Male Infertility

Gastro-oesophageal Reflux in Infancy

Hyperlipidaemia

Antepartum Haemorrhage

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Breast-feeding is the best source of infant nutrition. Good maternal nutrition is important for preparation and maintenance of breast-feeding. When infant formula are to be used, a mother should be aware of the negative effect on breast-feeding along with the financial and social implications of formula feeding. The difficulty of weaning the child from breast milk and the care that must be taken to prevent partial formula feeding from interrupting the lactation. A health care professional should be consulted before initiating formula feeding.

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Paediatrics

181 Gastro-oesophageal Reflux in Infancy

Gastro-oesophageal reflux is very common in infancy. This review summarizes the approach to infants with symptoms and signs of reflux, differential diagnosis, investigations with their limitations, and non-pharmacological, pharmacological and surgical treatment.

Hemant Bhavsar, Mick Cullen, R Mark Beattie

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193 Antepartum Haemorrhage

Antepartum haemorrhage is a relatively common entity with potentially serious implications for the mother and the fetus. This review concentrates on two cases of antepartum haemorrhage due to placental abruption and morbidly adherent placenta, and highlights the predisposing factors, management and treatment according to evidence-based practice and the most recent guidelines.

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213 Male Infertility
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VCY Lee, EHY Ng, PC Ho
8th International Symposium on Respiratory Diseases & ATS in China Forum 2012
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GYNAECOLOGY

Long-acting reversible contraception in the US

The US has a particularly high rate of unintended pregnancy (about half of all pregnancies), leading to many abortions and adverse consequences for women’s health. About half of the unintended pregnancies are a result of failure of contraception and half a result of failure to use contraception. The annual failure rate for oral contraceptive pills is about 9% overall and higher in teenagers and other high-risk groups. Long-acting reversible contraceptive methods, including intrauterine devices (IUDs) and subdermal implants, have failure rates of < 1%. A low uptake of IUDs may partially explain the high rate of unintended pregnancy in the US. Now, a US prospective cohort study has underlined the effectiveness of long-acting reversible contraception.

In St Louis, Missouri, a total of 9,256 women aged 14–45 at risk of unintended pregnancy were recruited between August 2007 and September 2011. They were provided with a contraceptive method of their choice free of cost with an emphasis on the advantages of long-acting reversible contraception. A total of 7,486 participants were included in the analysis. There were 334 unintended pregnancies. The contraceptive failure rate was 4.55 per 100 person-years with pills, patch, or ring, and 0.25 per 100 person-years with long-acting reversible contraception, a significant 22-fold improvement with long-acting reversible contraception. The risk of unintended pregnancy in participants using pills, patches, or rings was almost twice as high in younger women (< 21 years) as in older women. Among women using long-acting reversible contraception, age did not affect the failure rate.

The use of long-acting reversible contraceptive methods reduces the risk of unintended pregnancy.


OBSTETRICS

Third stage of labour: Active management with or without controlled cord traction

Postpartum haemorrhage (PPH) is an important cause of maternal morbidity and mortality, especially in developing countries. Active management of the third stage of labour reduces the risk of PPH by > 60%. Active management includes administration of oxytocin and controlled cord traction, but the importance of controlled cord traction is unknown. Omitting controlled cord traction might simplify and improve services in resource-poor countries. A randomized trial in eight countries (Argentina, Egypt, India, Kenya, the Philippines, South Africa, Thailand, and Uganda) has suggested that controlled cord traction might be omitted safely.

A total of 24,390 women with singleton pregnancies were randomized to full package (FP) or simplified package (SP) management of third stage.

All women were given oxytocin 10 IU immediately after the birth, with cord clamping at 1–3 minutes. The SP consisted of placental delivery with gravity and maternal effort. The FP consisted of controlled cord traction immediately after uterine contraction and cord clamping. Blood loss of 100 mL or more occurred in 239/11,621 (2%) in the SP group and 219/11,621 (2%) in the FP group. The risk ratio of 1.09 (0.91–1.31) had a 95% confidence interval upper margin exceeding the pre-stated non-inferiority margin of 1.3. There was one case of uterine inversion in the FP group.

Although the pre-stated non-inferiority limit was exceeded, these researchers conclude that omitting controlled cord traction had very little effect on the risk of severe PPH, and haemorrhage prevention programmes in non-hospital settings could safely focus on the use of oxytocin.


Birth defects after assisted conception

Evidence suggests that assisted reproduction technologies, ie, in vitro fertilization (IVF) and intracytoplasmic sperm injection (ICSI), are associated with increased risk of birth defects. This could be due to factors within the technologies or to factors in the patients who take up the technologies. A study in South Australia has provided more data.

