salt loss in CAH may be expected from day 4).
2 The 17α-hydroxyprogesterone (17α-OHP) to screen for 21-OHD (this is sent to a specialized laboratory and the result may take several days).
3 ACTH (usually collected on ice).

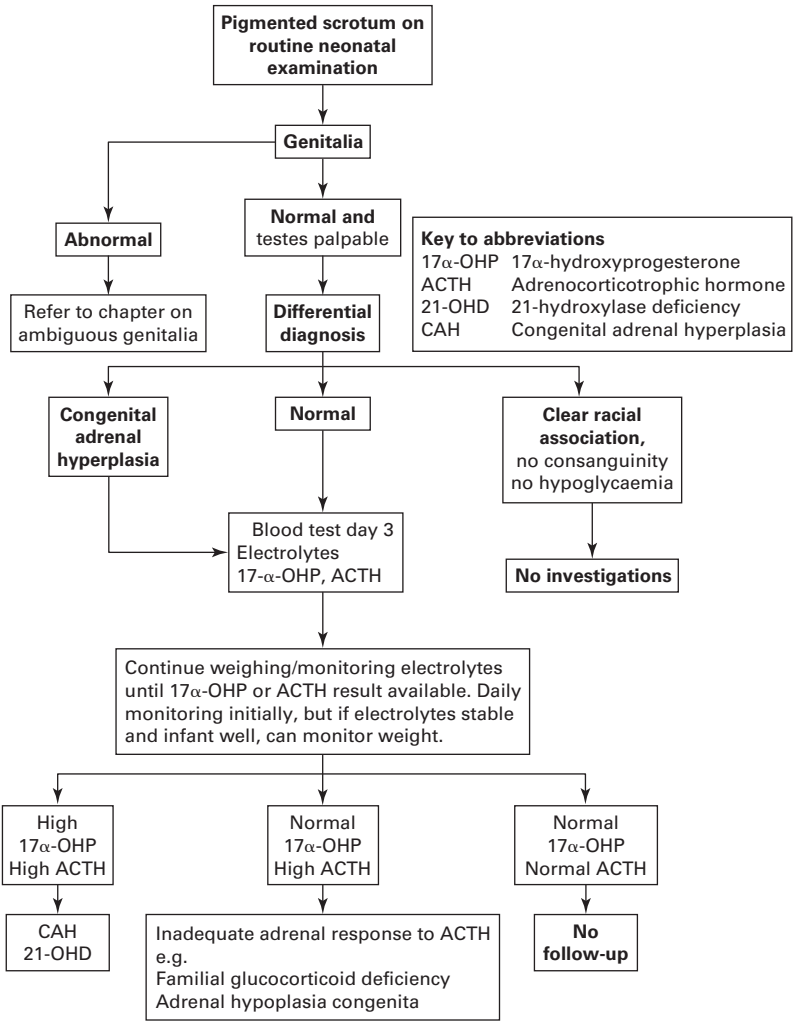

Figure 11.1 Flowchart for management of pigmented scrotum

The infant should be reviewed daily (with daily weighing, and blood electrolyte measurements initially) until the 17α-OHP result is available. If the process of waiting for the 17α-OHP result is going to take several days, and the blood electrolyte results are normal over 2–3 days of measurement (starting from day 3), in a healthy baby, then monitoring weight (i.e. gain) and well-being on daily/alternate day review may be sufficient. Hospitalization is not essential after the first 24 h if feeding is satisfactory, provided that the infant returns for daily review from day 3 as above. The infant should be readmitted promptly if there is hyponatraemia (or a trend in this direction), a rise in plasma potassium, or excessive or continued weight loss (refer to CAH, Chapters 10 and 13). If the ACTH result is known early, and is normal (i.e. not elevated), then CAH is unlikely and monitoring not essential while awaiting the 17α-OHP result.

If there is a strong suspicion of CAH, then a paediatric endocrinologist should be involved at an early stage, and certainly before the infant is discharged home.

If the pigmentation is not isolated to the scrotum, then measurement of ACTH is particularly important, and conditions causing adrenal failure should be suspected. Measurements of blood glucose and cortisol should be included (see Chapter 12).

What to tell parents

This pigmentation is probably normal, but can rarely be due to the lack of an enzyme in the adrenal gland, which while treatable can cause life-threatening salt loss in newborn infants if not treated promptly.

Follow-up can be discontinued once the ACTH and 17α-OHP results are known to be normal.

USEFUL LINKS

17α- hydroxyprogesterone levels: Appendix 3.
CAH diagnosis and management: Chapters 10 and 13.
Adrenal failure: Chapter 12.

Adrenal failure

Clinical presentation

- Hypoglycaemia (see Chapter 2).
- Collapse (see Chapter 13).
- Hypotension (see Chapter 14).
- Ambiguous genitalia (see Chapters 8 and 10).
- Skin pigmentation (commonly, but not exclusively, scrotal, see Chapter 11).
- Hyponatraemia (see Chapter 15).

Approach to the problem

- Assess perfusion.
- Measure blood pressure.
- Measure blood glucose.
- Measure blood sodium and potassium.
- Is there a history of asphyxia? (Bilateral adrenal haemorrhage.)
- History of maternal steroid excess (therapeutic administration or Cushing's syndrome).

Differential diagnosis

- Other causes of hypoglycaemia e.g. hyperinsulinism, or metabolic cause (see Chapters 2 and 3).
- Other causes of circulatory collapse, e.g. sepsis (see Chapter 13).
- Addisonian crisis (structural or functional absence of pituitary or adrenal glands).

Primary adrenal failure

- Congenital adrenal hyperplasia (CAH, including lipoid CAH caused by an abnormality in the steroidogenic acute regulatory (StAR) protein).

- Adrenal hypoplasia congenita (AHC).
- Adrenoleucodystrophy (ALD).

Secondary adrenal failure

- Adrenal suppression following steroid therapy.
- Adrenocorticotrophic hormone (ACTH) deficiency (see Chapter 7).
- ACTH resistance (familial glucocorticoid deficiency or FGD).
- Antenatal steroids administered to the mother.
- Maternal Cushing's disease/syndrome.
- Postnatal steroid therapy.

Investigations

Immediate

- Three random blood cortisol measurements (timing is not important) to look for low cortisol levels. (Plasma cortisol is difficult to interpret on a single sample because of the pulsatile nature of cortisol secretion, therefore taking 2–3 random samples makes it less likely that all will fall at a nadir. Cortisol may also be easier to interpret in the first week of life when cortisol levels are higher.)
- Plasma ACTH (to look for elevated ACTH).
- Synacthen test (see Appendix 2) to examine adrenal response. Response will be poor but not absent in chronic ACTH deficiency; absent response in FGD.
- Urine steroid profile for AHC or CAH.
- Adrenal ultrasound scan (USS) for haemorrhage or hypertrophy.

Medium term

- Blood measurement for very-long-chain fatty acids (ALD), if there is a poor response to Synacthen.
- Genetic analysis/referral (see anatomy and physiology of the neonatal adrenal gland).
- Brain MRI for abnormalities associated with adrenal abnormalities.

Management of Addisonian crisis

- Resuscitation as required.
- Treatment of hypoglycaemia (see Chapter 2).
- Refer to a paediatric endocrinologist.
- Steroid replacement (see Appendix 5).
- Salt replacement (see Chapter 13).

What to tell parents

A brief explanation of the effects of steroids (maintaining blood glucose, blood pressure, and response to stress), and therefore the problems of adrenal deficiency. Initially it may be difficult to ascertain whether there is a problem with the adrenal gland, but it is important to perform tests (blood cortisol, urine steroid profile, and Synacthen test) that will show how the gland is working. In the interim it may be necessary to give steroid therapy until the results are known.

Further information depends on the test results (i.e. diagnosis).

Home management

- Steroid replacement (see Appendix 5).
- Intramuscular hydrocortisone injection for emergencies (see Chapter 10 and Appendix 5).
- Blood glucose monitoring.
- Steroid card.

ANATOMY AND PHYSIOLOGY OF THE NEONATAL ADRENAL GLAND

The fetal adrenal gland

The human fetal adrenal gland consists of three zones: the inner fetal zone (FZ) which has the enzymes to produce dehydroepiandrosterone sulphate (DHEAS) from early gestation (lacking expression of 3β-hydroxysteroid dehydrogenase, HSD); the transitional zone (TZ) which contains

the enzymes for cortisol production (functionally identical to FZ in early gestation but expresses 3β-HSD after 25–30 weeks); and the outer definitive zone (DZ) which provides a reservoir of progenitor cells, and in late gestation acquires the capacity to produce mineralocorticoids.

DHEAS production by the fetus is important as it provides the placenta with the substrate for oestrogen synthesis. The fetal adrenal cortex produces DHEAS and cortisol from early gestation (6–12 weeks), but controversy exists as to whether cortisol is produced de novo or derived from the metabolism of progesterone. The fetus appears to be protected from high levels of cortisol in utero, as cortisol is converted to biologically inactive cortisone by the enzyme 11β-HSD2 in placental and fetal tissues. Eighty per cent of maternal cortisol is inactivated in its passage across the placenta. Synthetic glucocorticoids, such as dexamethasone, are a poor substrate for this enzyme and so reach the fetus to exert pharmacological effects.

The fetal adrenal gland is probably under the control of ACTH from the fetal pituitary, but the placenta also produces ACTH and corticotrophin-releasing hormone (CRH). In other species the adrenal gland is involved in the initiation of parturition with a surge in cortisol. A similar role has not been demonstrated in humans, but the subtle changes in metabolism and control of cortisol with increasing gestation make it likely that it plays a part.

The adrenal gland after birth

The fetal zone occupies 80% of the adrenal cortex at term. There is remodelling after birth, with a rapid diminution in the size of the FZ. Reduction in the size of the FZ is mirrored by a fall in DHEAS levels in infants born at term, but FZ androgen production persists in infants born prematurely, and may be linked to maturation rather than birth. The large number of circulating steroids in the newborn period can interfere with hormone assays, and this can make interpretation of results difficult.

Cortisol levels in term and preterm infants

After birth biologically active cortisol predominates over cortisone in the circulation, although not to the same extent as adults. Plasma cortisol in

well term infants rises after birth to ~200–300 nmol/L, then falls to around 100–120 nmol/L by day 7, and can fall to below 100 nmol/L in the second week of life. Cortisol levels in preterm infants are higher than well term infants (but similar to sick term babies). Cortisol rises after birth to ~300–400 nmol/L in preterm infants falling to ~280 nmol/L by day 7, and falling further thereafter. Cortisol is released in a pulsatile manner, with five secretory bursts/6 h, and the cortisol production rate is around 8 mg/m^2/day in term infants, and 21 ± 11 mg/m^2/day in preterm infants. Diurnal variation in cortisol develops at 8–12 weeks in term infants. Preterm infants >31-week gestation develop diurnal variation at a similar postnatal when in the home environment, but hospitalized infants below this gestation do not.

Although cortisol production rates in preterm infants are not low, some differences in HPA response to stimulation have been associated with differences in clinical course. This has raised the hypothesis that preterm infants may not produce sufficient cortisol for their requirements. Attempts to link random plasma levels of cortisol with clinical outcome/illness severity have been largely unsuccessful. However, a reduced cortisol response to ACTH in preterm infants in the first week of life has been associated with an increased incidence of chronic lung disease, and similar findings have been reported with CRH testing.

Steroid therapy in the perinatal period

Antenatal steroids prior to preterm delivery reduce mortality and the serious complications of prematurity, but steroid treatment after birth appears to have different effects. Randomized-controlled trials of early postnatal steroid administration have shown a reduction in lung disease, but at the expense of an increased risk of cerebral palsy. It is also possible that steroid therapy may have detrimental effects on alveolar development. Postnatal dexamethasone for the treatment of chronic lung disease was widely used in the 1990s following a study demonstrating a reduced duration of ventilation (but not hospital stay), and for historical reasons large doses of dexamethasone were given. This practice has largely been abandoned since the publication of data linking postnatal dexamethasone to cereberal palsy in preterm infants. Treatment with more physiological doses of hydrocortisone are currently being investigated in the context of clinical trials.

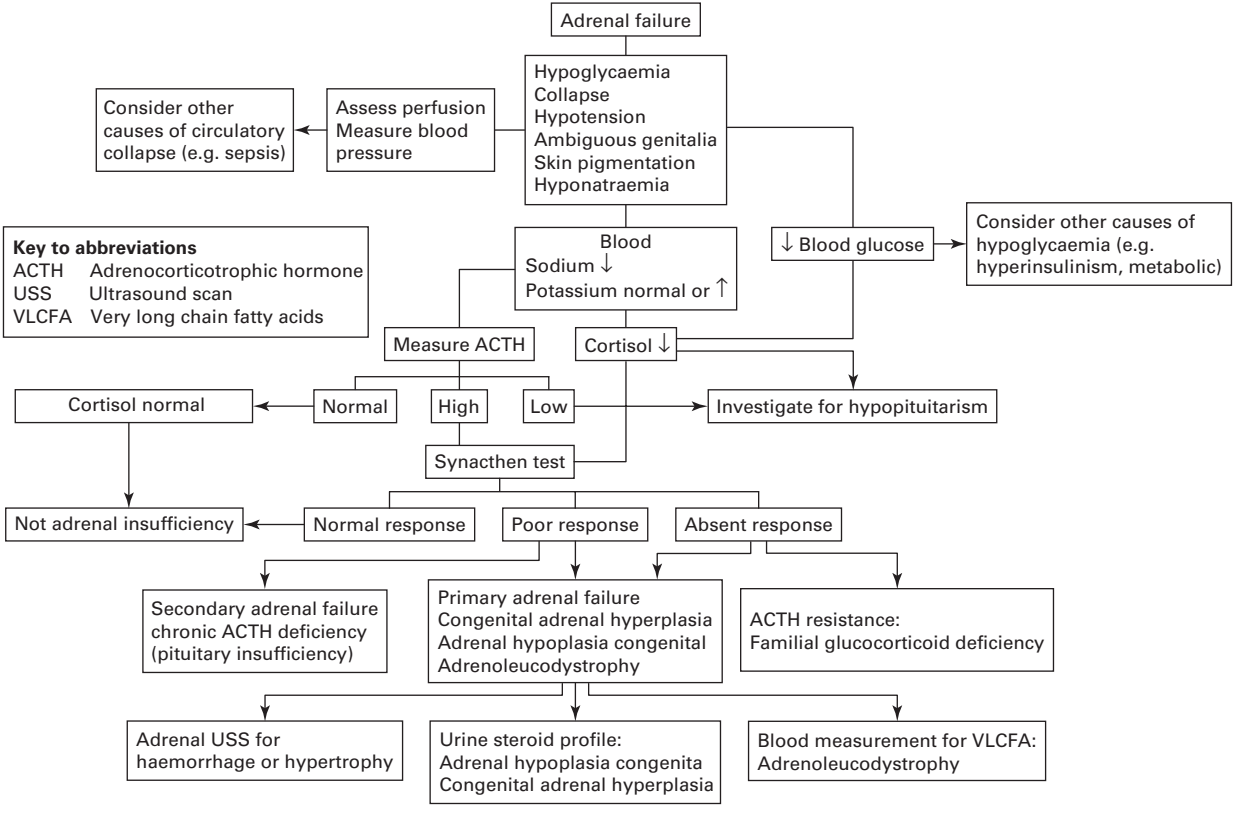

Figure 12.1 Flow chart: Adrenal failure

Adrenal suppression following postnatal steroids

Both systemic and inhaled steroids are associated with adrenal suppression in neonates, the severity and duration related to the duration of steroid treatment. Following a 7-day course of dexamethasone basal and ACTH-stimulated cortisol levels are suppressed at 24 h, but not at 48 h or 10 days. Following a 3-week course data vary, but 1–7 days post-treatment low baseline and reduced response to ACTH have been reported, which are no longer evident at 28 days. A low threshold for steroid cover (2–3 × replacement dose) should be used in infants becoming unwell shortly after stopping a steroid course of >10 days duration.

INHERITED CONDITIONS ASSOCIATED WITH CONGENITAL ADRENAL INSUFFICIENCY

Genes in adrenal development

The transcription factors DAX1 and SF1 have an important role in differentiation and development of the adrenogonadal primordium, which give rise to both the adrenal cortex and the gonads. SF1 is the major gene with an important role in regulation of steroidogenesis, reproduction, and male sexual differentiation. Nuclear localization of DAX1 is tightly coupled with that of SF1, and DAX1 is thought to be a transcriptional repressor of SF1 action. DAX1 is expressed in adrenal cortex, testis, ovary, anterior pituitary, and hypothalamus.

DAX1 mutations

These mutations cause AHC, an X-linked disorder causing adrenal insufficiency, hypogonadotrophic hypogonadism, and impaired spermatogenesis.

SF1 mutations

These mutations can be dominantly or recessively inherited and are associated with adrenal failure and XY sex-reversal with the presence of

Müllerian structures. The developing testes appear to be more SF1 dose dependent than the adrenals and so not all have adrenal failure.

StAR mutations

These mutations cause congenital lipoid adrenal hyperplasia (large adrenals full of cholesterol esters). Absence of aldosterone production causes salt loss, but presenting later than infants with 21-hydroxylase deficiency (21-OHD). Lack of testosterone production by Leydig cells leads to XY sex-reversal.

Adrenoleucodystrophy

X-ALD is an X-linked peroxisomal disorder causing progressive demyelination of the central nervous system, adrenal cortical insufficiency, and accumulation of saturated very-long-chain fatty acids (VLCFAs) in tissues and body fluids by impaired β-oxidation in peroxisomes.

Adrenal hypoplasia congenita

DAX1. Affected boys present with salt-losing primary adrenal failure, usually within the first month of life (peak incidence 2 weeks, but some present much later). When duplicated, the gene is also associated with XY sex-reversal.

Congenital adrenal hyperplasia

For more details, see Chapter 10.

P450 oxidoreductase deficiency

This is a recently identified form of CAH causing genital ambiguity in males, and mild virilization in females. Mild increase in 17-hydroxyprogesterone (17-OHP), also increased deoxycorticosterone (DOC), corticosterone, is suggestive of both 21-hydroxylase and 17α-hydroxylase deficiencies, which is explained by deficiency in P450 oxidoreductase, an electron transfer protein. The findings are similar to those described in Antley–Bixler syndrome

(skeletal dysplasia with genital anomalies, see Chapter 5). Interestingly, maternal fluconazole treatment during pregnancy can give similar features.

Familial glucocorticoid deficiency

This rare autosomal dominant disorder is caused by a lack of response to ACTH at receptor level, resulting in low plasma cortisol with high ACTH, and an absent cortisol response to ACTH stimulation. FGD usually presents with skin pigmentation and hypoglycemic convulsions in the first year of life. Aldosterone levels are normal.

USEFUL LINKS

Hypoglycaemia: Chapter 2.
Collapse: Chapter 13.
Hypotension: Chapter 14.
Ambiguous genitalia: Chapters 8 and 10.
Pigmented scrotum: Chapter 11.
Hyponatraemia: Chapter 15.
Dysmorphic features: Chapter 5.

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Collapse

Clinical presentation

Collapse.

Pointers to an endocrine cause

- Dysmorphic facies and micropenis or ambiguous genitalia (suggesting hypopituitarism, especially if associated with hypotension, see Chapter 7).
- Pigmented scrotum (see Chapter 11).
- Hypoglycaemia (see Chapter 2).
- Low plasma sodium and raised potassium suggesting an adrenal cause (see Chapters 12, 15, and 16).
- Hypernatraemia (suggesting diabetes insipidus, see Chapter 17).
- History of birth asphyxia.
- Parental consanguinity or history of neonatal death.

Approach to the problem

The differential diagnosis depends on the age (and gestation) of the infant.

Rapid assessment of circulatory status (heart rate, blood pressure (BP), pulses, and perfusion) and resuscitation as appropriate.

Differential diagnosis

- Acute problem with ventilation (including aspiration).
- Sepsis.
- Acute blood loss (placenta, arterial line, intraventricular haemorrhage, and gut).
- Necrotizing enterocolitis.

- Duct-dependent cardiac lesion, e.g. hypoplastic left heart (assess peripheral pulses).
- Metabolic (inborn error of metabolism).
- Addisonian crisis (structural or functional absence of pituitary or adrenal glands, e.g. pituitary infarction, toxoplasmosis, adrenal hypoplasia congenita, adrenocorticotrophic hormone (ACTH) resistance, and stressed infant with congenital adrenal hyperplasia).
- Salt losing crisis in congenital adrenal hyperplasia.

Examination should be performed for signs of respiratory, cardiovascular, or gut abnormality, and investigations undertaken to exclude non-endocrine causes.

Investigations for possible endocrine causes

- Blood gas for acid–base status.
- Blood glucose and hypoglycaemia screen if indicated (see Chapter 2).
- Blood electrolytes and creatinine.
- Blood cortisol and growth hormone (consider in a term infant if there is no clear alternative cause for the collapse).
- Blood 17α-hydroxyprogesterone and ACTH.
- Urine steroid profile.
- *Metabolic screen*: Plasma amino acids, urine amino and organic acids at the time that the infant is unwell. Plasma ammonia.

Management

- Initial resuscitation and treatment of the underlying cause.
- *For Addisonian crisis*: Intravenous (IV) bolus of 25 mg hydrocortisone (often with IV glucose and saline) given over a minimum of 3–10 min). Repeated 4–6 hourly in first 24 h. In severe cases avoid under-replacement with hydrocortisone (better too much than too little).
- *For salt losing crisis in congenital adrenal hyperplasia*: Is peripheral perfusion and BP adequate? If not, the infant will need resuscitation with normal saline (start with 10 mL/kg and repeat), followed by enough salt to replace the salt deficit and cope with ongoing losses. Under-replacement of salt is common and serious. The infant will also require fludrocortisone (oral), but this will only be effective once total body sodium is adequate (see Chapter 10 and Appendix 5).

Hypotension

Clinical presentation

- Hypotension:
  - Incidental finding on monitoring.
  - Collapse.

Definition

Blood pressure (BP) must be compared with norms for gestational age, but as a rule of thumb the mean BP should be greater than or equal to the gestational age of the baby (i.e. mean BP ⩾25 mmHg in a 25-week gestation infant).

Approach to the problem

Assessment

- The trend in BP over time, i.e. is the hypotension transient, improving, or worsening.
- The context, i.e. well or ill infant.
- The effect on the infant: adequacy of perfusion, urine output, and acidosis.

Differential diagnosis

- Spurious (BP electrode at the wrong height or not calibrated).
- Immaturity per se (BP rises over the first 24–48 h of life).
- Maternal drugs, e.g. β-blockers (consider use of glucagon if the hypotension is refractory, see Appendix 5). *Note*: Also watch for hypoglycaemia with β-blocker use.
- Volume depletion (raised lactate, acidosis, poor perfusion, and reduced urine output).

- Cardiac impairment:
  - secondary to overdistension of the lungs with high-frequency oscillatory ventilation (HFOV);
  - secondary to asphyxia particularly in term infants.
- Sepsis/shock/necrotizing enterocolitis.
- Circulatory collapse due to inadequate ventilation.
- Adrenal insufficiency:
  - secondary to immaturity;
  - adrenal hypoplasia congenita;
  - congenital adrenal hyperplasia and stressed, e.g. by illness or surgery;
  - bilateral adrenal haemorrhages;
  - secondary to adrenocorticotrophic hormone (ACTH) deficiency (congenital hypopituitarism (look for micropenis, hypo- or hypertelorism/other dysmorphic features) or pituitary infarction, see Chapters 5 and 7);
  - maternal high dose steroid therapy or Cushing's syndrome (see Chapter 18);
  - following postnatal high dose steroid therapy for chronic lung disease in the preterm infant (see Chapter 12).