Out of a total of 308,974 births, 6,163 were the result of assisted conception. The rate of any birth defect was 8.3% after assisted conception and 5.8% without assisted conception. Unadjusted data showed a 47% increase in risk after assisted conception, but after adjustment for parental factors the increase fell to 28%. There was no significant increase in adjusted risk after IVF, but after ICSI this risk was increased significantly by 57% after adjustment. The risk was increased for a wide variety of defects including cardiovascular, musculoskeletal, urogenital and gastrointestinal abnormalities and cerebral palsy. Women with a history of infertility had an increase in risk irrespective of whether or not they had had a previous birth after assisted conception.

Factors in the parents may be responsible for much of the increased risk, but ICSI may be independently associated with increased risk.


Cervical pessary to prevent preterm birth in women with a short cervix

Cervical pessaries have been used for 50 years to prevent preterm births associated with short cervix, but there has been no randomized trial. Now, a multicentre trial in Spain has confirmed the effectiveness of this method.

The trial included 385 women with a cervical length of 25 mm or less on routine transvaginal scanning at 18–22 weeks’ gestation. Randomization was to insertion of a cervical pessary at 20–23 weeks or no intervention. Spontaneous delivery before 34 weeks occurred in 6% (pessary) vs 27% (controls), a highly significant difference. There were no serious adverse effects from use of a pessary.

Insertion of a cervical pessary reduces the risk of preterm birth in women with a short cervix.


First-trimester abortion: Cervical preparation with misoprostol

Almost a third of all pregnancies worldwide end in induced abortion, often by vacuum extraction in the first trimester. It is important to prepare the cervix for cervical dilation, and osmotic dilators, mifepristone, and prostaglandin analogues are used for this purpose. Misoprostol, a prostaglandin E1 analogue, is cheap and widely used orally, sublingually, or vaginally. A multinational study has shown that vaginal misoprostol is effective in reducing the risk of complications after first-trimester vacuum extraction abortion.

A total of 4,972 women were randomized at 14 centres in nine countries to vaginal misoprostol (two 200-µg tablets) or vaginal placebo, 3 hours before first-trimester vacuum aspiration abortion. Follow-up was for 2 weeks, and full data were analysed for 4,858 women. There was a significant 32% reduction in risk of complications in...
the misoprostol group compared with the placebo group. Incomplete abortion occurred in <1% (misoprostol) vs 2% (placebo), a significant difference. Uterine re-evacuation was necessary in <1% vs 2%. Pelvic inflammatory disease occurred in 1% of each group. Three women in the placebo group, but none in the misoprostol group, had cervical tears, and uterine perforation occurred in two (placebo) and three (misoprostol). Abdominal pain occurred in more women in the misoprostol group (55% vs 22%) than did vaginal bleeding (37% vs 7%).

Misoprostol given 3 hours before first-trimester vacuum extraction abortion reduces the risk of complications. A Lancet commentator suggests that it should be used routinely.


**Elective induction of labour at term**

The merits of elective induction of labour at term have long been debated. A study in Scotland has suggested that elective induction might reduce perinatal mortality but increase admissions to the neonatal unit.

The retrospective cohort study included 1,271,549 singleton births at >36 completed weeks in which there was no contraindication to induction of labour. At gestations between 37 and 41 completed weeks, elective induction of labour was associated with reduced perinatal mortality compared with expectant management. At 40 weeks, the reduction was from 1.8 to 0.8 per 1,000, a significant 61% reduction after adjustment for maternal age, parity, year of birth, birth weight, deprivation, and mode of delivery. The odds of spontaneous vertex delivery were increased significantly by 26% after induction of labour. The rate of admission to the neonatal unit was increased significantly by 14%. Elective induction of labour at 40 weeks would prevent one neonatal death in 1,040 deliveries and result in seven extra admissions to the neonatal unit.

Elective induction of labour at term would reduce perinatal mortality without increasing the rate of operative delivery but with an increase in neonatal unit admissions.


**Intra-national equity in maternal and child health interventions**

Progress towards Millennium Development Goals 4 and 5 (child mortality and maternal mortality) is monitored by Countdown to 2015. Within-country inequalities in provisions have been highlighted by a reanalysis of data from 54 countries about provision for 12 maternal, neonatal, and child health interventions between 2000 and 2008. The 12 interventions concerned family planning, skilled antenatal care, antenatal visits (four or more), skilled birth attendant, early breastfeeding, insecticide-treated bednets for children, diphtheria-pertussis-tetanus immunization, measles immunization, full immunization, vitamin A supplementation, oral rehydration therapy, and pneumonia care seeking. Provision often differed according to household wealth. The greatest difference between rich and poor was for skilled birth attendant coverage and for four or more antenatal visits. The most equitable countries were Uzbekistan and Kyrgyzstan, and the least equitable, Chad, Nigeria, Somalia, Ethiopia, Laos, and Niger, followed by Madagascar, Pakistan, and India. Community-based interventions were more evenly provided than health facility-based interventions.

More efforts are needed to provide health interventions to the poor in developing countries.


**Childhood acute lymphoblastic leukaemia: Outcomes after induction failure**

A few children with acute lymphoblastic leukaemia (ALL) do not respond to induction chemotherapy. These patients have been considered to be a high-risk group, but data from 154 cooperative study groups in Europe, North America, and Asia have shown that they can be divided into subgroups with different prognoses.

Out of a total of 44,017 patients aged 0–18 years treated for ALL between 1985 and 2000, 1,041 (2.4%) had induction failure (leukemic blasts in blood, bone marrow, or any extramedullary site after 4–6 weeks of remission–induction therapy). Children with induction failure often presented with...
high-risk features such as older age, high leucocyte count, T-cell phenotype leukaemia, Philadelphia chromosome, and 11q23 rearrangement. After an average follow-up of 8.3 years, the estimated 10-year survival was 32%. Features associated with a poor prognosis included age 10 years or older, T-cell leukaemia, 11q23 rearrangement, and 35% or more blasts in bone marrow at the end of induction therapy. Features associated with a better prognosis included age 1–5 years, B-cell leukaemia, and high hyperdiploidy (modal chromosome number > 50). In T-cell leukaemia, allogeneic stem-cell transplantation improved outcomes. Among children with precursor B-cell leukaemia and no adverse genetic features, 10-year survival was 72% with chemotherapy alone.

Children with ALL who do not respond to induction therapy can be divided into different prognostic groups.


Infant vitamin D supplementation in Kabul: No effect on pneumonia incidence

A sero-epidemiological study elucidated the dengue antibody status of children in two endemic Southeast Asian countries by analysing stored serum samples obtained from 49 healthy Filipino children in 1993 and from 45 healthy Indonesian children from 1999 to 2000.

Analysing dengue virus infection antibodies in Filipino, Indonesian children

Dengue fever (DF) and dengue haemorrhagic fever (DHF) are endemic in tropical and subtropical areas of the world. Caused by dengue virus (DENV) infection, their global incidence is estimated at 50 to 100 million cases each year, of which about 250,000 to 500,000 cases have been identified as the more severe DHF.

Using an in vitro serological assay system, the researchers found that children from both countries were more likely to possess DENV-enhancing antibodies than neutralizing antibodies, and that these enhancing antibodies did not have reduced activity in the presence of complement.

The authors concluded that children from these countries in which DF and DHF are endemic have relatively high levels of complement-independent enhancing antibodies against some DENV types. They also suggested that the study highlights the advantages of their assay system in elucidating antibody status in endemic countries. Further studies, they added, would be required to determine how the balance of enhancing and neutralizing activities in sera correlates to DF and DHF, so as to analyse how antibody factors are involved in increased disease severity.


A total of 3,046 children aged 1–11 months were randomized to oral vitamin D$_3$, 100,000 IU or placebo every 3 months for 18 months. The incidence of pneumonia was 0.145 per child per year in the vitamin D group and 0.137 per child per year in the placebo group, a non-significant difference. A toxic level of calcifediol (25-hydroxyvitamin D) was found in only two of 652 children tested.

Vitamin D given every 3 months did not prevent pneumonia. Further trials with more frequent dosing in other populations are indicated.

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References:
2) Mc Clung M et al. ASBMR 1998
3) Keil D. et al., Geburtsh Frauenheilk 2002; 62; 991-995

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WHAT IS GASTRO-OESOPHAGEAL REFLUX?

Gastro-oesophageal reflux (GOR) is the non-forceful regurgitation of milk and other gastric contents into the oesophagus (regurgitation). It should be distinguished from vomiting which is an active process requiring the forceful contraction of the diaphragm and abdominal muscles. It is a normal physiological phenomenon, particularly common in infancy. It is also seen in older children and adults less frequently and only pathological when it occurs in excess.

FUNCTIONAL REFLUX

More than 50% of normal infants regurgitate more than twice a day. Functional reflux is regurgitation without morbidity or clinical signs suggestive of gastro-oesophageal reflux disease (GORD).

Reflux is most common between 1 and 4 months. Major factors include the high fluid volume per kilogram ingested at that age compared with older children/adults, posture and the functional immaturity of the lower oesophageal sphincter. By 12–18 months, most symptomatic reflux will have resolved as the sphincter matures, the infant adopts an upright posture, and is established on a mixed rather than milk-predominant diet.