Investigations

Investigations should be done in the following order of priority:

- Measure blood pH, base excess, and lactate.
- Measure urine output.
- Suspect sepsis, and consider investigations (and treatment) as indicated.
- Measure plasma sodium, potassium, and blood glucose (low sodium and high potassium in mineralocorticoid deficiency, low glucose in glucocorticoid deficiency).
- Take samples for plasma cortisol if the hypotension is persistent or considering steroids as part of treatment (take 2–3 samples, the timing is not important). If cortisol levels are subsequently found to be low, check thyroid function – and refer to Chapter 7 (Hypopituitarism) and Chapter 12 (Adrenal failure).

Management

Immediate

- Resuscitation/restoration of circulating volume as appropriate.
- Pressor support if indicated, e.g. infant compromised.

- Hydrocortisone if resistant to pressor support. Hydrocortisone 2 mg/kg IV followed by 1 mg/kg 8–12 hourly, withdraw over 2–4 days (see Appendix 5).
- Glucagon if secondary to maternal β-blockade. Glucagon 300 μg/kg IV. Repeat dosing or infusion is usually required (see Appendix 5).
- Assess fluid balance.

Medium term

Consider steroid therapy while awaiting diagnosis.

Long term

This depends on diagnosis.

What to tell parents

A simple explanation of the cause of hypotension in relation to their baby.

If an endocrine cause is suspected, or treatment with hydrocortisone is being considered, an explanation that steroids are necessary to maintain BP should be included.

USEFUL LINKS

Hypopituitarism: Chapter 7.
Congenital adrenal hyperplasia: Chapters 10 and 13.
Adrenal failure: Chapter 12.

CONTROL OF BP

BP is maintained constantly, to ensure adequate perfusion of the tissues. Systemic BP depends on cardiac output and peripheral vascular resistance. In response to hypotension, baroreceptors in the carotid sinus and aortic arch relay information to the vasomotor centre in the brain stem. This results in the sympathetic nervous system activating adrenaline and noradrenaline release from the adrenal medulla to increase cardiac contractility (β-receptors) and vasoconstriction (α-receptors) in a rapid response. Although the renin–angiotensin system (see Chapter 17) is primarily

responsible for long-term maintenance of BP, it is also activated rapidly in response to hypotension. BP rises in response to the potent vasoconstrictor effect of angiotensin II, and the reduction in renal fluid loss and retention of sodium by aldosterone.

Glucocorticoids are involved in maintaining vascular pressor response, and it has been suggested that hypotension in preterm infants may be a sign of adrenal insufficiency. Until recently there was a lack of evidence to support this, i.e. a lack of association between cortisol levels and BP. More recently, an association has been made between stimulated hypothalmic–pituitary–adrenal responses in preterm infants (human corticotrophin-releasing hormone (hCRH) test on days 7 and 14) and BP, with a poorer response to hCRH in infants with hypotension in first 2 weeks. On the day 7 hCRH test, basal and peak cortisol, and the change in cortisol, were associated with the lowest BP recorded in the first 2 weeks of life and the BP at the time of the test. ACTH levels, however, were not associated with BP, nor were cortisol levels on day 14.

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Hyponatraemia

Clinical presentation

- Incidental finding on blood test.
- Collapse (see Chapter 13).

Definition

Plasma sodium <130 mmol/L.

Approach to the problem

To distinguish between water overload (excessive intake or inadequate output) and sodium depletion (excessive salt loss).

Other features to look for:

- Pigmented scrotum (see Chapter 11) or ambiguous genitalia (see Chapters 8 and 10) suggesting congenital adrenal hyperplasia.
- Plasma potassium measurement.
- Palpable kidney, or mass (renal vein thrombosis, adrenal haemorrhage).
- Family history of renal problems.
- Blood pressure (liable to be raised in renal rather than adrenal disorders).

Differential diagnosis

May be informed by consideration of:

- Postnatal age (low glomerular filtration rate in the first few days of life).
- Gestational age (renal immaturity resulting in salt loss).

Water overload:

- *Iatrogenic*: This is the commonest cause, and may start before birth, i.e. secondary to excess maternal intravenous (IV) fluid administration.
- Renal failure.

- Syndrome of inappropriate antidiuretic hormone secretion (SIADH) (*intracranial pathology*: asphyxia, meningitis; *intrathoracic pathology*: pneumothorax).

Salt depletion:

- Immaturity (extreme preterm infant usually from the end of first week of life).
- Congenital adrenal hyperplasia (usually days 4–10).
- Congenital adrenal hypoplasia.
- Renal impairment, e.g. polyuric phase of acute tubular necrosis (ATN), congenital nephrotic syndrome, Bartter syndrome (hyperprostaglandin E syndrome, associated with life-threatening hypokalaemia). Congenital renal abnormality (there may be a history of polyhydramnios secondary to excessive urine output in utero).
- Gut loss (secretory diarrhoea, stoma output following gut resection, congenital chloride diarrhoea).
- Iatrogenic (repeated cerebral spinal fluid (CSF) removal by ventricular taps).
- Aldosterone biosynthetic defect.
- Aldosterone resistance (salt loss, hyperkalaemia, and hypotension) is also known as pseudohypoaldosteronism. The autosomal dominant (AD) renal form of Type I is caused by mutations in the mineralocorticoid receptor, it tends to be milder and although neonatal salt loss may be severe, salt supplements may not be required after infancy. The autosomal recessive (AR) form of Type I is caused by mutations involving the epithelial sodium channel, and is severe with symptoms persisting into adulthood. Treatment is with salt supplements (as unresponsive to mineralocorticoid treatment). Sweat, salivary glands, and colonic mucosa may also be affected.

Investigations

Immediate

- Assessment of previous fluid intake.
- Current weight in relation to birth or previous weight(s):
  - Lack of normal postnatal weight loss or weight gain suggests fluid retention.
  - Weight loss suggests sodium (and water) loss.

- How old is the baby, and what is the plasma potassium?
  - If the plasma potassium is raised, then the infant either has aldosterone deficiency (or resistance) or renal impairment. The latter is not necessarily associated with a rise in urea or creatinine at the outset, e.g. perinatal renal vascular problem, and early stages in renal dysplasia.
- Start to document urine output.
- Make serial measurements of blood sodium.
- Blood osmolality (can be estimated by 2[Na + K] + [urea] + [glucose]).
- Blood potassium, urea, and creatinine.
- Urinary sodium, potassium, osmolality, and creatinine (paired with plasma osmolality and creatinine). Infants with CAH have an inappropriately high urinary sodium.

Further tests (if not iatrogenic)

- Plasma 17α-hydroxyprogesterone (performed in specialist centres) usually takes several days.
- Urine steroid profile (expensive, specialist laboratory) may take more than a week.
- Karyotype, if any ambiguity of genitalia. Result takes 3–5 days, but fluorescence in situ hybridization/polymerase-containing reaction (FISH/PCR may be available within 24–48 h, see Chapter 8).
- Plasma renin activity if CAH suspected (also save sample for aldosterone). Special collection methods may be required, see Appendix 4.
- Renal and adrenal ultrasound scan (USS): for abnormal kidney (e.g. dysplastic and polycystic), damaged kidney (ATN, renal vein thrombosis), adrenal hyperplasia, or haemorrhage.
- Head USS if intracranial pathology suspected.
- Blood gas for acid/base balance.
- Urinalysis for blood and protein.

Management

Immediate

Aim to normalize the blood sodium by identifying the underlying cause.

- If the infant has been on an IV infusion, and is in the first week of life, the most likely diagnosis is iatrogenic fluid overload, which will be managed

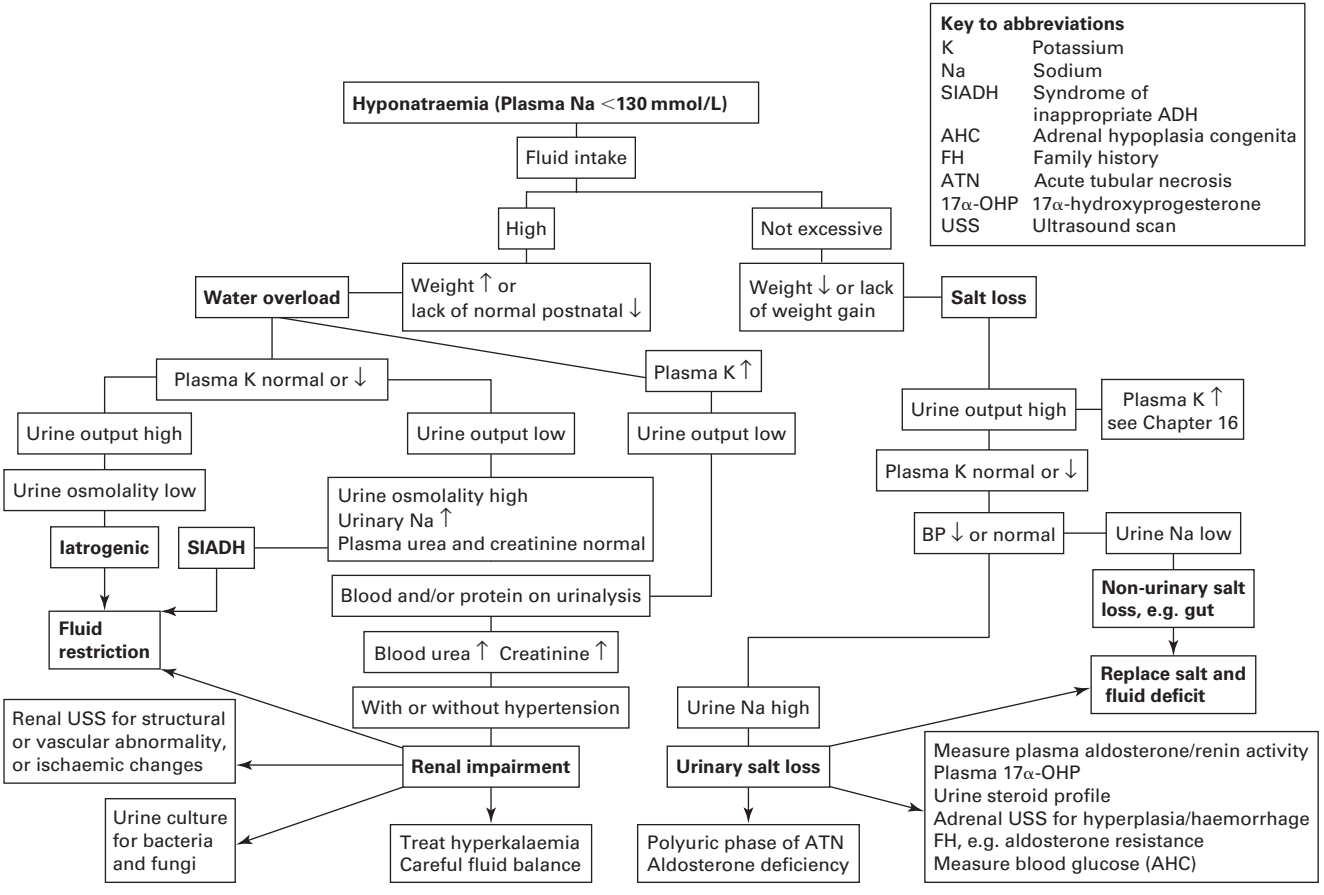

Figure 15.1 Flow chart: hyponatraemia

by fluid restriction (watch out for hypoglycaemia, which may necessitate an increase in the concentration of IV dextrose infused).
- Urgent measurement of urine sodium will show whether the infant is losing sodium excessively, or attempting to conserve sodium.
- Is the urine concentration (specific gravity/osmolality) appropriate for the blood sodium, i.e. is the infant trying to get rid of excess water?
- If salt loss is secondary to CAH, see Chapter 13.
- If in doubt collect the samples, fluid restrict the infant and add a little salt.

Long term

- Congenital adrenal hyperplasia, see Chapter 10.
- *Renal*: Management will be by a renal specialist. The prognosis depends on the underlying renal abnormality and the severity of renal impairment. Continuous ambulatory peritoneal dialysis (CAPD) may be used in renal failure where intra-abdominal space permits (but may be difficult if space compromised by large polycystic kidneys). Renal transplant is usually delayed until the age of 4 years, when it is more likely to be successful.
- *Pseudohypoaldosteronism*: The infant should be under the care of a paediatric endocrinologist. The baby will require salt supplementation and monitoring of plasma sodium. The infant may grow out of the need for salt supplements in the AD form.

Home management

- Aldosterone deficiency is treated by mineralocorticoid (fludrocortisone 25 μg b.d. increased gradually as required to a maximum of 100 μg b.d.) and salt supplementation (5 mmol/kg/day).
- Aldosterone resistance is treated by salt supplementation, the amount titrated against blood sodium level. Close monitoring of blood sodium is required, particularly in early infancy. Genetic counselling is appropriate.

What to tell parents

A simple explanation of the likely causes: water overload, salt loss, occasionally rarer causes such as hormone deficiency (or transient hormone excess).

USEFUL LINKS

Congenital adrenal hyperplasia: Chapter 10.
Collapse: Chapter 13.
Adrenal failure: Chapter 12.
Hyperkalaemia: Chapter 16.
Hormonal control of salt and water balance: Chapter 16.
Formulary: Appendix 5.

Hyperkalaemia

Clinical presentation

Incidental finding on blood biochemistry.

May be anticipated in the presence of oliguria associated with renal impairment.

Signs of cardiotoxicity:

- widened QRS complexes or tall, tented T-waves on ECG;
- dysrhythmias, such as ventricular tachycardia or fibrillation.

Definition

Blood potassium level >6.5 mmol/L.

Approach to the problem

- Is the biochemistry result true? How was the sample collected, and could it have been haemolysed? Repeat the sample as a matter of urgency.
- How many hours/days old is the infant? (Mild hyperkalaemia is not uncommon in extremely low birth weight (ELBW) infants in the first few days of life).
- Review history for antecedents of renal impairment (asphyxia and birth trauma).
- Is there a family history of renal problems? (e.g. polycystic kidneys).
- Look for contractures (suggestive of reduced fetal urine output causing oligohydramnios).
- Look for genital pigmentation (see Chapter 11) or ambiguity (see Chapters 8 and 10) suggestive of congenital adrenal hyperplasia.

Differential diagnosis

- Spurious (haemolysed blood sample).
- Renal impairment (including structural defects, e.g. urethral valves, dysplastic kidneys, and renal vascular accidents).
- Tissue damage (especially in immature infants with extensive bruising).
- Immaturity of renal potassium excreting capacity in ELBW infants.
- Acidosis (causing shift of potassium out of cells into extracellular fluid).
- Excessive potassium administration in medication (e.g. potassium dihydrogen phosphate) or addition of potassium to intravenous (IV) fluids (prescribed or inadvertently given).
- Aldosterone deficiency (congenital adrenal hyperplasia or specific aldosterone synthetic defect, see Chapters 10 and 12).
- Aldosterone resistance (see Chapter 12).
- Haemolysis of blood transfusion (mismatched blood, wrongly handled blood bag, e.g. overheated by use of inappropriate heater (e.g. overhead cot heater) or blood warmer set at too high temperature; use of old blood with consequently high potassium content for exchange transfusion).
- Urinary tract infection (UTI).
- Renal tubular acidosis.

Assessment

- Assess urine output and quality (urinalysis for blood, protein, and specific gravity).
- Measure blood pressure (if raised, suggests a renal problem).
- Has the infant had an umbilical venous or arterial catheter, if so where was the tip on X-ray? (i.e. was there a risk of renal vascular thrombosis).
- Has there been frank haematuria? (suggestive of renal vein thrombosis).
- Are the kidneys enlarged on palpation? (suggesting congenital abnormality or renal vein thrombosis).

Investigations

- Plasma sodium measurement (low in aldosterone deficiency or resistance, and low in renal impairment).
- Plasma urea and creatinine (raised in renal impairment, but creatinine may also rise with tissue damage).

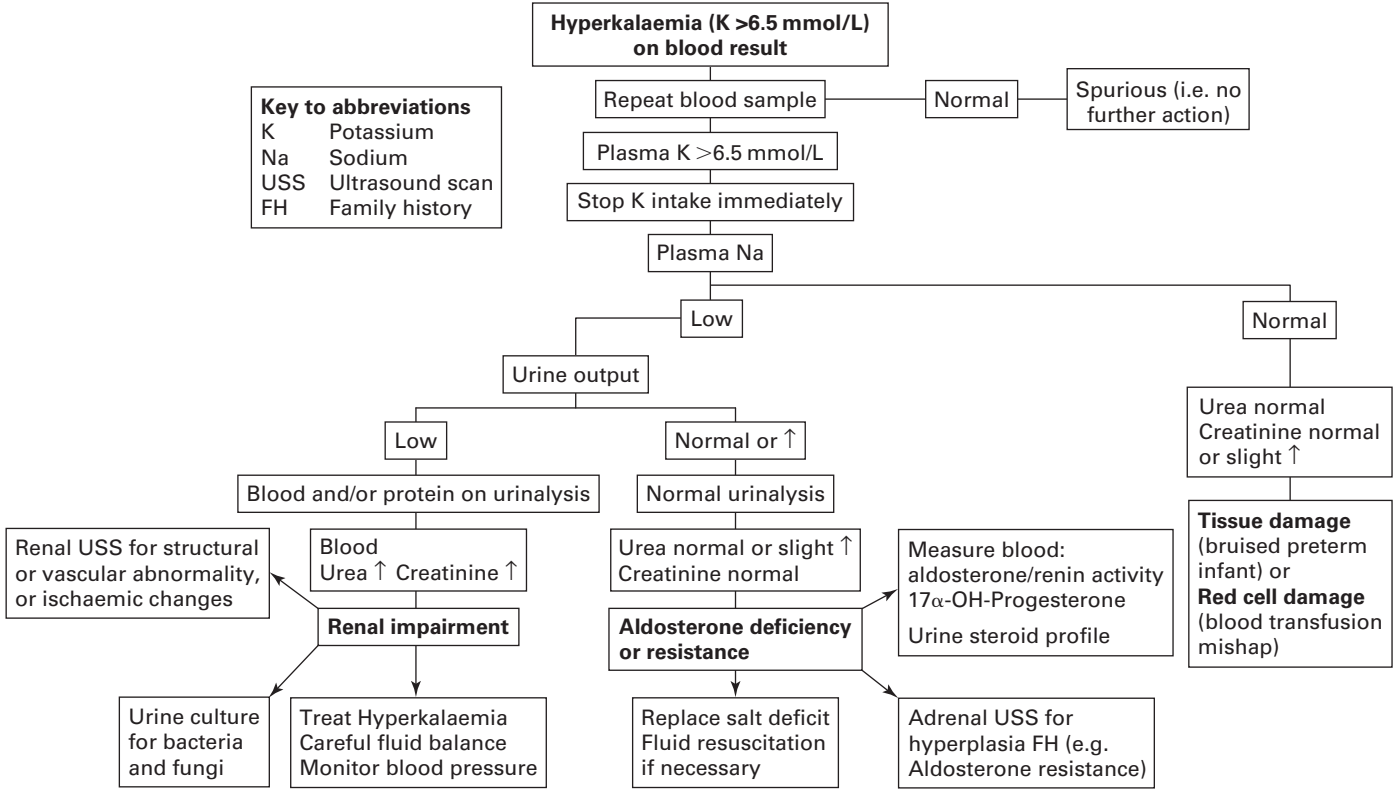

Figure 16.1 Flow chart: hyperkalaemia on blood result

- Urine electrolytes and osmolality (paired with plasma osmolality if hyponatraemic).
- USS/Doppler of the renal tract for abnormalities, umbilical/renal vessels for signs of thrombosis, and adrenal glands for size/haemorrhage.
- Plasma renin and aldosterone to exclude deficiency (specialized laboratory test where result may take a week or more, and sample may need to be collected on ice, see Appendix 4).
- Plasma 17α-hydroxyprogesterone (specialized laboratory, result in days; for interpretation, see Appendix 3 and Chapter 10).
- Urine steroid profile (specialized laboratory, days or weeks; see Chapter 10).
- Suprapubic aspirate of urine for culture (not necessary in the first 2 days of life).

See hyperkalaemia on blood result flow chart (Figure 16.1).

Management

Immediate

- Stop potassium intake.
- Treat the underlying cause where possible.
- If the cause is likely to be aldosterone deficiency or resistance, replace sodium deficit and give fludrocortisone, see Chapters 10 and 13, and Appendix 5.
- ECG monitoring: Assess whether circulating potassium (K) needs to be reduced urgently, e.g. plasma K still rising and/or ECG changes.
  - Mild to moderate hyperkalaemia (K 7–7.5 mmol/L) is not uncommon in the first few days of life in extremely preterm infants, and seldom leads to signs of toxicity.
  - Severe hyperkalaemia (K > 8 mmol/L) is life threatening and requires urgent treatment.
  - Calcium resonium (rectally) is the only treatment that removes potassium from the body (125–250 mg/kg 6–8 hourly, see Appendix 5).
  - Normalizing acid–base balance with bicarbonate and/or reducing pCO_2 will drive potassium into the cells.
  - If there is evidence of myocardial excitability, calcium gluconate (by *slow* infusion to avoid asystole) will help to prevent arrhythmias, but does not lower the potassium level; 0.5 mL/kg (max 2 mL/kg) of 10% solution, i.e. 0.11 mmol/kg calcium solution slowly IV over 5–10 min

with ECG monitoring, preferably via a central line. There is a risk of cardiotoxicity/asystole particularly with rapid infusion (see Appendix 5).
– Salbutamol infusion promotes intracellular uptake of potassium by inducing Na/K-ATPase (4 μg/kg over 10 min, see Appendix 5).
– An infusion of glucose and insulin will drive potassium into the cells, but requires an adequate glucose intake, titrating insulin to maintain normoglycaemia (0.2 g/kg/h dextrose and 0.1 units/kg/h insulin, see Appendix 5).
– Peritoneal dialysis can be used acutely, under advice from a renal specialist.

Medium/long term

Counselling/prognosis depends on the diagnosis.

- Renal impairment may be acute or chronic, and even if transient may require reassessment later (e.g. glomerular filtration rate (GFR) or imaging later in infancy). Advice should be sought from a renal specialist.
- Renal transplant is rarely successful before 4 years of age, but young children can be maintained on chronic ambulatory peritoneal dialysis.
- Aldosterone biosynthetic defect (see Chapter 12).
- Congenital adrenal hyperplasia (see Chapters 10 and 13).
- Genetic referral for intrinsic renal abnormalities where inheritance is important, e.g. polycystic kidneys or where the kidney abnormality may be part of a syndrome. This is also relevant for aldosterone deficiency or resistance.

What to tell parents

A simple explanation of the mechanisms leading to hyperkalaemia and the potential dangers of severe untreated hyperkalaemia. Further explanation depends on the cause of the hyperkalaemia, but the condition can rarely be caused by a hormone deficiency.

USEFUL LINKS

Congenital adrenal hyperplasia: Chapters 8 and 10.
Adrenal insufficiency/aldosterone biosynthetic defect: Chapters 11–13.
Formulary: Appendix 5.

Hypernatraemia

Clinical presentation

- Incidental finding on biochemistry result.
- Dehydration with or without collapse.

Definition

Plasma sodium >145 mmol/L.

Approach to the problem

To distinguish between **water depletion** (inadequate intake or excessive loss) and **sodium excess** (excessive salt intake).

Differential diagnosis

- Inadequate fluid intake:
  - Inadequate milk intake which is most likely in breastfeeding primigravidae.
  - Inadequate intravenous (IV) fluid intake in the extreme preterm infant with high insensible losses through the skin/respiratory tract.
- Excessive fluid losses:
  - Urine (diabetes insipidus (DI), renal concentrating defect, polyuric phase of acute tubular necrosis (although usually associated with renal salt loss), and osmotic diuresis secondary to glycosuria).
  - Gut (vomiting or nasogastric aspirates, and secretory diarrhoea).
  - Skin (cystic fibrosis, CF in hot country, skin may taste salty when kissed).

- Excessive salt administration:
  - Sodium bicarbonate infusions.
  - IV saline including flushes.
  - Malicious salt poisoning.

Identify those causes which have urgent implications in terms of management, e.g. DI, septo-optic dysplasia, and renal concentrating defect.

The commonest cause of hypernatraemia in the term infant is inadequate milk intake.

Assessment

Hypernatraemic dehydration requires urgent identification and treatment:

- Examine for signs of severe dehydration, e.g. sunken fontanelle, reduced skin turgor, and dry mouth. (*Note*: These are late signs in the dehydrated infant with feeding difficulties.)
- Weigh the infant and compare this with previous weights.
- Ask about the number of wet nappies per day.
- Is the infant passing 'changing stool'? (When the colour and consistency of the stool changes from meconium to milk-fed stool, i.e. an indicator of milk intake.)
- Could poor feeding be secondary to underlying infection or a metabolic problem?
- If the infant is vomiting, what is the underlying cause (anatomical or metabolic)?
- Examination for midline defects – e.g. central cleft palate and/or lip, hypo- or hypertelorism, or micropenis, any of which might suggest pituitary pathology. Look for other symptoms/signs suggestive of pituitary pathology such as hypoglycaemia, hypothermia, and prolonged jaundice (see Chapter 7).
- Look for other dysmorphic features which may be associated with a primary renal problem, e.g. abnormal tone and posture (particularly of the hands) in arthrogryposis renal dysfunction cholestasis (ARC) syndrome.
- Enquire about consanguinity, or a history of neonatal deaths.

Investigations

Initial

- Blood electrolytes urea, creatinine, and osmolality (urgent results, i.e. same day).

- Urine output, urinalysis for blood and protein (renal dysfunction), and concentration (specific gravity at the bedside gives an initial indication).
- Urine electrolytes, osmolality, and creatinine (ideally paired with a blood sample) (urgent results, i.e. same day).
- Blood glucose (with hypoglycaemia screen if low, see Chapter 2, including cortisol, IGF1, and GH measurements as indicators of pituitary function, see Chapter 7).
- Blood gas and lactate for acid–base status as an indicator of tissue perfusion.
- Urine for reducing substances and blood for galactose-1-phosphate uridyl transferase (to identify galactosaemia), if there is a history of vomiting or jaundice.
- Urine culture if a renal cause is suspected.
- Calculation of the fractional excretion of sodium may be helpful (see Appendix 3).

Further investigations

- Head ultrasound scan (Head USS) for associated midline defects, ophthalomology opinion, and blood tests for suspected hypopituitarism/septo-optic dysplasia as detailed in Chapter 7.
- Renal USS (primary renal problem).
- Genetics opinion if associated abnormalities (e.g. ARC syndrome) and in DI.

Management

Immediate

- In salt overload:
  - Stop salt intake.
  - Maintain normal hydration and allow the kidneys to excrete the excess salt.
  - Monitor blood electrolytes.
  - Both preterm and term infants have a low capacity for the rapid excretion of a salt load, and it is therefore better to guard against salt overload in the first instance.
- In water deprivation/dehydration:
  - Restore normal plasma volume (orally if dehydration is secondary to feeding problems and the infant is able to tolerate), without allowing

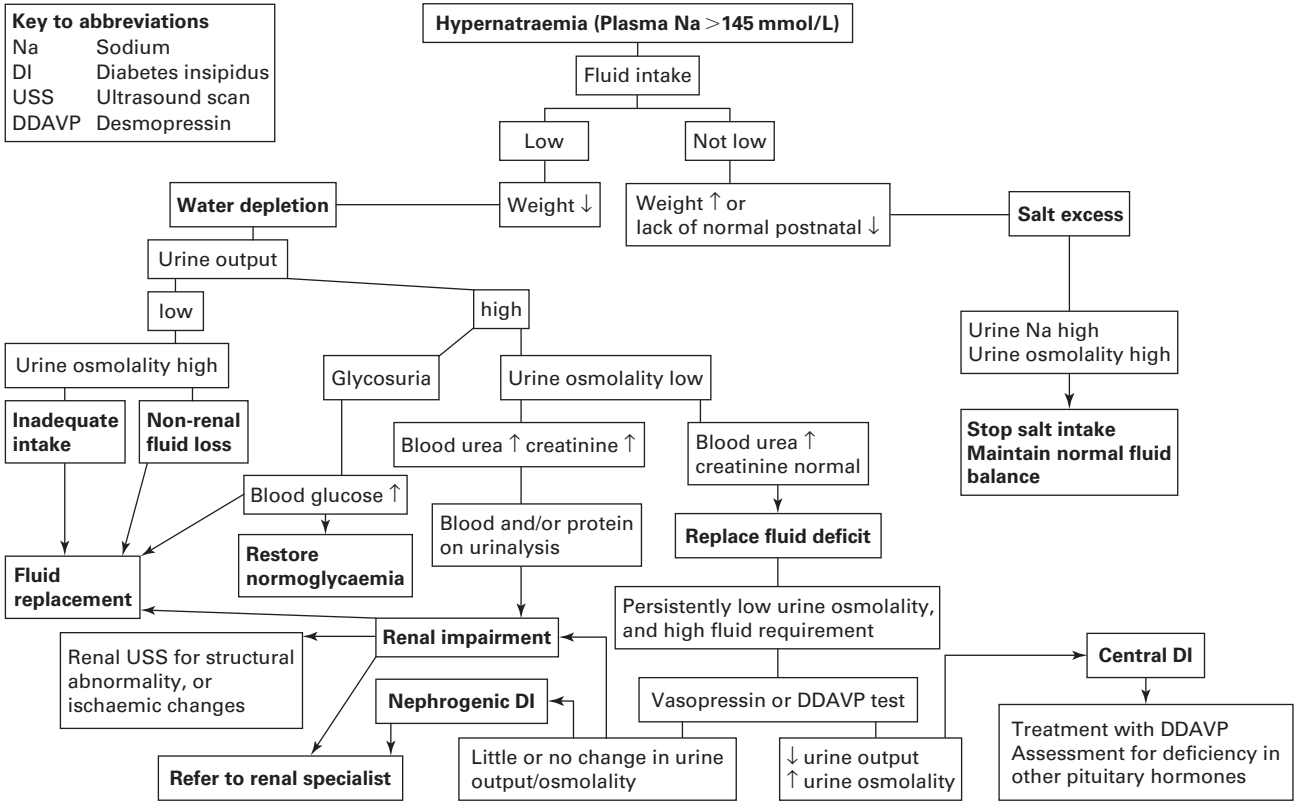

Figure 17.1 Flow chart: Hypernatraemia

plasma sodium to drop too rapidly (i.e. aim for a slow fall in blood sodium, e.g. <1 mmol/h initially, and <10 mmol/24 h).
- Monitor fluid input and output carefully.
- Monitor urine concentration (specific gravity, osmolality).
- Continue to monitor body weight once or twice daily.

Investigation and management of DI

Consider a test dose of vasopressin (or DDAVP) if there is a strong suspicion of DI (polyuria with an inappropriately low urine osmolality for the blood osmolality) (see Chapter 7 and Appendix 2 and 5). This will distinguish between central DI and nephrogenic DI (no response to vasopressin in the latter). A suboptimal response to vasopressin may be seen in a primary renal concentrating defect. IV vasopressin may be preferable to DDAVP for the diagnosis and initial management because of its shorter half-life, and because it can be given as a continuous IV infusion, which can be titrated against urine output. This is particularly useful in preterm infants. DDAVP can also be used diagnostically, and is available in IV, intranasal, and oral preparations, but has a longer half-life than vasopressin. DDAVP is used for maintenance therapy in DI. The main danger with the administration of vasopressin or DDAVP is acute fluid overload, which can result in cerebral oedema. It is therefore safer to be in a slightly negative fluid balance at the time of the test dose, and to limit fluid input to 1.5 × fluid output after the test dose is given.

For diagnosis and early management of DI

Aqueous vasopressin by continuous IV infusion. Starting at 1 mU/kg/h (0.001 U/kg/h). Usual dose range: 0.5–2.0 mU/kg/h.

For management of central diabetes insipidus

Intranasal solution of DDAVP: Start with 0.25 μg every 12 h, increasing gradually until a satisfactory response is achieved. The usual maximum dose is 5–20 μg every 12 h.

IV or SC injection of DDAVP: Start with 0.02 μg every 12 h and increase gradually until a satisfactory response is achieved.

See Appendices 2 (tests) and 5 (formulary) for more details.

Interpretation of vasopressin/DDAVP test

For further information, refer to Appendix 2.

Medium term

Central DI: monitoring of fluid balance and electrolytes. DDAVP dosage and administration.

Primary renal disorder, including nephrogenic DI, requires referral to a renal specialist both for immediate and long-term management.

What to tell parents

Your baby has high salt levels in the blood. This is usually due to a lack of fluid (dehydration), but can sometimes be due to an excessive amount of salt in the body. If the problem is dehydration, this may be due to a lack of fluid input (milk or IV fluid) or to the kidneys producing too much urine. Monitoring the concentration of urine will be helpful in distinguishing between the two, as will tests to see how well the kidneys are working. Rarely, the problem can be due to lack of the hormone that controls the way the kidney concentrates urine. If so, replacement of this hormone can be given, but requires close monitoring especially in the newborn period. Infants and children with this hormonal deficiency do not usually run into difficulty on treatment if they have a sense of thirst and free access to fluid. (However, children without a sense of thirst can be extremely difficult to manage). The hormone that controls water balance comes from the pituitary gland, and deficiency in this hormone is sometimes associated with lack of other hormones from that gland, either now or in the future. All of these hormone deficiencies can be treated, but it is important the infant/child is monitored regularly in order to detect them.

Home management for the infant with central DI

Regular weighing of the baby and observation of how wet the nappies are, and how much milk the baby is demanding (with the aim of contacting the hospital if any of these change).

Regular/frequent hospital review to measure blood electrolytes (more than once a week in the early stages).

Open access for hospital review and local telephone numbers to use for advice/emergency.

For associated pituitary hormone deficiencies see Chapter 7.

For blood glucose monitoring and emergency management of hypoglycaemia, see Chapters 2 & 3.

For steroid emergency doses, (see Chapters 10 &12 and Appendix 5).

Community/liaison nurse, where available, to support the family at home.

USEFUL LINKS

Hypopituitarism: Chapter 7.
Tests: Appendix 2.
Formulary: Appendix 5.

SUPPORT GROUPS/SOURCES OF INFORMATION

The pituitary Foundation: www.pituitary.org.uk
Serono booklet: Emergency Information Pack for Children with Cortisol and GH Deficiencies and those Experiencing Recurrent Hypoglycaemia: www.bsped.org.uk/patients/serono/05_EmergencyInformationPack.pdf

HORMONAL CONTROL OF SALT AND WATER BALANCE

Renin–angiotensin system

The renin–angiotensin system is the main regulator of aldosterone secretion. Renin is a proteolytic enzyme secreted by juxtaglomerular cells surrounding the afferent arteriole in the kidney, adjacent to the macula densa. Renin is released in response to a fall in plasma volume. Renin converts angiotensinogen (from the liver) to angiotensin I, which is subsequently converted to Angiotensin II (a potent pressor) by angiotensin converting enzyme (ACE) primarily in the lung. Angiotensin II acts directly on the zona glomerulosa cells in the adrenal cortex to produce aldosterone. Aldosterone acts on the distal tubule and collecting ducts of the kidney to increase sodium reabsorption and excretion of potassium and hydrogen. Both cortisol and aldosterone can act on the mineralocorticoid receptor (MR), but there is local enzyme inactivation of cortisol in the kidney to prevent cortisol acting on the MR at this site (deficiency in this enzyme causes

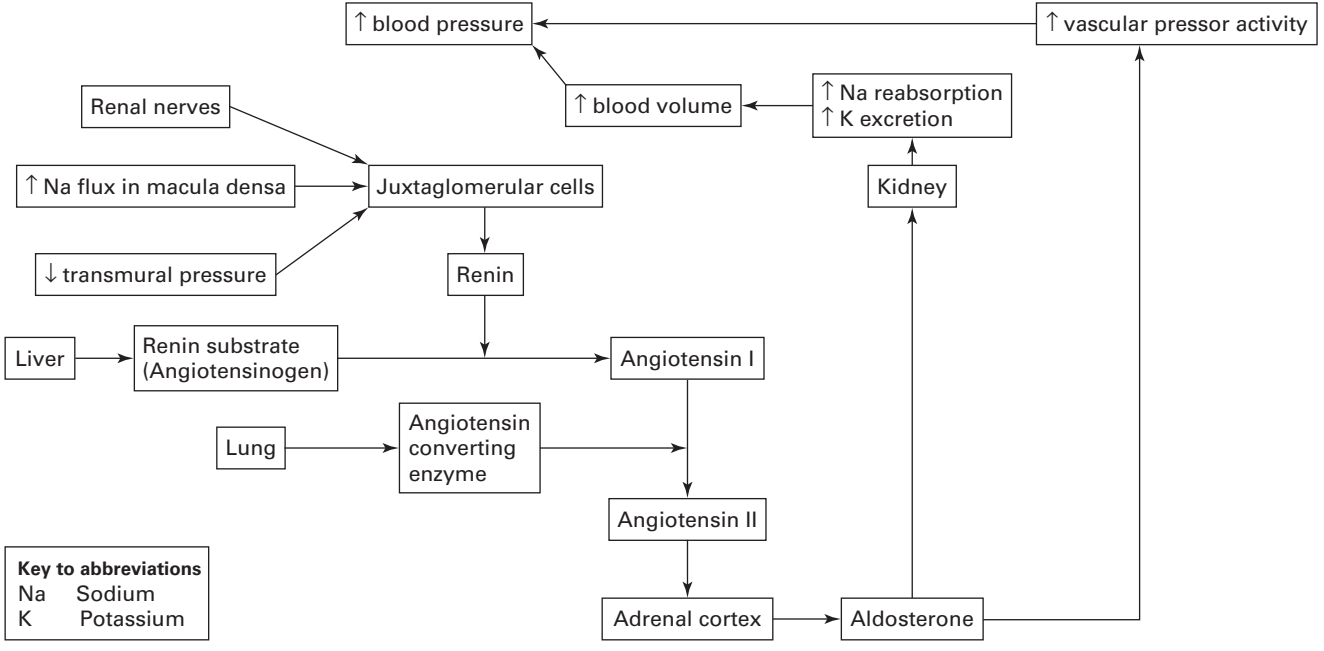

Figure 17.2 Hormonal control of salt and water balance

apparent mineralocorticoid excess). Aldosterone raises blood pressure by increasing plasma volume, and by increasing the sensitivity of arteriolar muscle to vasoconstrictors.

Antidiuretic hormone

Antidiuretic hormone (ADH) or arginine vasopressin (AVP) is synthesised in the supraoptic and paraventricular nuclei of the hypothalamus, and passes down the hypothalamic–hypophyseal tract to be stored in the posterior pituitary. ADH is released from the posterior pituitary in response to osmotic pressure in the circulation, and causes retention of water by the kidney. As plasma osmolality falls, hypothalamic osmoreceptors suppress further ADH secretion. ADH acts on vasopressin (V_2) receptors in the final section of the distal convoluted tubule and on the collecting ducts in the kidney to increase their permeability to water, causing water reabsorption (due to the high interstitial osmolality). ADH (vasopressin) is also a potent vasocontrictor. Relative or absolute deficiency of ADH causes DI. Central (pituitary) DI may be primary and is usually associated developmental abnormalities of the hypothalamus and pituitary gland and may therefore be associated with other hormone deficiencies. Cortisol is required to excrete a water load, therefore ACTH deficiency can mask or diminish the effects of ADH deficiency, and so fluid balance should be monitored when infants are started on hydrocortisone for pituitary insufficiency. Central DI can also be caused by perinatal damage to the pituitary gland (e.g. birth asphyxia). DI is more rarely caused by failure of the kidney to respond to ADH (nephrogenic DI), an X-linked V_2 G-protein coupling abnormality on chromosome Xq2.8. In the neonate, ADH excess is commoner than deficiency, and is usually a result of intracranial pathology (e.g. birth ashyxia), or lung pathology (atrial natriuretic peptide). Other stimuli for ADH secretion include pain and nausea. Inappropriate ADH secretion is usually transient. The diagnosis is made by comparison of the plasma and urine osmolality (urine inappropriately concentrated for a low plasma osmolality), and is treated by fluid restriction (see Chapter 15).

Maternal steroid excess

Clinical presentation

- Antenatal history of maternal steroid treatment.
- Maternal Cushing's syndrome.

What is the risk of transient neonatal adrenal insufficiency?

Approach to the problem

- With maternal Cushing's syndrome the infant is at risk of adrenal insufficiency.
- With maternal steroid therapy: assess the type and dose of steroid (the placenta inactivates a proportion of most steroids). It is difficult to predict risk to the infant as data are lacking in this area.

Investigations

Blood glucose in all infants.

In infants who have signs of adrenal insufficiency (hypoglycaemia, hypotension, and unwell):

- Three to five random samples for cortisol over the first 2–3 days.
- Synacthen test (see Appendix 2).

Management

- The infant should not be for early discharge home, i.e. should be in hospital for ⩾48 h.

- Pre-feed blood glucose monitoring over the first 2–3 days, to detect hypoglycaemia.
- Assessment of circulation: tissue perfusion and blood pressure.
- Consider cortisol measurements or a synacthen test if the infant is hypoglycaemic or unwell (see Appendices 2 and 3).
- Consider hydrocortisone therapy if unwell.

Immediate

- Resuscitation, if unwell including hydrocortisone 25 mg IV bolus (see Appendix 5).
- If adrenal suppression is suspected (e.g. low blood glucose) but the infant is not unwell:
  - Take blood samples for cortisol measurements.
  - Consider a synacthen test (see Appendix 2).
  - Consider treatment with replacement hydrocortisone (3.75–5 mg/day divided into 3 doses, weaning to 2.5–4 mg/day divided into 3 doses (see Appendix 5).
- In both of the above
  - Monitor blood glucose.
  - Refer to a paediatric endocrinologist.

Medium term

This should be under the care of a paediatric endocrinologist. If hydrocortisone has been started it will be weaned down slowly before discontinuing treatment. A synacthen test may be performed after hydrocortisone has been stopped.

What to tell parents

Some of the steroids in the mother's bloodstream are transferred to the baby. Occasionally this can be sufficient to switch off the baby's own production of steroids. The baby's steroid production will return, but rarely the baby may require steroid treatment until this happens. It is important to look out for signs of steroid deficiency in the baby in the first 2–3 days of life, which includes measurements of blood sugar and blood pressure. It is therefore important that the baby stays in the hospital for monitoring for 2–3 days after birth.

EFFECTS OF MATERNAL STEROID ADMINISTRATION

There are very few data available on the effects of maternal steroid therapy in humans. In animals maternal steroid therapy increases fetal resorption, decreases fetal size and viability, and increases the incidence of cleft palate. In humans, a review (in 1960) of 272 pregnancies reported 1 abortion, 8 stillbirths, 15 premature deliveries, 4 cleft palates (on steroids before the 14th week), and 1 neonatal adrenocortical failure of 3 days duration. A separate small study of six neonates exposed to prolonged maternal prednisolone, compared with eight neonates who were not, showed no difference in basal or adrenocorticotrophin hormone (ACTH) stimulated cortisol levels.

Although pregnancy is rare in maternal Cushing's syndrome due to ovulatory disturbance, it does occur, with adrenal adenoma being more common than pituitary-dependent adrenal hyperplasia. ACTH-independent, pregnancy-induced Cushing's syndrome has also been described. A review of 65 pregnancies in 58 patients with Cushing's syndrome reported maternal pregnancy complications of hypertension (64.5%), pre-eclampsia (9.3%), glucose intolerance (32.3%), congestive cardiac failure (10.8%), and 3 deaths (7.7%). There were 2 miscarriages, 5 stillbirths, 5 neonatal deaths, and 42 preterm deliveries (20–28 weeks); 17 out of 65 had a birth weight $<$10th centile, but data were not available for all the cases. This series also reported two cases of Addisonian crisis in neonates soon after birth, decreased fetal adrenal size in a stillbirth at 32 weeks (narrowing and cystic degeneration of the fetal zone), and 1 cleft palate. Pregnancy-dependent Cushing's syndrome has also been reported to cause neonatal adrenal insufficiency.

Antenatal steroids used in the management of preterm labour cause transient suppression of fetal heart rate variability, and fetal biophysical activity. Repeated courses reduce birth weight and head circumference. In mice, repeated courses reduced lung growth. Permanent changes in the hippocampus have been reported in primates, and increased blood pressure and reduced glucose tolerance in rodent offspring. In humans, lower cord blood cortisol levels have been reported after antenatal steroids and lower plasma cortisol at 2 h of age, however no difference in baseline (days 2, 4, 6) or ACTH-stimulated cortisol levels, or difference in blood cortisol level days 1 and 3, or difference in ACTH or cortisol response to corticotrophin-releasing hormone (CRH) on days 7 and 14. Reduced pulse amplitude in cortisol secretion on the first day of life has been demonstrated in infants exposed to

antenatal steroids, but no difference in number or duration of cortisol secretory bursts. In summary, antenatal steroids given for preterm labour do cause subtle changes in circulating cortisol, although these are probably not of clinical significance.

USEFUL LINKS

Dynamic tests: Appendix 2.
Formulary: Appendix 5.
Adrenal failure: Chapter 12.
Collapse: Chapter 13.
Hypoglycaemia: Chapter 2.

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Hypercalcaemia

19

Clinical presentation

Incidental hypercalcaemia.
Mild hypercalcaemia: 2.75–3.2 mmol/L is usually asymptomatic.
Moderate to severe hypercalcaemia: (>3.2 mmol/L) anorexia, gastro-oesophageal reflux, vomiting, constipation (rarely diarrhoea).
Other symptoms and signs:

- *Polyuria* (may result in dehydration).
- *Hypertension* (secondary to vasoconstrictive effect of hypercalcaemia).
- *Shortened ST segment and heart block* (secondary to direct effect on cardiac conduction).
- *CNS symptoms*: irritability, hypotonia, drowsiness, seizures, stupor, and coma.

Chronic hypercalcaemia: usually presents with failure to thrive.

Hyperparathyroidism may be associated with bone deformities or fractures (inadequate mineralization), respiratory difficulties (if ribcage affected), hepatosplenomegaly, and anaemia.

Definition

Total calcium >2.75 mmol/L ionized calcium >1.4 mmol/L.

Approach to the problem

- Assessment of calcium and phosphate intake, particularly in:
  - Preterm infants receiving breast milk without supplementation of phosphate.
  - Infants on prolonged low-phosphate-containing parenteral nutrition.

- Assessment of vitamin D intake:
  - Check milk formulation and vitamin D supplementation.
- History of birth trauma/perinatal asphyxia and signs of subcutaneous (SC) fat necrosis.
- Assessment of maternal mineral metabolism (calcium concentration and vitamin D status) and therefore parathyroid status.
- Family history hypocalciuric hypercalcaemia.
- Dysmorphic features of Williams syndrome with murmur of supravalvular aortic stenosis or peripheral pulmonary branch stenosis (see Chapter 5).

Differential diagnosis

- Iatrogenic:
  - Hypophosphataemia.
  - Vitamin D excess.
  - Vitamin A excess.
  - Excessive calcium supplements.
  - Extracorporeal membrane oxygenation.
  - Thiazide diuretics.
- Functional hyperparathyroidism: raised parathyroid hormone (PTH) and serum Ca, with low PO_4, and normal or raised alkaline phosphatase):
  - Maternal hypocalcaemia (secondary to pseudohypoparathyroidism, renal tubular acidosis).
  - Congenital parathyroid hyperplasia.
  - Inactivating mutations in the calcium-sensing receptor gene:
    - Familial hypocalciuric hypercalcaemia (heterozygous manifestation).
    - Neonatal severe hyperparathyroidism (homozygous manifestation).
  - Jansen's metaphyseal chondrodysplasia (caused by constitutive mutation in the PTH/PTH-related peptide (PTHrP) receptor).
  - Persistent PTHrP.
- Non-parathyroid hypercalcaemia:
  - Disorders of vitamin D metabolism.
  - Williams syndrome.
  - Idiopathic infantile hypercalcaemia.
  - SC fat necrosis.
  - Inborn errors of metabolism:
    - Lactase deficiency.
    - Disaccharidase deficiency.

  - Infantile hypophosphatasia.
  - Blue diaper syndrome.
- Endocrine disorders:
  - Congenital hypothyroidism.
  - Thyrotoxicosis.
  - Adrenal insufficiency.
- Down syndrome.
- IMAGe association (intrauterine growth retardation, metaphyseal dysplasia, adrenal hypoplasia, and genital anomalies).
- Malignancy.

Investigations

Investigations should be done in the following order of priority:

- Blood:
  - Calcium (either total, corrected for albumin, or ideally, ionized).
  - Phosphate.
  - Albumin.
  - Alkaline phosphatase.
  - Magnesium.
  - Creatinine and electrolytes.
  - PTH.
  - Vitamin D level (25-OHD).
  - Sample for DNA (mutational analysis of calcium-sensing receptor (CaSR) or Williams (elastin) gene, $1,25(OH)_2D$).
- Urine:
  - Urinary calcium.
  - Urinary phosphate.
  - Urine creatinine.
- Skeletal survey.
- Maternal mineral status (calcium, phosphate, PTH).

Management

Immediate

Reduce intake of calcium and vitamin D (low calcium infant formulas are available).

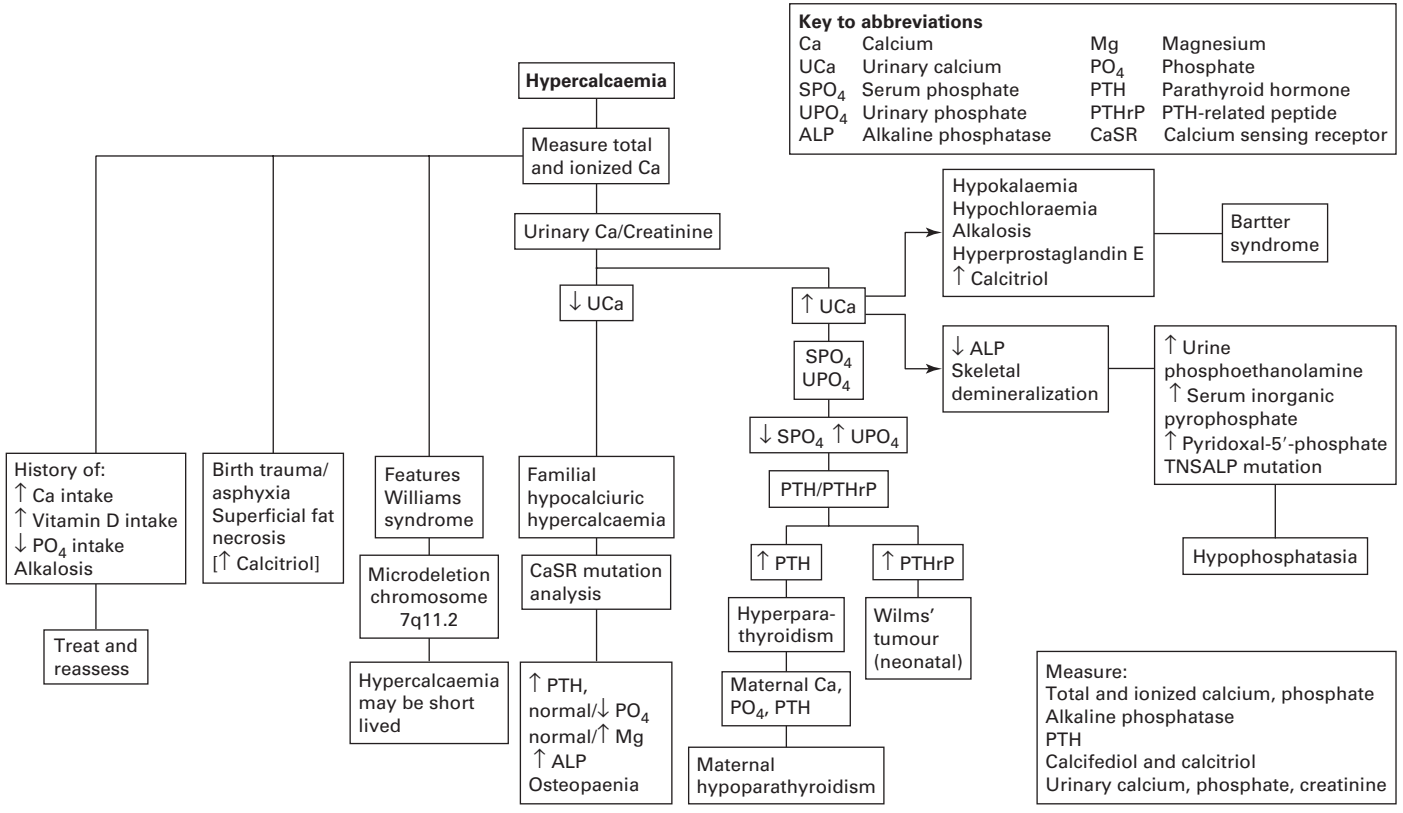

Figure 19.1 Flow chart: Hypercalcaemia

Mild, asymptomatic hypercalcaemia, thriving baby: conservative management.

Hypercalcaemia secondary to maternal hypocalcaemia: appropriate calcium and phosphate supplementation in milk.

Severe hypercalcaemia:

- Seek advice from paediatric endocrinologist.
- Avoidance of excessive calcium and vitamin D intake.
- Hydration with normal saline.
- Loop diuretics to enhance saline-induced calciuresis. (*Note*: Avoid dehydration, as this results in reduced glomerular filtration rate which may worsen hypercalcaemia, and lead to nephrocalcinosis with long-term diuretic use.)
- Bisphosphonates (e.g. pamidronate 0.5–2.0 mg/kg) have obviated the need for urgent subtotal parathyroidectomy in babies with neonatal severe hyperparathyroidism. This should be administered under guidance from a paediatric endocrinologist. Significant hypocalcaemia may occur.
- Parathyroidectomy, if hyperparathyroidism uncontrolled on bisphosphonates. (*Note*: Calcium will drop rapidly after surgery and calcium replacement may be required.) This will require a specialist surgeon.

Non-parathyroid-dependent forms of hypercalcaemia:

- Short course of steroids may be effective but the side effects of prolonged glucocorticoids precludes their use long term.
- Treatment with bisphophonates or calcitonin may be required.

Medium term

Introduce normal formula milk as calcium levels normalize.

Monitor serum and urinary calcium levels to confirm the effectiveness of dietary therapy and to avoid hypocalcaemia and rickets.

Long term

Growth is sensitive indicator of effective treatment.

If a CaSR mutation or Williams syndrome is suspected the family may require genetic counselling.

What to tell parents

Explanation for the high calcium if one is available. If a CaSR mutation is suspected, paternal and sibling calcium levels should be checked (and the mother's if not already done).

USEFUL LINKS

Calcium physiology: Chapter 20.

SUPPORT GROUPS

Williams Syndrome Foundation (UK): www.williams-syndrome.org.uk
Williams Syndrome Foundation (USA): www.wsf.org
Williams Syndrome Association: www.williams-syndrome.org

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Hypocalcaemia

Clinical presentation

- Incidental asymptomatic hypocalcaemia on blood results (usual presentation).
- Neuromuscular irritability: myoclonic jerks, jitteriness, exaggerated startle responses, seizures.
- Apnoea, cyanosis, tachypnoea, vomiting, laryngospasm.
- Cardiac symptoms and signs: tachycardia, heart failure, prolonged QT interval on electrocardiogram (ECG), decreased contractility. Severe vitamin D deficiency may present with cardiomyopathy.

Definition

Total calcium <2.2 mmol/L/ionized calcium <1.2 mmol/L.

- *Note*: physiological hypocalcaemia occurs after birth as the transplacental calcium supply is cut, there is insufficient supply from the GI tract and insufficient release of parathyroid hormone (PTH) from the immature parathyroid gland.
- Total calcium levels drop to about 2 mmol/L and ionized to about 1 mmol/L.
- The nadir in calcium level occurs within the first 48 h.

Approach to the problem

Hypocalcaemia is common, it is usually due to one of the following:

- Physiological, or an exaggeration of the normal physiological response.
- Iatrogenic and short lasting.

Other causes of hypocalcaemia are rare.

Aetiologies are conventionally grouped according to the time of onset:

- *Early*: within the first 4 days of life.
- *Late*: after 4 days of age.

History: Preterm, birth depression, infant of a diabetic mother, abnormality in maternal calcium metabolism.

Examination:

- Symptoms and signs of hypocalcaemia as above.
- Dysmorphic features of 22q deletion syndrome/CATCH-22 (*C*ardiac anomaly, *A*bnormal facies, *T*hymic aplasia, *C*left palate, *H*ypocalcaemia, deletion on chromosome 22q) (see Chapter 5).

Exclude other differential diagnoses of common non-specific symptoms (sepsis, meningitis, hypoglycaemia, hypomagnesaemia, intracranial haemorrhage) including urgent blood sugar.

Ionized calcium level should be measured in the preterm baby as the normal relationship with total calcium is atypical.

Differential diagnosis

- Early onset (first 4 days):
  - Prematurity.
  - Perinatal asphyxia/stress/trauma.
  - Infant of a diabetic mother (exacerbated by relative hypomagnesaemia).
  - Pre-eclampsia.
  - Maternal hyperparathyroidism (intrauterine hypercalcaemia suppresses parathyroid activity in the fetus, resulting in impaired parathyroid responsiveness to hypocalcaemia after birth. Hypocalcaemia may be severe and prolonged).
- Late onset (days 5–28):
  - This is usually iatrogenic and caused by excessive intake of phosphate.
- Rarer causes:
  - Vitamin D deficiency (usually secondary to maternal vitamin D deficiency. This may be associated with maternal anticonvulsant use – phenobaritone or phenytoin).
  - Malabsorption of calcium or vitamin D.
  - Hypomagnesaemia.
  - Transient hypoparathyroidism.
  - Transient PTH resistance.
  - Renal failure.

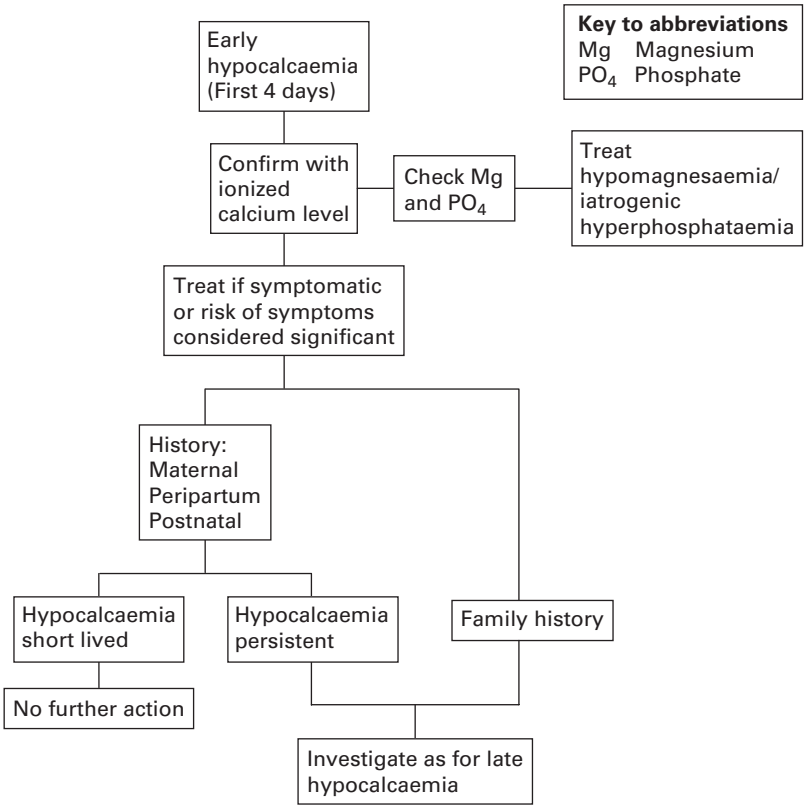

Figure 20.1 Flow chart: Early hypocalcaemia

- Congenital hypoparathyroidism:
  - 22q deletion syndrome (see Chapter 5). (Hypoparathyroidism may be transient, with resolution during infancy, but may be exacerbated by the use of loop diuretics for heart failure.)
  - Activating mutations in Ca sensing receptor (mild variant of hypoparathyroidism; autosomal dominant hypocalcaemia).
  - Agenesis of parathyroid glands.
  - Metabolic syndromes:
    - Kenny–Caffey syndrome.
    - Mitochondrial trifunctional protein deficiency.
    - Long-chain fatty acyl CoA dehydrogenase deficiency.
    - Kearns–Sayre syndrome.

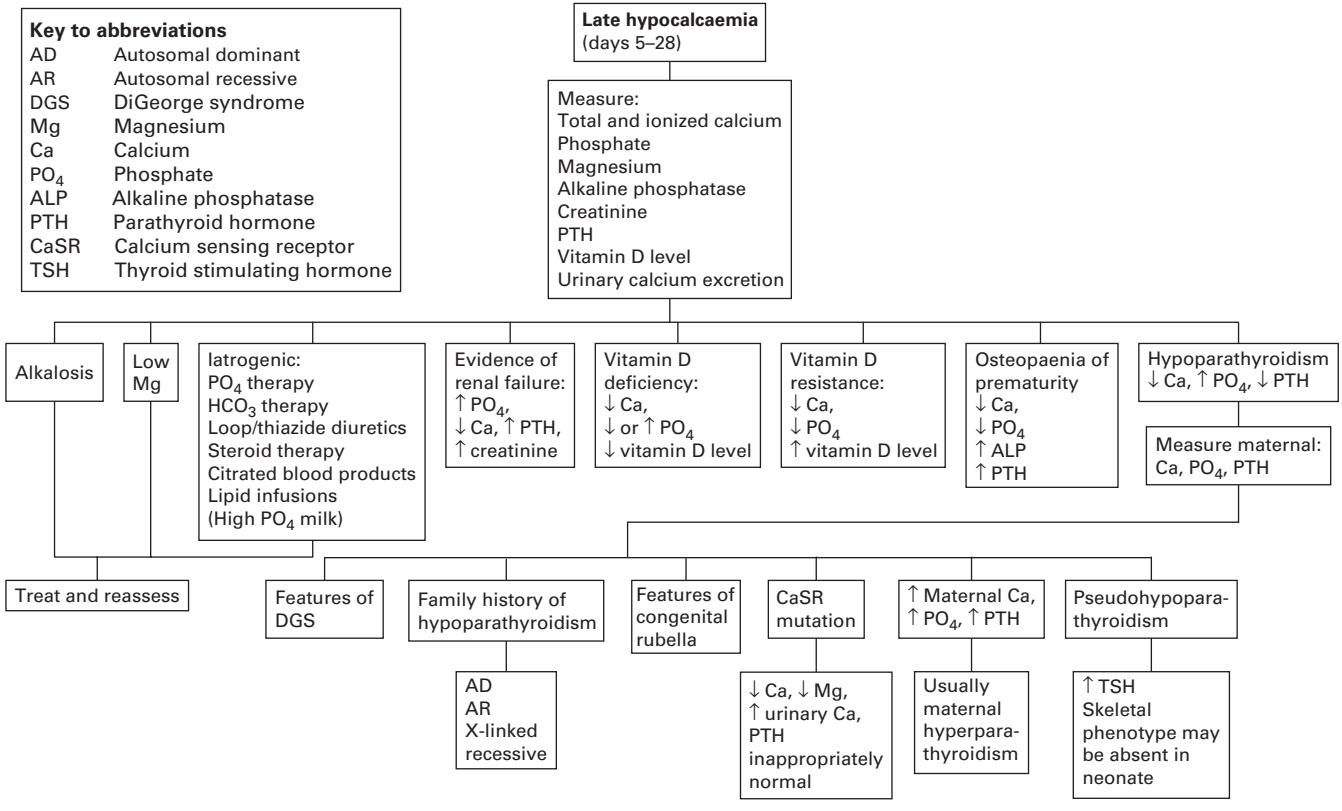

Figure 20.2 Flow chart: Late hypocalcaemia

- Iatrogenic:
  - Phosphate therapy.
  - Citrated blood products.
  - Lipid infusions.
  - Bicarbonate therapy.
  - Diuretics (loop diuretics and thiazide diuretics).
  - Glucocorticoids.
  - (Historically high-phosphate-containing milk feeds, e.g. cows milk.)
- Alkalosis.

Investigations

Investigations should be done in the following order of priority:

- Blood
  - Calcium level (ideally ionized calcium)
  - Phosphate
  - Magnesium
  - Alkaline phosphatase
  - Albumin
  - pH
  - Creatinine and electrolytes
  - PTH level (needs to be received by laboratory within 2 h, see Appendix 4)
  - Vitamin D level
  - Sample to the cytogenetics laboratory for processing for further investigation if necessary (mutational analysis).
- Urine
  - Calcium
  - Phosphate
  - Creatinine
  - Glucose
  - Amino acids
  - Cyclic AMP (cAMP).
- Determine
  - Urinary Calcium/Creatinine ratio
  - Urinary PO_4 excretion (tubular reabsorption of phosphate) (see Appendix 3).
  - X-ray of wrist for evidence of rickets or osteopenia.

– Assessment of maternal mineral metabolism status.

For diagnosis, see Late hypocalcaemia Figure 20.2.

Management

Immediate

- Early hypocalcaemia is usually self-limiting. Treat with oral or intravenous (IV) calcium salts if symptomatic or QT interval prolonged.
- If symptomatic or severe hypocalcaemia (ionized calcium <0.72 mmol/L), correct with IV infusion of calcium salts.
  – For correction of arrhythmias or in emergencies give 0.5 mL/kg (maximum 2 mL/kg) of 10% calcium gluconate solution (0.11 mmol/kg calcium) slowly IV over 5–10 min with ECG monitoring and preferably via a central line. This can be repeated but watch for cardiotoxicity.
  – Ideally use a continuous infusion 2.5 mL/kg (0.55 mmol/kg calcium) of 10% solution given over 24 h. Avoid boluses or intermittent infusions if possible as these can cause wide excursions in serum calcium concentrations and can cause asystole. Ideally the infusion should be given via a central venous catheter as it is irritant to veins and extravasation may cause soft-tissue injury and scarring. Calcium chloride is particularly irritant and probably should not be used.
- Oral supplements are hypertonic and should be avoided in babies at risk of necrotizing enterocolitis.
- Hypomagnesaemia may be treated with 50% magnesium sulphate 100 mg/kg/dose (0.2 mL/kg of 50% w/v solution = 0.4 mmol/kg magnesium) as slow IV infusion over 30 min every 6–12 h or as intramuscular injection. (IV magnesium salts are intensely vasodilatory if given too quickly.)

Medium/long term

- If severe or persisting hypocalcaemia, additional treatment with vitamin D (IV or orally) with calcium may be necessary.
- Vitamin D deficiency should be treated with supplemental vitamin D 5–50 μg/day (200–2000 IU/day).
- Hypoparathyroidism should be treated with alphacalcidol (20–100 ng/kg/day). Vitamin D deficiency must always be eliminated first, and if necessary treated with vitamin D.

Long term

Assessment of paternal and sibling calcium levels if mutations in calcium-sensing receptor gene suspected.

Referral to geneticist/appropriate specialist if mutations in calcium-sensing receptor gene, 22q deletion syndrome, or a metabolic syndrome diagnosed.

What to tell parents

Early hypocalcaemia is likely to reflect immaturity/illness severity and should resolve within days.

Further discussions on persisting hypocalcaemia will be directed by results of investigations/likely diagnosis.

USEFUL LINKS

Formulary: Appendix 5.
Normal values: Appendix 3.
Dysmorphic features: Chapter 5.

CALCIUM PHYSIOLOGY

Extracellular fluid concentrations of calcium are normally kept within narrow limits despite wide variations in both intake and the demands of the growing skeleton, principally under the control of PTH and vitamin D. In the fetus, PTH-related peptide (PTHrP) is probably the main regulator of the positive calcium balance across the placenta.

Approximately 99% of total body calcium is in the skeleton, which in combination with 89% of total body phosphorus, constitutes the major inorganic mineral of bone. Approximately 50% of total serum calcium is in the biologically active ionized form at normal serum protein concentrations. A further 10% is complexed to organic and inorganic acids. The remainder is protein-bound and biologically inactive but provides a reserve of acutely available calcium if required. Extracellular fluid pH influences

the proportion of calcium bound to protein. Alkalosis increases this, thereby decreasing the amount of ionized calcium. Conversely, acidosis increases ionized calcium by decreasing protein binding. Increases in extracellular fluid concentrations of anions such as bicarbonate, phosphate, citrate and editic acid will increase the proportion of bound calcium thus reducing ionized calcium.

Vitamin D

Vitamin D (calciferol) is formed by the action of sunlight on exposed skin, or derived from the diet and converted in the liver to 25-hydroxyvitamin D (25-OHD). Levels are dependent on the supply of vitamin D and are not regulated and hence serum levels of 25-OHD reflect vitamin D status.

25-OHD is converted in the proximal renal tubule to the active metabolite 1,25-dihydroxyvitamin D (calcitriol, 1,25-$(OH)_2D$), which should be considered a hormone. The main stimuli for calcitriol synthesis are PTH, PTHrP and hypophosphataemia (directly) and hypocalcaemia (indirectly via PTH). Other factors including insulin-like growth factor I, oestrogens, prolactin, and growth hormone also have a stimulatory role and occasionally, abnormal levels of 1,25-$(OH)_2D$ may be formed by macrophages invading patches of subcutaneous fat necrosis. Calcitriol production is inhibited by elevated levels of calcium and phosphorus. The principal actions of calcitriol are to stimulate calcium absorption from the intestine and to aid mineral deposition into bone. The latter requires alkaline phosphatase.

Parathyroid hormone

PTH is secreted from the parathyroid glands in response to falling levels of ionized calcium detected by calcium-sensing receptors, via a magnesium-dependent cAMP mechanism. PTH activates synthesis of calcitriol in the kidney, increases calcium reabsorption from the distal tubule and phosphate excretion from the proximal tubule. It also promotes excretion of bicarbonate and amino acids which, in states of PTH excess, can result in a secondary Fanconi syndrome. In bone, PTH stimulates osteoclast activity, promoting reabsorption of calcium and phosphate, raising serum levels. However in physiological concentrations, PTH may have a mineralization-promoting effect.

Calcitonin

Calcitonin is secreted from the C-cells of the thyroid gland in response to elevated calcium levels. Although its actions are largely opposite to those of PTH, it is not as potent and has little part to play in calcium metabolism in postnatal life.

Fetus

The fetus is entirely dependent on the mother for calcium and phosphorus required for skeletal development and tissue growth and function. From 15 weeks gestation both total and ionized concentrations are higher in the fetus than mother due to active transport across the placenta, stimulated by PTHrP produced in the fetal parathyroid glands, the placenta, the chorion and amnion and augmented by vitamin D from the fetal kidney and placenta. Calcium levels are independent of maternal calcium levels.

The most rapid accretion of calcium in the fetus occurs in the third trimester, with 30–35 g/day actively transported across the placenta. About 200 mg of calcium is added to the fetal skeleton at the end of pregnancy. Whole body bone mineral density is related to gestation as well as body length and weight.

While PTHrP levels are high in the fetus, PTH levels are low. PTH does not stimulate placental calcium transport but is secreted from fetal parathyroid glands in response to hypocalcaemia, and suppressed in response to hypercalcaemia.

Neonate

At birth cord blood calcium levels correlate with gestational age and are about 0.25–0.5 mmol/L higher than maternal levels. With clamping of the cord, calcium levels fall rapidly in the first 6 h, ionized calcium reaching a nadir of 1.2–1.45 mmol/L at 24 h. The newborn baby is now dependent on parathyroid PTH secretion, dietary calcium, renal calcium reabsorption, skeletal calcium stores, and vitamin D. PTH levels increase on the first day of life in response to the fall in serum calcium levels peaking at 48 h. However there is a nadir in serum calcium levels within the first 2 days of life. Calcitriol levels also rise. In the first 2–4 weeks after birth, there is increased efficiency

of intestinal absorption of calcium. Renal tubular handling matures over this period. Accretion of bone calcium continues at a rate of 150 mg/kg/day.

Serum phosphate levels are maximal in the neonate as there is decreased glomerular filtration, and increased tubular reabsorption.

Early hypocalcaemia is caused by an exaggeration of normal fall in serum calcium. Late hypocalcaemia is considered to be a manifestation of relative resistance of immature kidney to PTH resulting in retention of phosphate levels and loss of calcium.

In the preterm baby hypocalcaemia after birth is common. Possible mechanisms include a blunted increase in PTH, a prolonged increase in calcitonin, rapid accretion of skeletal calcium and relative resistance to vitamin D-induced resorption of bone and absorption of calcium from the gut.

As the maternal calcium concentration and vitamin D status during pregnancy influences vitamin D levels and parathyroid function in the fetus, investigation of hypercalcaemia and unexplained hypocalcaemia should include an analysis of calcium metabolism in the mother. If defects in the calcium-sensing receptor are suspected, calcium levels in the father and siblings should be assessed.

SUPPORT GROUPS

22q11 group (England and Wales) http://www.vcfs.net
Hypoparathyroidism Association: http://www.hypoparathyroidism.org

FURTHER READING

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Investigation and management of babies of mothers with thyroid disease

21

Autoimmune thyroid disease in the mother may influence fetal thyroid function by transplacental passage of thyroid receptor immunoglobulins which may either block or stimulate the fetal thyroid-stimulating hormone (TSH) receptor. In addition, thionamides used in the treatment of thyrotoxicosis in the mother may cross the placenta and render the fetus hypothyroid.

Maternal hypothyroidism

- This is usually secondary to Hashimoto's thyroiditis and the mother may be producing thyroid inhibiting or rarely thyroid stimulating antibodies so the baby may develop transient hypo or very rarely hyperthyroidism.
- If the maternal TSH receptor antibody titre is known, the risk to the baby can be assessed. TSH *receptor* antibody titres do not differentiate *stimulating* from *blocking* antibodies and both may co-exist (high titres will increase risk of hypo or hyperthyroidism). The TRH receptor antibody results differ depending on laboratory methods, and so normal levels will need to be assessed with reference to the laboratory norms.
- If maternal TSH receptor antibody titre is normal, a Guthrie card TSH will suffice.
- If the TSH receptor antibody titre is elevated or unknown, review the baby at 10 days to 2 weeks and measure TSH and fT4.
- As risk of postnatal hypo or hyperthyroidism in baby is small, some would advocate no investigations are required.

- If the maternal hypothyroidism is secondary to congenital aplasia or hypoplasia of the thyroid gland there should be no significant increased risk to the baby of hypothyroidism and Guthrie card TSH level should suffice.
- If the hypothyroidism is secondary to treatment (surgery or radioiodine) for Graves' disease the baby is at risk of neonatal thyrotoxicosis and will need to be managed as described under "Maternal Thyrotoxicosis" below.

Maternal thyrotoxicosis

This includes a *current* or *past* history of maternal thyrotoxicosis, especially those treated with surgery or radioiodine (who may now be clinically hypothyroid). Thyrotoxicosis is nearly always due to Graves' disease and persisting thyroid stimulating antibodies renders the baby at risk of neonatal thyrotoxicosis. Co-existing inhibiting antibodies may cause neonatal hypothyroidism.

- Maternal TSH receptor antibody levels should be assessed during pregnancy.

Maternal TSH receptor antibody level:

- *Normal* – review baby at 5–10 days
- *Elevated or unknown:*
  - *Birth:* cord blood for fT4, TSH, TSH receptor antibodies (although the results are not usually available in the first few days of life when thyrotoxicosis or hypothyroidism is usually detected, it is useful for the long term management of thyrotoxicosis) and examine for sign of thyrotoxicosis
  - *2–7days*, fT4, TSH and examine for signs of thyrotoxicosis
  - *10–14 days*, fT4, TSH and examine for signs of thyrotoxicosis

Results need to be interpreted in light of normal values for age (Appendix 3). A **suppressed** TSH is abnormal even with a normal fT4 and suggests stimulating antibodies are present and the baby is at risk of thyrotoxicosis.

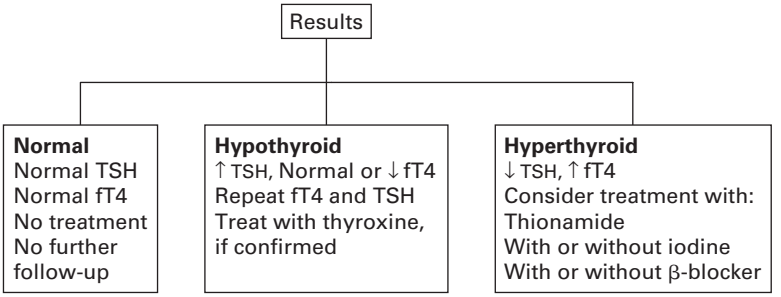

Figure 21.1 Flow chart: maternal thyrotoxicosis

Initial eu- or hypothyroidism may be followed by thyrotoxicosis. This may occur if the mother is being treated with thionamides at the time of delivery (these may affect the fetal thyroid and once cleared from the baby's blood, the effect of thyroid-stimulating antibodies in the baby's blood may result in thyrotoxicosis). Alternatively, there may be thyroid blocking and stimulating antibodies co-existing in the blood. Occasionally the baby may have central hypothyroidism (low fT4, low TSH) caused by an elevated fT4 in the fetus (from maternal or fetal thyrotoxicosis) suppressing the fetal hypothalamic-pituitary-thyroid axis.

Maternal or familial thyroid disease

22

HISTORY OF MATERNAL HYPOTHYROIDISM

Clinical presentation

History of maternal hypothyroidism.

Approach to the problem

History:

- History of maternal thyroid disease.
- Family history of thyroid disease.
- Age of onset (primary hypothyroidism will have presented at birth or early childhood, whereas Hashimoto's thyroiditis usually presents in later childhood or adulthood; the latter, by producing antibodies which cross the placenta, can affect neonatal thyroid function).
- Hyper- or hypothyroid symptoms (or both) in mother.
- If mother is hypothyroid secondary to treatment including drugs, surgery or radioiodine for thyrotoxicosis treat baby as at risk of thyrotoxicosis (see below).
- Maternal thyroxine treatment for hypothyroidism during pregnancy.
- Known thyroid-stimulating hormone (TSH) receptor antibody titres in pregnancy.

Symptoms and signs of hypothyroidism: see Chapter 24 – abnormal neonatal thyroid function tests.

Investigations

- If maternal hypothyroidism is secondary to Hashimoto's thyroiditis (usual cause) the baby is at risk of hypo- or rarely hyperthyroidism.
- Review maternal notes for TSH receptor antibody titres:
  - If normal, Guthrie card TSH measurement is sufficient.
  - If elevated or not measured, review baby at 7–10 days for TSH and fT4. However, risk is small.
- If maternal hypothyroidism is secondary to aplasia or hypoplasia of the thyroid gland (i.e. congenital hypothyroidism), elevated TSH in baby will be picked up on Guthrie test. (About 5% of cases of congenital hypothyroidism are inherited.)
- If maternal hypothyroidism is secondary to treatment of Graves' disease, treat as though at risk of thyrotoxicosis (see Chapter 21 and below, and Figure 21.1).

Management

Immediate

If the baby is hypothyroid, refer to a paediatric endocrinologist and treat with thyroxine 50 μg once daily (10–15 μg/kg/day) for 10 days, then 37.5 μg once daily pending repeat thyroid function tests; however if mild TSH elevation (<30 mU/L) use a smaller starting dose of thyroxine (37.5 μg once daily) immediately and take blood for repeat thyroid function tests.

If hypoplasia or aplasia of the thyroid gland is suspected, arrange a technetium or iodide scan while TSH level is high to confirm the anatomical diagnosis. This is done in most, but not all centres, and treatment should not be delayed in order to perform the scan. Some units do not define the anatomy, but will reassess the need for thyroxine at 3 years.

Medium term

If baby is hypothyroid secondary to thyroid blocking antibodies, change to T3 (which has a short half-life) before stopping and reassessing.

Long term

Monitoring of thyroid function, growth and development, and bone age. Treatment will be lifelong in cases of congenital hypothyroidism.

What to tell parents

Explain the reason for investigations. If thyroid function tests are normal, reassure. If the baby is hypothyroid explain reason and likely length of thyroid treatment (2–3 years if secondary to maternal thyroid blocking antibodies, lifelong if aplasia or hypoplasia of thyroid gland).

USEFUL LINKS

Ontogeny of fetal and neonatal thyroid function: Chapter 25.
Abnormal neonatal thyroid function tests: Chapter 24.

SUPPORT GROUPS

BSPED/Serono booklet: www.bsped.org.uk/patients/serono/15_Hypothyroidism.pdf
Nicks notes: www.bsped.org.uk/patients/nick/CHT.htm
British thyroid foundation: www.btf-thyroid.org

HISTORY OF MATERNAL THYROTOXICOSIS

Clinical presentation

- Maternal thyroid disease – hyperthyroidism flagged up by obstetricians or determined on newborn baby check.
- Maternal thyroid surgery scar.
- History of maternal radioiodine therapy.

The baby is at risk of neonatal thyrotoxicosis or is less commonly hypothyroidism.

Although neonatal thyrotoxicosis is rare, it is associated with a high mortality (12–20%) and needs to be anticipated in cases of maternal thyrotoxicosis; so if necessary, treatment can be instigated promptly.

Approach to the problem

- Maternal history:
  - Current or past medical history of maternal thyrotoxicosis.
  - Family history of thyroiditis.

  - Age of onset (thyrotoxicosis from birth suggests a mutation in the TSH receptor (below) whereas later onset thyrotoxicosis is likely to be Graves' disease producing TSH receptor antibodies).
  - Symptoms of hyper- or hypothyroidism (or both) in mother and duration.
  - Treatment including antithyroid drugs (propylthiouracil or carbimazole, surgery or radioiodine for thyrotoxicosis, and thyroxine for hypothyroidism).
  - The baby is more likely to be affected if the mother has received treatment during pregnancy.
  - Known TSH receptor antibody titres in pregnancy.
  - Antithyroid drugs (propylthiouracil, carbimazole, or methimazole) may cross the placenta and render the fetus hypothyroid. In contrast, thyroxine only crosses the placenta in small amounts. Hence blocking and replacing treatment is not appropriate in pregnancy and minimal doses of antithyroid therapy are used.
  - Anomalies associated with the use of carbimazole (methimazole) in pregnancy are rare but include cutis aplasia, choanal atresia, gastrointestinal anomalies including oesophageal atresia, developmental delay, hearing loss, and dysmorphic facial features.
  - Maternal thyrotoxicosis often remits in the third trimester, and therapy may be discontinued. The use of maternal antithyroid drugs in the third trimester increases the incidence of neonatal thyrotoxicosis.
- Symptoms and signs in fetus:
  - Tachycardia, arrhythmias, hydrops.
  - Hyperkinesis.
  - Intrauterine growth retardation (IUGR).
  - Goitre picked up on fetal ultrasound scan.
  - Advanced bone age may be detected on ultrasound of the lower femoral epiphysis.
  - Preterm delivery.
  - Death in utero.
- Symptoms and signs in neonate:
  - Symptoms may be present at birth or delayed for several days (particularly if the mother is on antithyroid medication at time of delivery).
  - Usually apparent by day 10.
  - Can occur up to 45 days after birth.

- Signs of hyperthyroidism:
  - Goitre.
  - Central nervous system – irritability, jitteriness, and restlessness.
  - Periorbital oedema, lid retraction, and exophthalmos.
  - Cardiovascular system – tachycardia, arrhythmia, and failure.
  - Systemic and pulmonary hypertension.
  - Hypermetabolism – voracious appetite, diarrhoea, failure to thrive, flushing, sweating, and tachypnoea.
  - Persisting acrocyanosis.
  - Hepatosplenomegaly and lymphadenopathy.
  - Thrombocytopenia – petaechiae and bruising.
  - Craniosynostosis, advanced bone age, and microcephaly.
  - Jaundice.
- Signs of hypothyroidism: for more details, see Chapter 24.

Differential diagnosis

Sepsis/heart failure form other causes.

Investigations

- If maternal TSH receptor antibody is titre known, determine whether the risk to the newborn is high or low.
- High risk is a titre approximately 5 times the upper limit of normal.
- However, lower titres may cause thyrotoxicosis.
- If the titre is unknown – assume the baby is at high risk.
- Take cord blood for TSH and fT4 (before the postnatal surge in thyroid hormones).
- Thyroid-stimulating immunoglobulin levels in neonate are predictive of the risk of hyperthyroidism (more so than maternal antibody titres) but the result in the neonate is not usually available in time to be of benefit to inform the neonatal management.
- Record heart rate (looking for tachycardia).

Management of thyrotoxic neonate

- It is not clear whether one should treat biochemical thyrotoxicosis in the absence of symptoms.
- Our personal practice is to treat these patients.

Immediate

- Refer to a paediatric endocrinologist.
- Thionamide:
  - either propylthiouracil 5 mg/kg p.o. every 12 h;
  - or carbimazole 250 micrograms/kg three times daily.
- As thionamides may take 24–48 h to have some effect, consider blocking release of thyroid hormones with iodine, e.g. *Lugol's solution* (5% KI) 1-drop (8 mg iodide) t.d.s.
- Sympathomimetic effects may require *β-blockade*, e.g. propranolol 250–750 μg/kg every 8 h orally to control symptoms (beware side effects – bradycardia, hypotension, and hypoglycaemia).
- *Corticosteroids* may be helpful, e.g. prednisolone 2 mg/kg/day, if symptoms are severe.
- *Sedatives* may be helpful.
- *Heart failure* may require appropriate treatment.
- Thyrotoxicosis has been successfully treated with iodine-containing contrast media – iopanoic acid or sodium ipodate 0.5 mg every 3 days.
- Exchange transfusion has been tried with limited success.

Breast feeding

Breast feeding is *not* contraindicated in mothers treated with thionamides after delivery. Both propylthiouracil and methimazole (to which carbimazole is metabolized) are detected in breast milk but appear not to affect neonatal thyroid function if mothers' dose of carbimazole is $<$15 mg/day and propylthiouracil dose is $<$150 mg/day. However, propylthiouracil is highly protein bound and excreted into the milk in much lower concentrations (0.025–0.077%) compared with methimazole, which has a serum-to-milk ratio of 1. Therefore for mothers on thionamides wishing to breast feed, propylthiouracil would be preferable.

Medium term

- Inform GP.
- Warn parents of the signs of thyrotoxicosis.
- If thyrotoxic, review approximately once or twice weekly initially and measure fT4 and TSH.

- It is easy to over treat the thyrotoxic baby so beware of drug-induced hypothyroidism.
- The duration of thyrotoxicosis is determined by the persistence of maternal thyroid-stimulating immunoglobulins in the baby's blood. Thyrotoxicosis usually remits after 8–20 weeks, and virtually all babies are euthyroid by 48 weeks.
- Wean antithyroid treatment when possible (usually done under the guidance of an endocrinologist).

Long term

- Once thyroid function normal off treatment, no further endocrine review required.
- Follow-up of growth and development may be considered.
- There is a risk of recurrence in future pregnancies.

What to tell parents

- If high risk of neonatal thyrotoxicosis is suspected antenatally, counsel parents before delivery.
- Consider hospital review for first few days, if high risk of neonatal thyrotoxicosis.
- Inform of likely time period for appearance of symptoms and signs, and treatment if required.
- Inform of need for follow-up.
- Breast feeding *not* contraindicated if mother is on thionamide therapy at normal doses.
- There is a risk of recurrence in future pregnancies.
- If family history of persisting thyrotoxicosis in other siblings, consider TSH receptor mutation.

USEFUL LINKS

Investigation and management of babies of mothers with thyroid disease: Chapter 21.
Ontogeny of fetal and neonatal thyroid function: Chapter 25.
Formulary: Appendix 5.

SUPPORT GROUPS

British thyroid foundation: www.btf-thyroid.org/
BSPED/Serono booklet: www.bsped.org.uk/patients/serono/15_Hypothyroidism.pdf

NEONATAL THYROTOXICOSIS IN ABSENCE OF MATERNAL AUTOIMMUNE THYROID DISEASE (RARE)

Clinical presentation

- Family history of TSH receptor mutation (autosomal dominant).
- Symptoms of thyrotoxicosis (above) in the absence of history or evidence of maternal thyroid disease producing thyroid-stimulating antibodies.
- Features consistent with McCune–Albright syndrome. This is polyostotic fibrous dysplasia, café-au-lait skin pigmentation, and autonomous endocrine hyperfunction. The latter includes gonadotrophin-independent precocious puberty, hyperthyroidism, hypercortisolism, pituitary gigantism, or acromegaly. Other features include hypophosphatemia, chronic liver disease, tachycardia, and rarely sudden death. McCune–Albright syndrome is the result of a postzygotic somatic activating mutation in the gene coding for the alpha subunit of the stimulatory G-protein (Gsa).

Approach to the problem

If thyrotoxicosis is anticipated (50% risk in offspring of parent with TSH receptor mutation), thyroid function should be monitored carefully after birth.

For symptoms and signs in fetus and neonate, see above.

Differential diagnosis

Sepsis/heart failure from other causes.

Investigations

- Confirm thyrotoxicosis on thyroid function tests interpreted in relation to normal changes in thyroid function immediately after birth (Appendix 3) (high free thyroxine level, and suppressed TSH level).

- Exclude maternal autoimmune thyroid disease (sample from mother or baby).

Management of thyrotoxic neonate

Immediate

See above – maternal thyroid disease – thyrotoxicosis.

Long term

- Thyrotoxicosis will be permanent and may require more definitive treatment such as surgery or radioiodine therapy.
- Genetic counselling.

What to tell parents

An explanation as to cause of overactive thyroid gland, and necessity for long-term treatment and inheritance required.

If McCune–Albright syndrome is diagnosed, long-term implications will need to be discussed, particularly precocious puberty and skeletal effects which may require orthopaedic input in childhood.

USEFUL LINKS

Normal ranges: Appendix 3.
Investigation and management of babies with thyroid disease: Chapters 21 and 22.
Thyroid anatomy and physiology: Chapter 25.
Formulary: Appendix 5.

SUPPORT GROUPS

McCune–Albright syndrome – contact a family: www.cafamily.org.uk
The Official Parent's Sourcebook on McCune–Albright syndrome: www.icongrouponline.com/health/McCune-Albright_Syndrome.html
McCune–Albright Syndrome Division of the MAGIC Foundation: www.magicfoundation.org

Health Information & Media – Publications McCune–Albright Syndrome: www.nichd.nih.gov/publications/pubs/mccunetoc.htm

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Goitre

Clinical presentation

Goitre.

Approach to the problem

- History of maternal thyroid disease (thyrotoxicosis or hypothyroidism, see Chapter 22).
- Family history of congenital hypothyroidism or thyrotoxicosis.
- Incidental finding either on antenatal ultrasound or postnatal examination.
- Examination for symptoms or signs of hyperthyroidism (see Chapter 22) or hypothyroidism (see Chapter 24).

Differential diagnosis

Hypothyroidism: Likely to be secondary to inborn error of thyroid hormone metabolism.
Thyrotoxicosis: Secondary to maternal thyroid-stimulating immunoglobulins or rarely mutation in thyroid-stimulating hormone (TSH) receptor.

Investigations

- TSH and free thyroxine (fT4).
- Thyroglobulin.

Differential diagnosis

Other neck masses.

Table 23.1 Classification of thyroid dyshormonogenesis, mutations, biochemistry, and imaging.

	Defect	Mutation	Thyroid hormones	Imaging
Iodine transport defect	Defect in iodide uptake at the basolateral membrane which is the rate-limiting step in thyroid hormone synthesis	Defect in sodium/iodide symporter (NIS)	fT4 and fT3 low TSH high TG very high	US: normal or hyperplastic thyroid gland Nucleotide scan: little or no uptake of tracer Salivary-serum ratio <10 (normal >20)
Defective peroxidase activity: Pendred's syndrome: sensorineural deafness, goitre, may be euthyroid if can maintain adequate iodine intake	Impaired ability to organify iodide	AR	fT4 and fT3 normal or low TSH high TG high or normal	US: normal or hyperplastic thyroid Nucleotide scan: rapid uptake of tracer and positive perchlorate test
Defective iodotyrosyl coupling	Defect in iodination of tyrosine residues in thyroglobulin and coupling to make T4 and T3 due to defect in TPO Defect in organification due to impaired NADPH-dependent hydrogen peroxide generation	TPO THOX1 and THOX2 (NADPH oxidases)	fT4 and fT3 normal or low TSH high TG very high	US: normal or hyperplastic thyroid Nucleotide scan: rapid uptake of nucleotide tracer, but no discharge by perchlorate

Absent or defective thyroglobulin	Defects in quantity of TG messenger RNA Defects in transport and incomplete glycosylation		fT4 and fT3 normal or low TSH high or normal TG low Abnormal serum iodoproteins with increased protein-bound thryoxine–iodine ratio	US: normal or hyperplastic thyroid Nucleotide scan: rapid uptake of tracer, but no discharge with perchlorate
Defective iodotyrosine deiodination	Defect in deiodinase activity leads to reduced recycling of iodine and depletion of stores	Pendrin gene (SCL26A4) member of the solute carrier family 26A	fT4 and fT3 normal or low TSH high TG very high Presence of MIT and DIT Elevated serum and urinary iodotyrosines	US: normal or hyperplastic thyroid Nucleotide scan: rapid uptake of nucleotide, inability to deiodinate injected radioactive DIT

TPO: thyroid peroxidase, NADPH: nicotinamide adenosine dinucleotide phosphate, TG: thyroglobulin, AR: autosomal recessive, and US: ultrasound.

Management

Immediate

- If *thyrotoxic*, treat as given in Chapter 22.
- If *hypothyroid*, treat with thyroxine 50 μg once daily (10–15 μg/kg/day) for 10 days then 37.5 μg once daily, pending repeat thyroid function tests.
- However, if mild TSH elevation (<30 mU/L) use smaller starting dose of thyroxine (37.5 μg) (see Appendix 5).

Medium term

- *Thyrotoxicosis* (see Chapter 22).
- *Hypothyroidism:* Investigations for dyshormonogenesis will determine site of enzyme defect:
  - Thyroglobulin levels.
  - Radionucleotide scan with perchlorate discharge test.
  - Specific gene mutations (see Table 23.1).
  - Ultrasound scan will show a normal or hyperplastic gland in all cases.
  - Hearing assessment (Pendred's syndrome associated with sensory neural hearing loss).

Long term

- *Thyrotoxicosis* (see Chapter 22).
- *Dyshormonogenesis*: thyroxine therapy will be required lifelong. Growth, development, thyroid function, and bone age assessment will be required throughout childhood.
- Genetic counselling will be required if dyshormonogenesis or a mutation in the TSH receptor is the cause.

What to tell parents

- Enlarged thyroid gland is secondary to underactive or overactive gland. Further investigations will be required to determine the cause and treatment.
- Once diagnosis made, inheritance pattern (if applicable) will need to be discussed.

USEFUL LINKS

Elevated TSH on Guthrie test: Chapter 24.
Elevated TSH flow chart: Figure 24.1.
Maternal or familial thyroid disease (hyper- and hypothyroid): Chapter 22.

SUPPORT GROUPS

In the UK there is no support group specifically for people with congenital hypothyroidism. An informal network exists within the British Thyroid Foundation:
The British Thyroid Foundation, PO Box 97, Clifford, Wetherby, West Yorks LS23 6XD. The following organization is also helpful:
Child Growth Foundation, 2 Mayfield Avenue, Chiswick, London W4 1PW, Tel: +44 20 8994 7625.

USEFUL INFORMATION FOR PARENTS

Institute of Child Health fact sheet: www.ich.ucl.ac.uk/factsheets/families/F040274/
Serono/Child Growth Foundation booklet: www.bsped.org.uk/patients/serono/15_Hypothyroidism.pdf

FURTHER READING

Beardsall K, Ogilvy-Stuart AL. Congenital hypothyroidism. *Curr Paediatr* 2004; 14: 422–429.
Ogilvy-Stuart AL. Neonatal thyroid disorders. *Arch Dis Child Fetal Neonatal Ed* 2002; 87: F165–F171.

Abnormal neonatal thyroid function tests

ELEVATED TSH ON GUTHRIE TEST (CONGENITAL HYPOTHYROIDISM)

Clinical presentation

- Elevated thyroid-stimulating hormone (TSH) on Guthrie test. Usually informed by direct contact from screening laboratory.

Approach to the problem

- Immediate recall of baby (ideally this should be to a paediatric endocrinologist).

History:

- History of maternal thyroid disease (transplacental antibodies).
- Family history of thyroid disease:
  - Inborn errors are autosomal recessive.
  - About 5% cases of aplasia/hypoplasia are inherited (autosomal recessive or dominant) – suspect if associated birth defects, unexpected neurological symptoms, and developmental delay.
- Drug history including antithyroid drugs (thionamides, e.g. carbimazole or propylthiouracil), iodine-containing medications such as contrast agents, amioderone, and antiseptics.
- Endemic or maternal iodine deficiency.
- Down syndrome.

Signs of hypothyroidism:

- At birth:
  - Post maturity.
  - Large size.
  - Coarse features.

  - Wide posterior fontanelle.
  - Delayed bone age (identifiable on knee X-ray, but this is not usually performed. The lower femoral epiphysis appears ⩾36 weeks' gestation).
  - Umbilical hernia.
  - Goitre.
- First month:
  - Sleepy, placid, and poor feeding.
  - Constipation.
  - Jaundice (conjugated or unconjugated).
  - Umbilical hernia.
  - Thick skin.
  - Poor perfusion: hypothermia, mottling, and peripheral cyanosis.
  - Oedema.
  - Bradycardia and cardiomegaly.
- Late signs:
  - Cretinous appearance.
  - Large tongue.
  - Hoarse cry.
  - Dry skin and hair.
  - Slow relaxation of tendon reflexes.
  - Developmental delay.
  - Growth failure.
  - Infantile proportions.
- Other neurological signs
  - Spasticity with shifting gait.
  - Incoordination with jerky movements.
  - Awkwardness.
  - Coarse tremor.
  - Increased deep tendon reflexes.
  - Cerebellar ataxia.
  - Strabismus and nystagmus.
  - Sensorineural hearing loss.

Differential diagnosis

- Error in Guthrie test.
- Transient hypothyroidism.

- Permanent hypothyroidism.
- Iodine deficiency.

Note: The Guthrie test will not pick up cases of central hypothyroidism as the TSH will not be elevated. It is very rare to have isolated TSH deficiency and babies with a hypothalamic or pituitary cause for hypothyroidism may be picked up because of other features of hypopituitarism (see Chapter 7). In some countries the screening test will utilize T4 measurements and hence central hypothyroidism will be detected.

Investigations

- Free thyroxine (fT4) and TSH.
- Imaging of thyroid gland: thyroid scintigraphy I^{123}, Tc^{99} (while TSH high) with or without ultrasound scan (USS). This will determine if there is a thyroid gland present and its anatomical position. This will aid in the diagnosis of the cause of hypothyroidism (see flow diagram 24.1).
- Thyroglobulin level (undetectable in athyreosis and some inborn errors of metabolism, elevated in others).
- Thyroid-binding globulin.
- TSH receptor immunoglobulins.
- Knee X-ray to assess skeletal maturation if necessary – this will assess the severity of the antenatal hypothyroidism.
- Gene analysis.

Management

Immediate

- Investigate as above.
- *Uncompensated hypothyroidism*, i.e. elevated TSH with low fT4:
  - Treat with thyroxine (10–15 μg/kg/day). For a term baby, start with 50 μg once daily for 10 days, then 37.5 μg once daily pending repeat thyroid function tests.
  - Do not delay treatment if there is difficulty getting a radioisotope scan as every day without treatment may influence intelligent quotient (IQ).
- *Compensated hypothyroidism*, i.e. elevated TSH with a normal fT4: See below.

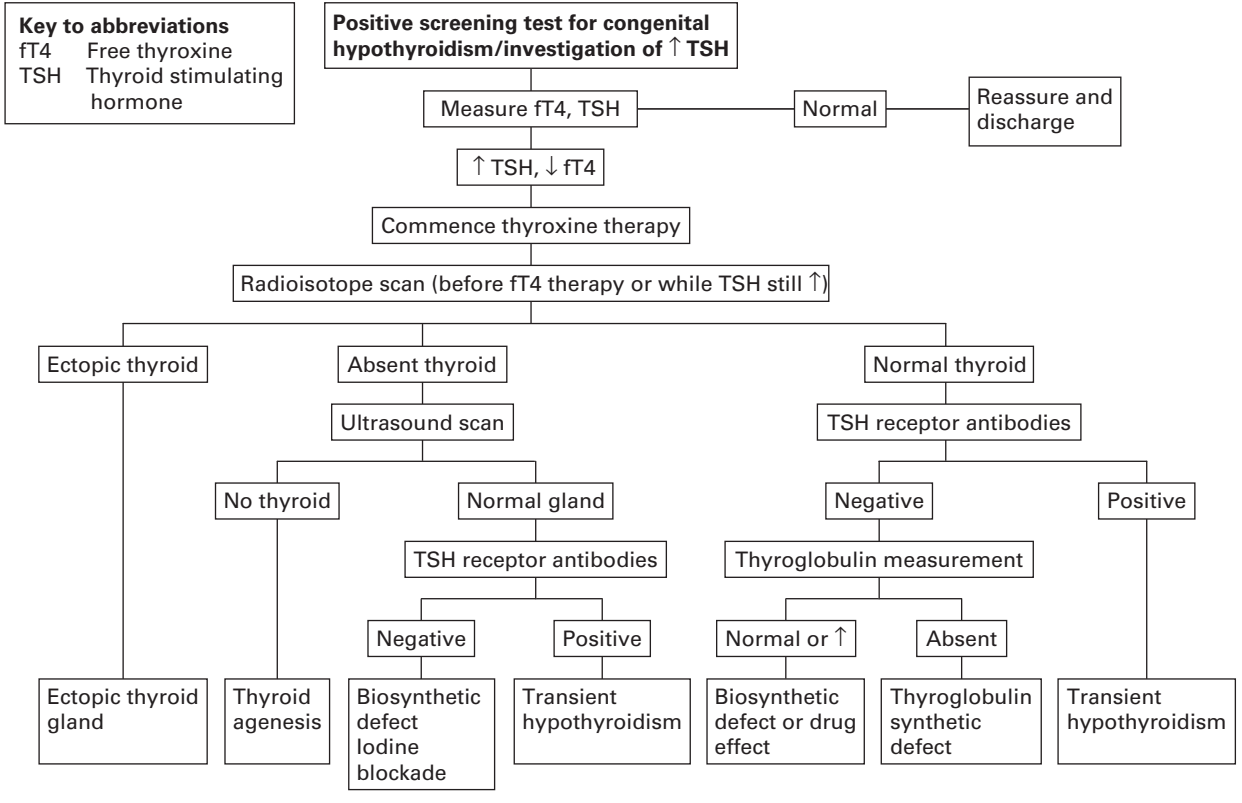

Figure 24.1 Flowchart: Positive screening for congenital hypothyroidism

Medium term

- The adequacy of treatment is monitored by regular measurement of fT4 and TSH (weekly or fortnightly initially, then 1–2 monthly in the first year) by a paediatric endocrinologist.
- Hearing assessment. (Pendred's syndrome is one of the causes of dyshormonogenesis, secondary to defective peroxidase activity. It has an autosomal recessive inheritance. Patients classically have a goitre and sensory neural deafness. A positive perchlorate discharge test suggests the diagnosis. Mutations in the Pendrin gene (SCL26A4) are found in some patients.)
- Reassessment at 2–3 years. If the diagnosis has been confirmed as aplasia, hypoplasia, or ectopia of the thyroid gland or an inborn error of thyroid hormone metabolism, then hypothyroidism will be permanent and reassessment is unnecessary. If transient hypothyroidism is suspected, then reassessment after stopping thyroid hormone replacement therapy at 2–3 years is usually undertaken.

Long term

Assess:

- Growth
- Development
- Thyroid function
- Bone age.

What to tell parents

The screening test has suggested that the thyroid gland is not functioning properly. This requires further investigation and prompt treatment. Treatment is easy and associated with normal outcome. Thyroxine should not be taken with milk.

USEFUL LINK

Ontogeny of fetal and neonatal thyroid function: Chapter 25.

SUPPORT GROUPS

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■ ELEVATED TSH BUT NORMAL THYROXINE LEVEL

■ Clinical presentation

- Usually picked up incidentally if thyroid function is assessed as part of screen for a neonatal problem such as prolonged jaundice.
- May be picked up on Guthrie screen (but TSH usually only mildly elevated and may be below cut-off point on Guthrie screen).

■ Approach to the problem

History:
- History of maternal thyroid disease (transplacental blocking antibodies).
- Family history of autoimmune thyroid disease.
- Drug history including antithyroid drugs (thionamides such as carbimazole or propylthyouracil), iodine-containing medications such as contrast agents, amioderone, and iodine-containing antiseptics;
- Endemic or maternal iodine deficiency;

Signs of hypothyroidism: None.

Differential diagnosis

- Normal (with elevated set point for TSH action, this is probably more common in babies with Down syndrome).
- Compensated hypothyroidism:
  - Transient secondary to maternal antibodies, drugs, iodine deficiency, or excess.
  - Permanent which may progress to uncompensated hypothyroidism.

Investigations

fT4 and TSH.

Management

- There is no consensus on management.
- Some would treat with thyroxine, and reassess at 2–3 year of age.
- Some would follow thyroid function (assessed every few weeks to months) until it either normalizes or uncompensated hypothyroidism becomes apparent.

USEFUL LINK

Ontogeny of fetal and neonatal thyroid function: Chapter 25.

FURTHER READING

Beardsall K, Ogilvy-Stuart AL. Congenital hypothyroidism. *Curr Paediatr* 2004; 14: 422–429.

Cody D, Kumar Y, Ng SM, Didi M, Smith C. The differing outcomes of hyperthyrotrophinaemia. *J Pediatr Endocrinol Metab* 2003; 16: 375–378.

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Fisher DA. Disorders of the thyroid in the newborn and infant. In *Pediatric Endocrinology*, second edition, Ed. Sperling MA. Saunders. pp. 97–110; 161–185.

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Heyerdahl S, Oerbeck B. Congenital hypothyroidism: developmental outcome in relation to levothyroxine treatment variables. *Thyroid* 2003; 13: 1029–1038.

Van Vliet G. Treatment of congenital hypothyroidism. *Lancet* 2001 July 14; 358: 86–87.

Hypothyroxinaemia in preterm babies

Clinical presentation

Usually incidental finding of hypothyroxinaemia in preterm baby when thyroid function assessed. In the UK, most of Europe and areas of the USA, thyroid-stimulating hormone (TSH) rather than thyroxine (T4) is measured as newborn screen for congenital hypothyroidism and hence hypothyroxinaemia without elevated TSH will not be picked up. Thyroid function may be assessed if there is a clinical suspicion of hypothyroidism, but more usually as part of a screen for prolonged jaundice.

Approach to the problem

Exclude primary hypothyroidism (elevated TSH, see Chapter 24) and central hypothyroidism (normal or low TSH, see Chapter 7).

Differential diagnosis

Hypopituitarism.

Investigations

- f T4 and TSH.
- Review blood sugar measurements and electrolytes and if necessary exclude hypopituitarism (see Chapter 7).

Management

Immediate

Although there is an association of low T4 levels, and morbidity and mortality in preterm babies, the data to date do not support thyroid hormone supplementation. Although one study has shown a possible benefit of thyroid hormone supplementation on the neurodevelopment of babies born between 25 and 26 weeks gestation, it also demonstrated a possible detrimental effect of thyroid hormone supplementation on neurodevelopment in babies born between 27 and 29 weeks gestation. Until further data are available, thyroid hormone supplementation in preterm babies either to prevent or to treat hypothyroxinaemia cannot be recommended outwith the context of a clinical trial.

Medium term

Follow thyroid function until normalized.

If hypothyroxinaemia persists with a normal or low TSH level, consider hypopituitarism (see Chapter 7).

What to tell parents

A low thyroid hormone level has been picked up on blood test. It is likely to be a reflection of prematurity and how sick the baby is. There is no evidence that treatment is beneficial and may even be harmful. The thyroid hormone level will need to be followed.

SUPPORT GROUPS

Not applicable.

FURTHER READING

Fisher DA. Disorders of the thyroid in the newborn and infant. In *Pediatric Endocrinology*, second edition, Ed. Sperling MA. Saunders. pp. 97–110, 161–185.

Rapaport R, Rose SR, Freemark M. Hypothroxinaemia in the preterm infant: the benefits and risks of thyroxine treatment. *J Pediatr* 2001; 139: 182–188.

Van Wassenaer AG, Kok JH, de Vijlder JJ, et al. Effects of thyroxine supplementation on neurologic development in infants born at less than 30 weeks' gestation. *New Engl J Med* 1997; 42: 87–92.

■ ONTOGENY OF FETAL AND NEONATAL THYROID FUNCTION

The thyroid gland develops from the fusion of a medial outpouching from the floor of the primitive pharynx, the precursor of the T4-producing follicular cells, and bilateral evaginations of the fourth pharyngeal pouch, which give rise to the parafollicular calcitonin-secreting cells. Development of the thyroid and decent into the neck are dependent on a number of transcription factors. Embryogenesis is complete by 10–12 weeks' gestation.

TSH is present in the fetal pituitary gland from about 10 weeks gestation and present in fetal serum at 12 weeks. T4 and triiodothyronine (T3) are present in the serum from about 12 weeks' gestation. Maternal T4 crosses the placenta throughout pregnancy in limited amounts and in the first trimester plays a critical role in central nervous system development.

From the second trimester, the continued transfer of T4 from mother to fetus remains important for those babies with primary thyroid abnormalities. In babies with a total inability to synthesize T4, cord blood levels are approximately 40% of normal, but neurological development is near normal if replacement therapy is started promptly after birth. In contrast, in situations in which there is severe maternal and fetal hypothyroidism, severe neurological impairment is seen. For example, in regions of endemic iodine deficiency, iodine supplementation must be provided to women before pregnancy or up to the end of the second trimester to protect the fetal brain from the effects of iodine deficiency. Supplementation delayed until the third trimester or neonatal supplementation does not improve neurological outcome.

From mid-gestation until 36 weeks' gestation, hypothalamic expression of thyrotrophin-releasing hormone (TRH), pituitary production of TSH, and thyroidal production of T4 rise steadily. Even when the fetal thyroid gland becomes autonomous, normal thyroid function in the mother may be important for normal neurological development.

About 90% of the thyroid hormone released from the thyroid gland is T4, with slightly less than 10% being T3. However, the bioactivity of thyroid hormone is regulated by enzymatic deiodination in peripheral tissues to either T3 (which is approximately 10 times more potent than T4) or reverse T3 (rT3, which is almost totally biologically inactive). Three iodothyronines are involved in this process. Type I deiodinase (D1) is located in the liver, kidney and thyroid, and is important for T3 production. Type II deiodinase (D2) is found in the brain, pituitary, and in brown adipose tissue. It is important for local T3 production within these tissues. Type III deiodinase (D3) is present in brain, skin, and intestine. T3 and T4 are also inactivated to sulphated analogues by sulphatransferase in fetal liver.

While the levels of T3 are low in the fetus, increasing only at the end of gestation, rT3 levels are high, only decreasing in late gestation and into the neonatal period. This minimizes endogenous thermogenesis and promotes anabolism. High D3 activity in the placenta and in fetal liver and the liver of preterm babies contribute to high rT3 levels. Both D1 and D2 are present from the third trimester, the increase in D1 activity mirrored by a rise in T3 from 30 weeks' gestation. Fetal tissues that are dependent on T3 (particularly the brain) rely on local conversion of T4 to T3 via D2.

In both the preterm baby and the fetus of similar gestation, the thyroid axis is immature, as manifest by reduced hypothalamic TRH production and secretion, immature thyroid gland response to TSH, inefficient capacity of the follicular cell of the thyroid to organify iodine, and a low capacity for converting T4 into active T3.

When a baby is born preterm, the level of T4 is lower than that of term babies and is correlated to the baby's gestational age and birth weight. Levels of TSH and T3 are normal to low, free thyroxine (fT4) concentrations are also low, and thyroglobulin levels are high. TSH and T4 responses to TRH are normal, indicating the site of immaturity is the hypothalamus. The hypothyroxinaemia is in part secondary to reduced levels of thyroid-binding globulin. These data would suggest that the hypothyroxinaemia of prematurity is physiological rather than pathological.

Normally, when a baby is delivered at term, with the fall in ambient temperature, there is a surge in TSH to about 80 mU/mL within about 30 min. This increase stimulates the thyroid gland to release T4 and T3, and these levels rise to well above normal levels. In term babies, the total and fT4 levels fall over the next 4–6 weeks, but levels are still higher among term

babies at age of 6 months than they are in older children and adults. T3 levels gradually reach infancy levels between 2 and 12 weeks of age.

In the preterm infant born after 30 weeks' gestation, there is a similar TSH, T4, and T3 surge, but the magnitude is attenuated. In these babies, T4 and fT4 levels increase over the next 6–8 weeks to levels comparable to those for babies born at term. However, in the preterm baby, born at <30 weeks' gestation and with very low birth weight (VLBW; <1500 g), the TSH and T4 surges are limited or absent, there is often a decrease in T4 levels in the first 1–2 weeks after birth, and transient hypothyroxinaemia is common. The more preterm the baby, the more marked the hypothyroxinaemia. In the majority of cases, the hypothyroxinaemia is associated with a normal TSH level. The severity of the neonatal illness is also reflected in the T4 levels, with the sickest having lowest T4 levels, possibly suggesting non-thyroidal illness (sick euthyroid syndrome), which may be an adaptive response to illness resulting in a depressed metabolic rate.

The reason for preterm hypothyroxinaemia is multifactorial and includes the loss of the maternal T4 contribution, immaturity of the hypothalamic–pituitary–thyroid axis, and immaturity of peripheral tissue deiodination. Iodine balance is negative in the first few weeks after birth in these VLBW babies, suggesting an inability to augment thyroidal iodine uptake and increase T4 secretion. These changes are further compounded among infants born in areas of the world with iodine deficiency due to low levels of environmental iodine, and by the use of iodine-containing antiseptics, drugs, and contrast agents. The relatively low T3 levels are not increased by T4 administration, probably due to low D1 levels in the liver as most of the circulating T3 comes from thyroidal production.

Appendix 1: Calculation of glucose infusion rate

Normal glucose requirements in newborn babies is 5–8 mg/kg/min:

$$\text{Glucose infusion rate (mg/kg/min)} = \frac{\%\ \text{glucose} \times \text{mL/kg/d}}{144}$$

or

$$\text{Glucose infusion rate (mg/kg/min)} = \frac{\%\ \text{glucose} \times \text{mL/h}}{6 \times \text{body weight (kg)}}$$

or

Use figures below:

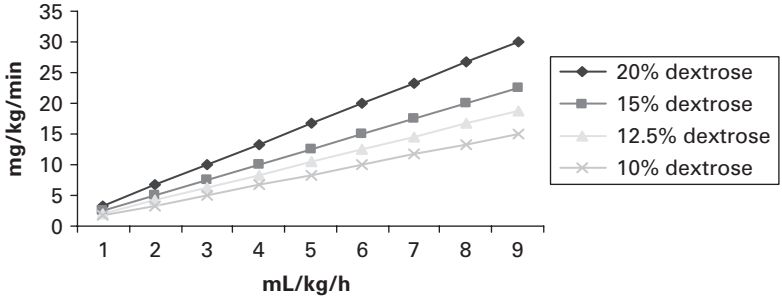

Figure A1.1 IV dextrose equivalents

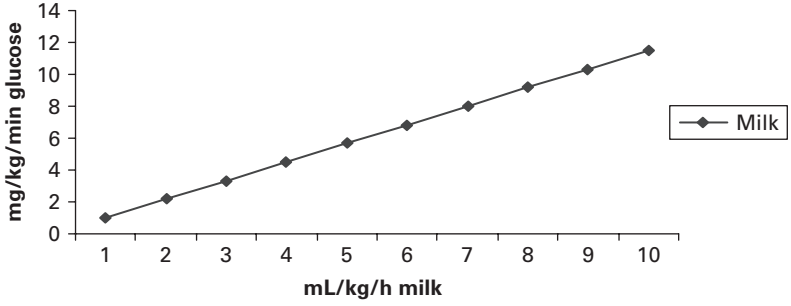

Figure A1.2 Milk feed

To calculate mg/kg/min glucose received:

- *IV fluids*: Read off on *x*-axis volume receiving in mL/kg/h and determine corresponding *y*-axis depending on glucose concentration received.
- *Milk feeds*: Read off on *x*-axis volume of milk receiving in mL/kg/h and determine corresponding *y*-axis reading in mg/kg/min.
- *Combination of milk and IV feeds*: Add the two values together.

Appendix 2: Dynamic tests

In the neonate dynamic testing should not be undertaken without suitable indwelling lines, and under the advice of a paediatric endocrinologist. For pituitary function testing, or corticotrophin-releasing hormone (CRH) test, this means an arterial line for sampling. A short Synacthen test can usually be performed without an arterial line.

Anterior pituitary function tests

- Measurement of random free thyroxine (fT4) and thyroid-stimulating hormone (TSH, after the initial postnatal surge in the first 2 days of life) provides information about pituitary and thyroid function.
- Baseline gonadotrophin levels (leuteinizing hormone, LH; follicle stimulation hormone, FSH) can also be informative, as they should be relatively high in the newborn period.
- Measurement of cortisol and growth hormone (GH) at the time of hypoglycaemia can be helpful, but, unlike older infants and children, the normal neonate may produce a good GH response to hypoglycaemia, but a poor cortisol response.
- Measurement of several (at least 3) random cortisol levels is useful, as cortisol is released in a pulsatile manner and may be low (e.g. 50 nmol/L) in normal infants if measured at the nadir. Timing is not important as diurnal variation does not appear for 8–12 weeks. All samples could be on the same day (and therefore the results could be reported together).
- The time to get the most stressed response in adrenocorticotrophin hormone (ACTH) and cortisol is in the situation where there have been numerous attempts at cannulation of a vein or artery. This is also an important time to obtain a stressed sample before formal pituitary function testing (this can either remove the need to perform a formal test, or add information if the post-glucagon results are equivocal).

- **Only if an infant has had the measurements above, and these suggest pituitary insufficiency, should dynamic pituitary function testing be considered under the supervision of a paediatric endocrinologist.**
- Some clinicians use a short Synacthen test as a measure of ACTH deficiency (chronic deficiency results in a poor cortisol response to ACTH stimulation), but this provides indirect evidence of pituitary function. The test, however, is both easy to perform (does not require additional lines) and safe.
- Anterior pituitary function testing is outlined below. It should only be undertaken under advice and supervision of a paediatric endocrinologist. Secure indwelling lines are mandatory (arterial line for sampling, venous line for resuscitation) and the infant must be monitored closely during the test, i.e. will require a designated nurse and doctor throughout the procedure. The biochemistry laboratory will need prior warning.

Glucagon stimulation test for GH and cortisol secretion

Indication

- Investigation of GH and cortisol deficiency in patients with suspected hypopituitarism.

Preparation

- Fasting: test should take place at least 2 h (maximum 4 h) after the last feed. No feeds during the test.
- Secure venous access (for resuscitation if required).
- Arterial access for sampling (if not possible to secure arterial access, repeated venous sampling will need to be undertaken).
- Ensure intravenous (IV) glucose (2 mL/kg 10%) and hydrocortisone 25 mg available for immediate resuscitation if required.

Procedure

- Draw baseline samples for glucose, GH, and cortisol.
- Give glucagon 15 μg/kg intramuscular (IM).

- (If performing combined pituitary function test, also administer thyrotrophin-releasing hormone (TRH) 7 μg/kg by slow IV injection and gonadotrophin-releasing hormone (GnRH) 2.5 μg/kg IV.)
- Measure glucose every 30 min (it is essential that accurate near patient glucose testing is available) for 180 min.
- Measure GH and cortisol every 30 min for 180 min.
- See suggested test proforma below.

Note: There may be severe reactive hypoglycaemia usually at around 2 h into the test. If this occurs, give 2 mL/kg 10% dextrose IV followed by a dextrose infusion. If the hypoglycaemia is very severe, give 25 mg hydrocortisone IV. Sampling should be continued. Feed at the end of the test and continue to monitor blood sugar until this is stable.

Interpretation

Following glucagon there is a rise in blood glucose and GH (peak at 30 min, declining to baseline by 90 min) and a fall in cortisol. After 90 min blood glucose falls and cortisol rises from 120 to 180 min.

- GH levels should rise to ⩾20 ng/mL.
- Cortisol rises to >600 nmol/L at 180 min in older infants, but the response increases with infant age. Lower responses would be expected in neonates, but precise data are lacking.

TRH test

Indication

- For the investigation of hypothyroidism particularly if a hypothalamic or pituitary cause is suspected. It adds little to basal levels of TSH and T4.

Preparation

- Fasting is not required.

Procedure

- Draw baseline sample for TSH and T4.
- Give TRH 7 μg/kg by *slow* IV injection over 3 min.
- Repeat TSH level at 20 and 60 min.

Note: This test can be used if an isolated problem of the thyroid axis is suspected. It is safe (in older children it can leave a bitter taste in the mouth and cause flushing and nausea especially if injected rapidly). It does not require the insertion of additional IV lines. Where a pituitary problem is suspected, the test is usually combined with other pituitary function testing.

Interpretation

- In a normal response the TSH should rise at 20 min with a fall at 60 min.
  - Basal values 0.5–5.0 mU/L (after the initial neonatal surge).
  - Increment 3–18 mU/L (more than twice the baseline).
- In primary hypothyroidism the basal TSH is elevated and there is an exaggerated TSH response to TRH.
- In pituitary causes of hypothyroidism, there is no change in TSH with TRH.
- In hypothalamic causes of hypothyroidism, there is a delayed TSH response to TRH such that it rises at 20 min and rises further at 60 min.

GnRH test

Indication

- This assesses the pituitary glands ability to secrete gonadotrophins (LH and FSH) in response to GnRH stimulation. It adds little to basal samples but the gonadal axis is most sensitive in the first few months of life before becoming quiescent until the onset of puberty.

Preparation

- Fasting is not required.

Procedure

- Draw baseline sample for LH and FSH.
- Give GnRH 2.5 μg/kg IV.
- Take blood samples for FSH and LH at 20 and 60 min.

Interpretation

- Normal response: The low basal FSH and LH levels increase at 20 min and decease at 60 min.

- It can be difficult to interpret in prepubertal child unless exaggerated which is consistent with primary gonadal failure (when basal gonadotrophins are also usually elevated).
- Pituitary failure would give a flat response but is not diagnostic.
- Hypothalamic abnormalities (e.g. Kallmann syndrome) give a delayed or exaggerated response but are not excluded by a 'normal' response.

Note: This test *cannot* be performed after an human chorionic gonadotrophin (hCG) test as hCG cross-reacts with the assay. There are no side effects.

Suggested Proforma for Combined Anterior Pituitary Function Testing

Baby..... Weight.....

To start at least 2 h (maximum 4 h) after a feed. No feeds during test.

Last feed given at.....

Insertion of venous and arterial cannulae

Following baseline sample (time 0) give:

Glucagon 15 μg/kg IM
TRH 7 μg/kg IV
GnRH 2.5 μg/kg IV

Note time.....

Insert other clock times in table below

Observe for hypoglycaemia, particularly late in test. Record blood glucose on table.

Give 2 mL/kg 10% dextrose if blood sugar falls <2 mmol/L, followed by infusion. Collect sample before glucagon/TRH/GnRH given (GH and cortisol), ideally at time of insertion of the vascular line (because infant will be stressed).

	0 baseline	20 min	30 min	60 min	90 min	120 min	180 min
Time (clock)							
GH	√		√	√	√	√	√
Cortisol	√		√	√	√	√	√
TSH	√	√		√			
LH	√	√		√			
FSH	√	√		√			
Blood glucose	√	√	√	√	√	√	√
Glucose result							
fT4	√						
ACTH*	√						

* On ice.

CRH test

Indication

- For investigation of the ACTH response to CRH to distinguish pituitary from hypothalamic causes of ACTH deficiency.

Preparation

- Fasting is not required.
- The hospital pharmacy may need to order the hCRH, and this sometimes has to come from Germany which can take several days.

Procedure

- Draw baseline sample for cortisol and ACTH.
- Give CRH 1 μg/kg slowly IV.
- Note 100 μg vial of CRH (Ferring) reconstituted with standard diluent provided, and then further diluted with sterile water to obtain concentration of 2 μg/mL.
- Take samples for cortisol and ACTH at 15, 30, and 60 min after CRH.

Interpretation

It is usual to measure both ACTH and cortisol in response to hCRH, but this poses practical difficulties. ACTH has an extremely short half-life and so requires special handling (usually collected on ice), and the assay may not be available in all laboratories. Measurement of cortisol alone in response to hCRH gives an indirect measure of pituitary and adrenal function, as it depends on the integrity of both glands.

CRH testing has been used in preterm infants on a research basis, but the optimal dose of CRH is yet to be established. A dose of 1 μg/kg is most usually used. It has been suggested that a dose of 1 μg/kg should lead to:

- a rise in ACTH of >9 pmol/L at 15 min (or a doubling of ACTH);
- a cortisol level above 360 nmol/L at 60 min; or
- a cortisol rise of 150–200 nmol/L at 30 min.

Side effects – dramatic flushing.

Posterior pituitary function tests

Vasopressin or DDAVP test for investigation of suspected diabetes insipidus

Consider a test dose of vasopressin (or 1-desamino-D-arginine vasopressin, DDAVP) if there is a strong suspicion of diabetes insipidus (DI) (polyuria with an inappropriately low urine osmolality for the blood osmolality) (see Chapter 17 and Appendix 5). This will distinguish between central DI and nephrogenic DI (in the latter there is no response to vasopressin or DDAVP). IV vasopressin may be preferable to DDAVP for the diagnosis because of its shorter half-life, and because it can be given as a continuous IV infusion, which can be titrated against urine output. This is particularly useful in preterm infants. DDAVP can also be used diagnostically, and is available in IV, intranasal, and oral preparations.

The main danger with the administration of vasopressin or DDAVP is acute fluid overload, which can result in cerebral oedema. It is therefore safer to be in a slightly negative fluid balance at the time of the test dose, and to limit fluid input after the test dose is given.

Vasopressin test protocol

- Weigh the infant. Measure urine output prior to the test (baseline).
- Ensure with the laboratory that osmolality results will be available urgently throughout the test.
- Measure paired blood and urine electrolytes, creatinine and osmolality immediately prior to the test.
- Start a continuous IV infusion of aqueous vasopressin starting at 1 mU/kg/h (=0.001 U/kg/h).
- Monitor urine output hourly, and restrict fluid input to insensible losses with previous hours urine losses.
- If there is no reduction in urine output increase vasopressin to 2 mU/kg/h.
- Measure blood electrolytes and paired blood and urine osmolality at least every 3 h.
- If there is still no response in 8–10 h, the test is negative.
- Reweigh the infant at the end of this period. Collect plasma and urine for electrolytes and osmolality.

DDAVP test protocol

Intranasal solution: Start with 0.25 μg 12 hourly, increasing gradually until a satisfactory response is achieved. Wait for the previous dose to wear off (i.e. increased urine output) before administering a further dose. The usual maximum dose is 5–20 μg 12 hourly.
IV or subcutaneous injection: Start with 20 nanograms 12 hourly and increase gradually until a satisfactory response is achieved.

See Appendix 5 for more details.

Interpretation of vasopressin/DDAVP test

The response will be measured by change in urine output (output should decrease with vasopressin or DDAVP in central DI), and in plasma and urine osmolality. In nephrogenic DI there is no response to vasopressin or DDAVP. A suboptimal response to vasopressin may be seen in a primary renal concentrating defect.

In practice the diagnosis of DI is made on the observation of excessive urine output, following which the response to vasopressin or DDAVP may confirm the diagnosis.

■ ADRENAL FUNCTION TESTS

■ Synacthen (ACTH) test

Indication

- In suspected adrenal insufficiency to assess adrenal cortical reserve (measurement of cortisol levels).
- In suspected congenital adrenal hyperplasia (CAH) where a peak 17α-hydroxyprogesterone (17α-OHP) of 100–200 nmol/L is suggestive of 21-hydroxylase deficiency (21-OHD) (higher reference range for preterm babies).

Preparation

- Fasting is not required.

Procedure

- Draw baseline blood sample for cortisol (and 17α-OHP if CAH suspected).
- Give Synacthen 36 μg/kg IM or IV.
- Repeat blood samples for cortisol (and 17α-OHP) at 30 and 60 min.

Interpretation in adrenal function

- Expected cortisol response would be a rise of 200 nmol/L from baseline, or a peak >500 nmol/L.
- Equivocal results are sometimes obtained in the neonatal period.

Interpretation in 21-hydroxylase deficiency

- With a block in cortisol synthesis 17α-OHP level will rise after Synacthen, but there will be little increase in cortisol.

Notes:

- The depot preparations are contraindicated in neonates.
- *Low dose tests*: The standard test involves a supramaximal dose. Much smaller doses have been used to assess the response of the adrenal gland to a more physiological stimulus (doses as low as 500 nanograms/1.73 M^2), usually on a research basis in preterm infants. This has the advantage that it may be more sensitive at picking up subtle abnormalities of adrenal function, but it does make a 'suboptimal' response difficult to interpret. What constitutes a normal response to such a low stimulus in the preterm infant has yet to be determined. One paper suggests that 1 μg/kg dose in a preterm infant should cause a three-fold rise from baseline within 60 min.

GONADAL FUNCTION TESTS

hCG test

Indication

- Determines whether functioning Leydig cells are present (i.e. capable of producing testosterone in response to LH).
- Delineates a block in testosterone biosynthesis from androstenedione (17β-hydroxysteroid dehydrogenase (HSD) deficiency) or conversion of testosterone to dihydrotestosterone (DHT) (5α-reductase deficiency).

Preparation

- None required.

Procedure

- Draw baseline blood samples for:
  - Testosterone.
  - Testosterone precursors: dehydroepiandrostenedione (DHEA) or DHEA sulphate (DHEAS), androstenedione.
  - Testosterone metabolite: DHT.
- Give 1–3 IM injections of high dose hCG (500–1500 IU) at 24 h intervals. At 72 h (or 24 h after the last injection) repeat blood samples for:
  - *Testosterone*.
  - *Testosterone precursors*: DHEA or DHEAS, androstenedione.
  - *Testosterone metabolite*: DHT.

Interpretation

- In the neonatal period, testosterone would be expected to reach adult levels after hCG with a two- to three-fold increase from basal levels.
- If testicular function is poor the response is blunted.
- An absent response with elevated gonadotrophins suggests primary gonadal failure.
- An absent response with elevation of testosterone precursors suggests a block in testosterone biosynthesis.
- A rise in testosterone with no rise in DHT suggests 5α-reductase deficiency.

Note: The recommended dose of hCG and frequency of injections varies widely between centres hence the choice range for recommended dose for this test.

Prolonged hCG test

Indication

- Assessment of testosterone production after 'priming' testes – generally used in patients with bilateral cryptorchidism in whom either gonadotrophin deficiency or anorchia is suspected

Preparation

None required.

Procedure

- Record penile size.
- Check karyotype and gonadotrophins have been assessed.
- Draw baseline blood samples for:
  - Testosterone.
  - Testosterone precursors: dehydroepiandrostenedione (DHEA) or DHEA sulphate (DHEAS), androstenedione.
  - Testosterone metabolite: DHT.
- Give high dose hCG (500–1500 IU) IM twice weekly for three weeks.
- At 24 h after the last injection repeat measurement of testosterone, DHEAS, androstenedione, DHT.
- Clinical response in terms of testicular descent, change in size of phallus and frequency of erections assessed.

Interpretation

- As for hCG test above.
- Assessment of clinical response.

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Appendix 3: Normal ranges

Thyroid hormones

Thyroid-stimulating hormone (TSH):

- Term: cord blood
  - Day 1: 3.0–120 mU/L
  - Day 2: 3.0–30 mU/L
  - Day 7: 3.0–10 mU/L
  - Day 7: 0.3–5 mU/L
- 28–36 weeks gestation:
  - First week: 0.7–27 mU/L

Free thyroxine (fT4):

- Term:
  - Days 1–3: 16.7–48.3 pmol/L
  - Days 4–10: 13.7–28.0 pmol/L
- 29–36 weeks gestation:
  - Days 1–3: 11.3–24 pmol/L
  - Days 4–10: 10.0–30.0 pmol/L
- 25–30 weeks:
  - Birth to 7 days: 6.4–42.5 pmol/L

Free triiodothyronine (fT3):

- Term:
  - Days 1–3: 2.5–9.3 pmol/L
  - Days 4–10: 2.8–5.7 pmol/L
- 29–36 weeks:
  - Days 1–3: 1.2–7.3 pmol/L
  - Days 4–10: 1.2–4.9 pmol/L

Total thyroxine (now largely replaced by fT4):

- Term:
  - Days 1–3: 142–277 nmol/L
  - Weeks 1–4: 106–214 nmol/L

- 30–31 weeks gestation:
  - Days 0.5–3: 94–203 nmol/L
  - Days 3–10: 53–146 nmol/L
- 26–30 weeks gestation:
  - Days 3–4: 33.5–180 nmol/L

Total triiodothyronine (now largely replaced by fT3):

- Term:
  - Days 0.5–3: 0.6–2.5 nmol/L
  - Days 3–28: 1.1–3.5 nmol/L
- 31–37 weeks:
  - Days 0.5–3: 0.8–2.4 nmol/L
  - Days 4–20: 0.3–4.2 nmol/L
- 26–30 weeks:
  - Days 3–4: 0.4–2.0 nmol/L

Thyroxine binding globulin (TBG):

- Term:
  - Cord blood: 270–476 nmol/L
  - Days 1–5: 283–541 nmol/L
- 26–30 weeks:
  - Days 3–4: 154–489 nmol/L

Thyroglobulin:

- Term:
  - Cord blood: 15–101 μg/L
  - Birth to 35 months: 11–92 μg/L

TSH-receptor antibody:

- Normal: <10% inhibition
- 0–1 IU/L (Brahms TRAK assay)
- Very laboratory/assay-dependent, therefore seek local advice

Adrenal steroid hormones

Cortisol: Postnatal surge, falling rapidly over 6 h:

- Term:
  - Day 1: 100–367 nmol/L
  - Day 2: 168–312 nmol/L
  - Day 4: 142–205 nmol/L
  - Day 7: 122–125 nmol/L

  - Day 14: 98 nmol/L
- Preterm:
  - Can be >1000 nmol/L in severely stressed infants
  - Days 1–2: 350–450 nmol/L
  - Day 7: 151–600 nmol/L
  - Day 14: 130–358 nmol/L
  - 1–4 months: 47–191 nmol/L

Corticosteroid-binding globulin (CBG):

- Cord blood: 200–400 nmol/L
  - Day 21: 300–600 nmol/L

Dehydroepiandrosterone sulphate (DHEAS): Highest on the first day of life. Declines rapidly over first 2 weeks of life in term infants. In preterm infants higher at lower gestational ages:

- Term:
  - Day 1: 3.6 μmol/L
  - Days 2–3: 1.7–2.1 μmol/L
  - Days 4–30: 0.7–0.8 μmol/L
  - Days 30–90: 0.3–0.4 μmol/L
- Preterm:
  - Day 1: 3.9–10 μmol/L
  - Days 2–7: 1.6–3.5 μmol/L
  - Days 4–30: 1–1.6 μmol/L
  - Days 30–90: 0.6–0.8 μmol/L

17α-hydroxy progesterone (17α-OHP): Higher in preterm infants, particularly when stressed, and falls with increasing postnatal age:

- Term:
  - <20 nmol/L for term babies on day 3

Can be higher in stressed infants, but the sample should be repeated:

- Preterm:
  - First 2 weeks: 71–112 nmol/L
  - Sixth week: 11.5–28.5 nmol/L
  - 4 months: 6–6.9 nmol/L

Androstenedione: Falls rapidly in the first week of life. Risk of assay crossreactivity with other neonatal steroids:

- Term:
  - 0.7–10.1 nmol/L
  - 4 weeks: 1.64–1.68 nmol/L
  - 8 weeks: 1.34 nmol/L

- Preterm:
  - 1.6–12.4 nmol/L

11-deoxycortisol:

- 2 h: 23.4 nmol/L
- 6–24 h: 9.6–12.1 nmol/L
- Day 4: 8.5 nmol/L
- Day 7: 5.3 nmol/L

Aldosterone (see Renal below).

Pituitary hormones

Adrenocorticotrophic hormone (ACTH): There is a postnatal surge in adrenocorticotrophic hormone (ACTH), which is of short duration (hours). ACTH then rises with increasing postnatal age:

- Term:
  - 2 h: 36 pmol/L
  - 6 h: 22 pmol/L
  - 24 h: 13 pmol/L
- Preterm:
  - 2 h: 45–135 pmol/L
  - Day 7: 3.1–9.8 pmol/L
  - Day 14: 3.9–13.1 pmol/L

Growth hormone (GH):

  - Day 1: 5–53 μg/L
  - 1 week: 5–27 μg/L
- >20 μg/L in response to hypoglycaemia or stimulation.

Thyroid stimulating hormone (see Thyroid hormones above).

Luteinizing hormone (LH): Levels increase between 2 weeks and 3 months after birth, then decline to prepubertal values by the end of the first year. hCG is measured in the assay in the first 3 days of life:

- Boys:
  - Cord blood: 0.04–2.6 IU/L
  - 2 weeks: 4.85–10.02 IU/L
  - 1–18 months: 0.04–3.01 IU/L
- Girls:
  - Cord blood: 0.04–2.60 IU/L
  - 2 weeks: 0.29–7.91 IU/L
  - 1–18 months: 0.02–1.77 IU/L

Follicle-stimulating hormone (FSH): Levels in boys decline to prepubertal levels by the end of the first year. Levels fall to prepubertal levels in girls by the end of the second year:

- Boys:
  - 2 weeks: 1.22–5.19 IU/L
  - 1–18 months: 0.19–2.97 IU/L
- Girls:
  - 2 weeks: 2.08–30.45 IU/L
  - 1–18 months: 1.14–14.35

Prolactin:

- Days 1–7: 0.3–4.95 μg/L
- Weeks 1–8 levels fall to pubertal levels (boys: 0.03–0.18 μg/L, girls: 0.03–0.24 μg/L)

Gonadal hormones

Oestradiol: Levels are very elevated at birth:

- Fall to prepubertal levels during first week (<36.7 pmol/L).
- Between 30 and 60 days (boys): levels increase to 36.7–117 pmol/L, then decline to <55 pmol/L by 6 months.
- Between 30 and 60 days (girls): levels increase to 18–184 pmol/L, then decline to <55 pmol/L during the first year.

Testosterone: Due to the presence of steroids in the perinatal period that may cross-react with assay antibodies, the assay has to be highly specific, otherwise falsely elevated results are produced:

- Term male:
  - Newborn: 2.6–13.9 nmol/L
  - During first week: levels decrease rapidly to 0.7–1.7 nmol/L
  - Between 20 and 60 days: levels increase to 2.1–13.9 nmol/L
  - By 7 months: levels fall to prepubertal range to 0.1–0.3 nmol/L
- Term female:
  - Newborn: 0.7–2.2 nmol/L
  - During first month: levels fall to <0.3 nmol/L until puberty
- 31–35 weeks gestation:
  - Day 4: 1.3–6.9 nmol/L (male)
  - Day 4: 0.2–0.8 nmol/L (female)
- 26–28 weeks gestation:
  - Day 4: 2.0–4.3 nmol/L (male)

  - Day 4: 0.2–0.6 nmol/L (female)

Dihydrotestosterone (DHT):

- Term male:
  - Newborn: 172–2066 pmol/L
  - During first week: levels fall rapidly
  - Between 30 and 60 days: levels increase to 413–2927 pmol/L
  - By 7 months: levels fall to prepubertal levels (<175 pmol/L).
- Term female:
  - Newborn: <68.9–515.5 pmol/L
  - During first month: levels fall to <103 pmol/L until puberty.
- Preterm male: 344.3–1825 pmol/L
- Preterm female: 68.9–447.7 pmol/L

Anti-Müllerian hormone (Müllerian inhibiting substance) (AMH):

- Term male:
  - Day 1: 370 pmol/L
  - Day 2: 400 pmol/L
  - Day 10: 430 pmol/L
  - Day 15: 500 pmol/L
  - Day 20: 520 pmol/L
  - Day 30: 700 pmol/L

Inhibin B (males only):

- 220–360 pg/mL in the first month of life

Growth axis

Growth hormone (see Pituitary hormones above).

IGF-I:

- Term:
  - Birth to 2 months: 2–14.2 nmol/L
- Preterm:
  - Birth: 3–12.2 nmol/L
  - 2 months: 3–21.3 nmol/L

IGFBP-3:

- Term:
  - Birth: 7–17.5 nmol/L
  - Days 7–30: 17.5–59.5 nmol/L
- Preterm:
  - Days 0–30: 10.5–49 nmol/L

Glucose homoeostasis

Insulin:

- MUST be interpreted with simultaneous plasma glucose level
- Usually 2.8–13.5 μU/L depending on glucose level
- May be higher in preterm babies
- Should be immeasurable with hypoglycaemia

C-peptide:

- Cord blood: 0.10–0.49 nmol/L
- 36–60 h: 0.03–0.24 nmol/L
- Children (fasting): 0.13–0.73 nmol/L

Calcium homoeostasis

25-Hydroxyvitamin D:

- Newborn: 12.5–104.8 nmol/L
- Children and adults: 25–137.3 nmol/L

1,25-Dihydroxyvitamin D:

- Newborn: 0–30 days: 19.2–172.8 pmol/L
- Infants and children: 31 days to 17 years: 36–216 pmol/L

Parathyroid hormone, mid-region:

- Newborn: PTH levels increase up to 2.5 times the adult normal range in the first few days of life, then fall to within the adult normal range by about 6 months
- Children and adults: 1.05–8.42 pmol/L (with normal calcium)

Parathyroid hormone, intact (IPTH) (includes calcium):

- Children and adults <1.05–6.84 pmol/L

Renal

Aldosterone (serum):

- Term:
  - 3 days: 194–5105 pmol/L
  - 1 week: 139–4856 pmol/L
  - 1–12 months: 139–2497 pmol/L
- 26–28 weeks gestation:
  - Day 4: 139–17619 pmol/L

- 31–35 weeks:
  - Day 4: 527–3912 pmol/L

Aldosterone (urine):

- Newborn:
  - 1387–13874 nmol/day
  - 6278–43946 nmol/mmol creatinine

Plasma renin activity: Plasma renin activity in newborns is elevated and highly variable. Premature infants generally exhibit substantially higher values ranging from 1100–16,700 ng/dL/h:

- Term:
  - 1–7 days: 55.6–972.3 ng/L/s
  - 31 days to 11 months: 65.3–1027.9 ng/L/s
- Preterm:
  - 1–7 days: 305.6–4639.3 ng/L/s

Osmolality:

- 275–295 mosm/kg
- Osmolality (mosm/kg) = 1.86 (Na + K) + Glu + urea + 10 (all in mmol).

Tubular reabsorption of phosphate (TRP):

$$\text{TRP} = 1 - \frac{\text{Urine phosphate (mmol/L)}}{\text{Urine creatinine (mmol/L)}} \times \frac{\text{Plasma creatinine (}\mu\text{mol/L)}}{\text{Plasma phosphate (mmol/L)}} \times \frac{1}{10}$$

$$\text{TRP}(\%) = (1 - \text{FEP}) \times 100$$

where FEP (fractional excretion of phosphate) = (Urine phosphate × Plasma creatinine)/(Plasma phosphate × Urine creatinine). Normal values of TRP = 85–95%

TRP is influenced by changes in glomerular filtration rate (GFR) as well as dietary phosphate intake. A more reliable measure is Tubular Maximum of phosphate/GFR (TMP/GFR). This can be derived from RTP and plasma phosphorus using a normogram.

Fractional excretion of sodium (FeNa):

$$\text{FeNa} = \frac{\text{Urine sodium (mmol/L)}}{\text{Urine creatinine (mmol/L)}} \times \frac{\text{Plasma creatinine (}\mu\text{mol/L)}}{\text{Plasma sodium (mmol/L)}} \times \frac{1}{10}$$

FeNa should be <0.01 (or $<1\%$).

If oliguric, a low FeNa suggests there is not excessive ADH action and the infant may be sodium and water depleted.

If oliguric with high FeNa suggests excess exogenous or endogenous ADH.

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Appendix 4: Biochemistry Samples

Information on type of sample, volume required, and likely time until result available.

Sample	What sort of sample	Volume blood required (mL)	Approximate time until result available	Special transport instructions
Blood				
fT4	Serum	25	Next working day	
fT3	Serum	50	Weekly	
TSH	Serum	200	Next working day	
Total T4	Serum	50	1–3 week	
Thyroglobulin	Serum	2000	4–6 weeks	
Thyroid-binding globulin	Serum	2500	4–6 weeks	
TSH-receptor antibody	Serum	1000–3000	3–4 weeks	
IGF-I	Serum	13	2 weeks	
IGFBP-3			1 month	
GH	Serum	25	Up 2 weeks	
LH	Serum	25	Next working day	
FSH	Serum	100	Next working day	
ACTH	EDTA on ice	400	3–4 weeks	Rush to laboratory
Prolactin	Serum	25	Next working day	
ADH	Lithium heparin on ice	2000	4–6 weeks	Rarely indicated
Oestradiol	Serum	25	1 day	
Testosterone	Serum	100	1 week	

Dihydrotestosterone	Serum	1000–2000	4–6 weeks	
AMH			Not available in UK	
Inhibin B			Not available in UK	
Renin	EDTA or lithium heparin	400	3–4 weeks	*Not* on ice Rush to laboratory
Aldosterone	Serum/lithium heparin	450	3–4 weeks	
Cortisol	Serum	20	Twice weekly	Call laboratory for urgent analysis
17-OHP	Serum	250	3–4 weeks	Call laboratory for urgent analysis (takes 2 days)
11-deoxycortisol	Serum	2000	4–6 weeks	Not always available
DHEAS	Serum	5	3–4 weeks	
Androstenedione	Serum	250	3–4 weeks	
PTH	Serum or EDTA	150	1 week	To laboratory in <2 h
25 Vitamin D	Serum	100	2 weeks	
1,25 Vitamin D	Serum on ice	2000	4–6 weeks	Rarely performed
Insulin	Lithium heparin on ice	25	1 week	Call laboratory for urgent analysis
C-peptide	Lithium heparin on ice	25	1 week	
Free fatty acids				Contact laboratory
Ketones			2 weeks	
Ammonia	EDTA on ice		Next working day	
Lactate	Fluoride	200	Next working day	
β-hydroxybuterate				Contact laboratory
Amino acids	Lithium heparin	1000	1 week	
Pyruvate	Acid ppt at bedside		Contact laboratory	Rarely required

(*Continued*)

Sample	What sort of sample	Volume blood required (mL)	Approximate time until result available	Special transport instructions
Acetoacetate	Acid ppt at bedside		Contact laboratory	Rarely required
Urate	Serum	200	Next working day	
Lipid profile	Serum	500	Next working day	
Free + acylcarnitine	Blood spot	Blood spot	1 week (may take longer)	
Glucagon	Lithium heparin + trasylol	10,000	4–6 weeks	
Urine				
Urinary steroid profile	Plain	40,000	4–6 weeks	
Ketones	Plain	Ward analysis	Instant	
Reducing substances	Plain	500	Within 1 day	
Amino acids	Plain	5000	1 week	
Organic acids	Plain	5000	1 week	

This table provides some guidance to the volume, preparation, and likely turnaround time for samples taken in neonatal endocrinology. These however will vary to some extent depending on the laboratory methods, and whether the assays are available in-house or will need to be sent away.

Appendix 5: Formulary

ACTH (Synacthen) (Tetracosactrin) (Tetracosacide)	Short Synacthen test: 0–6 months – 36 μg/kg intravenous (IV) or intramuscular (IM). Maximum dose: 125 μg. Depot preparations contraindicated in neonates (see protocol in Appendix 2).
Alfacalcidol (1α-hydroxycholecalciferol)	20–100 ng/kg/dose every 24 h (up to 2 μg/kg/dose/24 h may be required).
Calcium gluconate Calcium gluconate 10% solution contains 0.22 mmol of calcium per millilitres	*For maintenance treatment of hypocalcaemia* 2.5 mL/kg (0.55 mmol/kg calcium) of 10% solution given continuously or in divided doses over 24 h. Maximum rate of administration for continuous infusion is 0.022 mmol/min calcium. Never add to solutions with bicarbonate or phosphate. Beware: extravasation can cause tissue necrosis. If this occurs seek plastic surgery advice. *Management of severe hyperkalaemia* Urgent IV correction for arrhythmias/emergencies. 0.5 mL/kg (maximum 2 mL/kg) of 10% i.e. 0.11 mmol/kg calcium solution slowly IV over 5–10 min with ECG monitoring and preferably via a central line. Can be repeated but watch for cardiotoxicity/asystole.
Calcium resonium	125–250 mg/kg repeated as necessary 6–8 hourly rectally. Mix powder with lubricating jelly before administering. Can cause rectal ulceration. Irrigate colon to remove resin after 6–12 h. Do not give orally.

(*Continued*)

Carbimazole	Treatment of thyrotoxicosis: 250 μg/kg 3 times daily. Higher initial doses of up to 1 mg/kg are occasionally required in thyrotoxic crisis.
Chlorothiazide	3.5–5 mg/kg 12 hourly with diazoxide. Chlorothiazide helps to counteract the fluid retention caused by diazoxide and has additional effects on suppression of insulin secretion. As with any diuretic, electrolytes should be monitored.
Corticotrophin-releasing hormone (CRH) corticorelin	CRH test: 1 μg/kg slowly IV. Refer to test protocol (see Appendix 2).
DDAVP (desmopressin)	DDAVP can be used for the diagnosis of diabetes insipidus, but the shorter half-life of vasopressin may make it preferable for this test (see Appendix 2). *Management of Diabetes Insipidus*: Intranasal solution: Start with 0.25 μg 12 hourly, increased gradually until a satisfactory response is achieved. The usual maximum is 5–20 μg 12 hourly. Oral dose: 1–4 μg 2–3 times daily. IV, or subcutaneous (SC) injection: Start with 20 ng 12 hourly and increase gradually until a satisfactory response is achieved. Both injection solution and intranasal solution may be diluted 1:10 with 0.9% sodium chloride immediately before use.
Diazoxide	5–20 mg/kg/day* orally or IV (avoid IV if possible) divided into three doses for intractable hypoglycaemia. Always with chlorothiazide. Diazoxide can also be given IV (but an alternative diuretic will be required). Avoid excessive fluid intake during diazoxide therapy. While on IV fluids, the total fluid intake should be restricted to 120 mL/kg/day, and electrolytes and body weight monitored daily. Monitor BP (intermittently) on diazoxide therapy. Side effects: fluid retention, hypertrichosis (chronic use), hyperuricaemia, hypotension, rarely leucopenia, and thrombocytopenia. Blood urate should also be monitored with chronic diazoxide use. *If there is no response to 15 mg/kg/day, then increasing the dose is pointless.

(*Continued*)

Dihydrotestosterone gel	Percutaneous: 0.2–0.3 mg/kg once daily for 3–4 months.
Fludrocortisone	Congenital adrenal hyperplasia: 25 μg b.d., increase to 50 μg b.d. if plasma sodium remains low, and can be increased to 100 μg b.d. in resistant cases. Monitor for hypokalaemia, particularly on larger doses. Must be given in crushed tablet form (100 μg tablets). In addition it is essential to give salt supplements (5 mmol/kg/day).
Glucagon	*Hypoglycaemia in the absence of IV access* Bolus: 100–200 μg/kg/dose SC or IM. For babies >4 weeks of age dose of 500 μg has been used. *In combination with Octreotide for PHHI* Continuous IV infusion 1–20 μg/kg/h (maximum 50 μg/kg/h) may be effective. *Hypotension secondary to maternal Labetalol* 300 μg/kg IV. Repeat dosing or infusion is usually required. Dose may be up to 10 times that required to treat hypoglycaemia. Glucagon infusion can cause hypokalaemia, vomiting, increased myocardial contractility, and increases growth hormone. *For testing of anterior pituitary function* 15 μg/kg IM (see protocol in Appendix 2).
Gonadotrophin-releasing hormone (GnRH)	For testing of anterior pituitary function 2.5 μg/kg IV (see protocol in Appendix 2).
Growth hormone	For management of growth hormone deficiency associated with hypoglycaemia and to prevent growth failure (a paediatric endocrinologist should decide whether use is appropriate). 0.2 mg SC (this is the lowest practical dose with current devices).
Human chorionic gonadotrophin (hCG)	For testing of testicular function (see Appendix 2 for protocol).

(*Continued*)

	Standard test 500–1500 IU IM daily for 3 days. *Prolonged test 500–1500 IU IM twice weekly for 3 weeks.*
Hydrocortisone	*Addisonian crisis*: IV bolus of 25 mg (often with glucose and saline given over a minimum of 3–10 min). Repeat 4–6 hourly in the first 24 h. Alternatively a continuous infusion of 100 mg/m^2/day can be given following the initial IV bolus. *Hypotension*: 2 mg/kg IV followed by 1 mg/kg every 8–12 h. Withdraw over 2–4 days. *Congenital adrenal hyperplasia*: 18–21mg/m^2/day For term infant initial dose 3.75–5 mg/day, divided into 3 doses. Pre-prepared oral solutions are dangerously unreliable, but crushed tablets can be used e.g. 2.5 mg in crushed tablet form (1/4 of 10 mg tablet), or 2.5 mg buccal tablets (Corlan pellets), which can be halved to give 1.25 mg (2.5 mg am, 1.25 mg afternoon, 1.25 mg nocte). Although pre-prepared solutions are not stable, hydrocortisone can be given by dissolving a 10 mg tablet in water immediately prior to administration, and giving a precise volume e.g. 2 mg = 0.2 mL if 10 mg dissolved in 1 mL. If the infant is at all unwell a higher dose (×2–3) should be used initially. Treatment should always be under the supervision of a paediatric endocrinologist. *Congenital adrenal hypoplasia*: 12–15 mg/m^2/day. In term infant give 2.5–4 mg/day divided into 3 doses as maintenance. Higher doses may be required. *Hypopituitarism*: 8–10 mg/m^2/day. In practice, dose the same as for congenital adrenal hypoplasia. *Surgical cover*: if on long-term steroids: 2.5 mg before and 6 hourly after surgery for 24–48 h. *Emergency management for infants with adrenal insufficiency at home* 25 mg IM.

(*Continued*)

Hypostop	1 mL/kg/dose.
Insulin	*For hyperglycaemia* with significant glycosuria No more than 0.05 IU/kg/h is usually needed. Add 25 IU/kg to 50 mLs IV solution, then 0.2 mLs/h = 0.1 IU/kg/h. Writing up a sliding scale may help; e.g.: Blood glucose >20 mmol/L Insulin at 0.2 mL/h (0.1 IU/kg/h) Blood glucose 8–20 mmol/L Insulin at 0.1 mL/h (0.05 IU/kg/h) Blood glucose <8 mmol/L Stop insulin infusion *For hyperkalaemia* Add 5 IU insulin to 50 mL of 20% dextrose and start at 1 mL/kg/h (0.2 g/kg/h dextrose and 0.1 IU/kg/h insulin). Infuse to keep blood glucose within the normal range.
Iodide	Lugols solution (5% potassium iodide). One drop t.d.s. (about 8 mg iodide/drop).
Magnesium sulphate *Note*: Magnesium sulphate 50% w/v injection contains 500 mg/mL or 2 mmol/mL of magnesium	Hypomagnesaemia: 100 mg/kg/dose (0.2 mL/kg of 50% w/v solution = 0.4 mmol/kg magnesium) as slow IV infusion over 30 min every 6–12 h. Commonly used regimen: give one dose of 100 mg/kg followed 12 h later by another dose of 100 mg/kg.
Nifedipine	0.25–2.5 mg/kg/day divided into 4 or 6 hourly regimen, start at lowest dose and work up as blood pressure (BP) tolerates. In practice it is almost impossible to administer <1 mg. If there is no arterial line, then measure BP before and at 15-min intervals after each dose, continuing for at least an hour.
Octreotide (analogue of somatostatin)	(100 μg somatostatin = 10 μg octreotide). *For management of hyperinsulinism* Somatostatin (octreotide) 5–25 μg/kg/day as a continuous infusion either IV or SC (start on low dose as causes vasoconctriction in the gut) usually accompanied by IV glucagon infusion 1–20 μg/kg/h. Intermittent SC dose 2–5 μg/kg every 6–8 h (up to 7 μg/kg every 4 h).

(*Continued*)

	Somatostatin infusion must be under ECG monitoring. Somatostatin also suppresses GH, TSH, ACTH, and can cause steatorrhoea, cholelithiasis, and abdominal distension. Rarely can cause alteration in liver function tests.
Pamidronate	0.5–2 mg/kg as an IV infusion. Monitor renal function, electrolytes, liver function, blood count, and BP.
Phosphate *Check phosphate preparation for concentration before prescribing* *Note that sodium and potassium phosphate injections contain different amounts of phosphate per millilitre.	1. Sodium glycerophosphate solution, 21.6% w/v, 10 mL contains equivalent of 20 mmol of sodium ions and 10 mmol of phosphate ions. Therefore 1 mL contains 1 mmol of phosphate. 2. Dipotassium hydrogen phosphate: 17.42% 1 mL contains 2 mmol K and *1 mmol PO_4 3. Sodium phosphate: 17.91% 1 mL contains 1 mmol Na and *0.5 mmol PO_4 Recommendations regarding infusion: Aim to give about 0.5–1 mmol PO_4/kg in 12 h. Maximum rate of potassium phosphate infusion is 0.5 mmol potassium/kg/h. Maximum rate of administration of phosphate for both sodium and potassium phosphate is 0.05 mmol/kg/h. IV phosphate should only be given through a cen tral venous catheter. May cause hypocalcaemia.
Potassium chloride	Administer according to serum potassium levels. Standard maintenance requirement is 2 mmol/kg/24 h. Maximum concentration for peripheral administration is 4 mmol/100 mL (40 mmol/1000 mL). Higher concentrations may be used centrally. Maximum rate of administration via peripheral line 0.2 mmol/kg/h. Maximum rate of administration via central line 0.5 mmol/kg/h with ECG monitoring.
Prednisolone	2 mg/kg/day.
Propranolol	*Treatment of sympathomimetic symptoms of thyrotoxicosis* 250–750 μg/kg 8 hourly orally.

(*Continued*)

	20–50 μg/kg IV over 10 min every 6–8 h (beware hypoglycaemia).
Propylthiouracil	Treatment of thyrotoxicosis. 5 mg/kg orally every 12 h (occasionally up to 10 mg/kg is required).
Salbutamol	IV for hyperkalaemia 4 μg/kg over 10 min. Dilute 200 μg/kg salbutamol to 50 mL with dextrose to give a solution containing 4 μg/kg/mL. Infuse 1 mL over 10 min.
Sodium bicarbonate	Millimols of $NaHCO_3$ needed for half correction: $\text{preterm} = \frac{0.6 \times \text{wt} \times \text{BE}}{2}$ $\text{term} = \frac{0.4 \times \text{wt} \times \text{BE}}{2}$ 4.2% is the preferred solution. Give no faster than 1 mmol/min IV. In emergency give 2 mmol/kg. *Note*: The 8.4% solution contains 1 mmol $NaHCO_3$ per millilitre and the 4.2% solution 0.5 mmol $NaHCO_3$/per millilitre.
Synacthen	See ACTH.
Testosterone enanthate	*For management of micropenis*: 25 mg testosterone once per month, IM injection for 3 months.
Thyrotrophin-releasing hormone (TRH)	7 μg/kg IV over 3 min for TRH test (see Appendix 2).
Thyroxine (Levothyroxine)	*Term baby* Give 50 μg once daily (10–15 μg/kg/day) for 10 days then 37.5 μg once daily pending repeat thyroid function tests. However if mild TSH elevation (<30 mU/L) use smaller starting dose of thyroxine (37.5 μg). Thyroxine should be given as crushed tablet, with a little milk (not soya) or water and should not be added to the bottle of milk. Dose should be repeated if the baby vomits immediately afterwards. Suspension is available, but is unstable and has a shelf-life of around a week.

(*Continued*)

	Preterm baby 10 μg/kg once daily by mouth.
Triiodothyronine (T3)	Start with 1 μg/kg 12 hourly IV. Total daily dose about 4 μg/kg.
Vasopressin	For diagnosis and early management of diabetes insipidus. Aqueous vasopressin by continuous IV infusion. Half-life approximately 30 min, with initial duration of action 2–3 h. Start at 1 mU/kg/h (=0.001 IU/kg/h). Usual dose range 0.5–2.0 mU/kg/h. Solution can be diluted in normal saline.
Vitamin D	For treatment of deficiency/severe or persisting hypocalcaemia: 5–50 μg/day (200–2000 IU).

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