GASTRO-OESOPHAGEAL REFLUX DISEASE

Gastro-oesophageal reflux disease is defined as ‘gastro-oesophageal reflux associated with troublesome symptoms or complications’. It refers to reflux with significant morbidity including faltering growth, respiratory disease, and oesophagitis or complications.
of oesophagitis such as stricture. Therefore, within the umbrella term *gastro-oesophageal reflux*, there is a considerable spectrum with a range of severity from an intermittent nuisance to a life-threatening disease.

Most children with GORD will present in the first year, but there are some who present later with symptoms including heartburn, acid regurgitation, and dysphagia.

**REFLUX OESOPHAGITIS**

Severe GOR can cause oesophagitis. Oesophagitis implies acid or, rarely, alkali-induced damage to the lower oesophagus. Intake of food by mouth stimulates gastric acid secretion. Reflux of this acid in the lower oesophagus can be painful. GORD is the most common cause of oesophagitis in children.

Crying and irritability may be symptoms of oesophagitis in infants, similar to adults’ complaint of heartburn and chest pain. Children with oesophagitis can develop food aversion as a consequence of experiencing pain when they eat, and food refusal can be the presenting feature. This is likely to be a significant factor in the faltering growth seen in some children with reflux. This can be difficult to diagnose and requires treatment of oesophagitis before dealing with feeding issues.

**SYMPTOMS OF GORD**

GORD can be oesophageal or extra-oesophageal depending on the presenting symptoms.

**Oesophageal**

1. Symptoms purported to be due to GORD
   - Especially in infants or younger children or older children without cognitive ability to reliably report symptoms
2. Symptomatic syndrome

- Older child or adolescent with cognitive ability to reliably report symptoms (typical reflux syndrome)

3. Syndromes with oesophageal injury
   - Reflux oesophagitis, reflux stricture, Barrett’s oesophagus and adenocarcinoma

**Extra-oesophageal**

1. Definite association
   - Sandifer’s syndrome, dental erosion
2. Possible association
   - Bronchopulmonary – asthma, pulmonary fibrosis, bronchopulmonary dysplasia
   - Laryngotracheal and pharyngeal – chronic cough, chronic laryngitis, hoarseness, pharyngitis
   - Rhinological and otological – sinusitis, serous otitis media
   - Infants – pathological apnoea, bradycardia, apparent life-threatening events

Risk factors for GORD include obesity, neurologic impairment, repaired oesophageal atresia or other congenital oesophageal disease, cystic fibrosis, hiatus hernia, repaired achalasia, lung transplantation, and a family history of GORD.

**DIFFERENTIAL DIAGNOSIS OF GORD**

- Infection, eg, urinary tract infection, gastroenteritis, peptic ulcer disease
- Intestinal obstruction, eg, pyloric stenosis, malrotation, intestinal atresia
- Food allergy and intolerances, eg, cow’s milk allergy, soy allergy, coeliac disease
- Eosinophilic oesophagitis (EO)
- Metabolic disorders, eg, diabetes, inborn errors of metabolism
- Psychological problems, eg, anxiety, irritable bowel syndrome
- Intestinal dysmotility, eg, primary achalasia sec-
PAEDIATRICS

ONDARY TO NEURODISABILITY

- Drug-induced vomiting, eg, cytotoxic agents
- Primary respiratory disease, eg, asthma, cystic fibrosis
- Rumination

APPROACH TO THE MANAGEMENT OF GOR

1. Physiological reflux is common in infancy and is a clinical diagnosis. For most parents, reassurance that the condition will resolve without treatment is all that is needed. It is important to consider the differential diagnosis.

2. Full assessment of infants is essential, including a full feeding history, to explore the possibility of overfeeding or difficulty with feeding. Careful attention needs to be paid to severity of symptoms, faltering growth and relevant social factors, eg, parental anxiety and stress (Table 1).

3. Severe cases need further assessments and investigation. These include barium study, pH study, impedance study, milk scan, oesophagoscopy, and oesophageal biopsy (described below).

4. There is a step-up approach to management.

5. Difficult cases require assessment by a multidisciplinary team including dietitian, speech and language therapist, paediatric gastroenterologist and paediatric surgeon.

INDICATIONS FOR INVESTIGATION OF PRESUMED GOR

- Need to confirm the diagnosis
- Faltering growth
- Excessive vomiting
- Features suggestive of oesophagitis
- Abnormal electrolytes/acidosis
- Unexplained or difficult-to-control respiratory disease

Table 1. History in a child with suspected gastro-oesophageal reflux disease

<table>
<thead>
<tr>
<th>Pattern of vomiting (predominant symptom)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Frequency/amount</td>
</tr>
<tr>
<td>Associated pain/discomfort</td>
</tr>
<tr>
<td>Is the vomit forceful?</td>
</tr>
<tr>
<td>Does the vomit contain blood or bile?</td>
</tr>
<tr>
<td>Are there any associated constitutional symptoms, eg, fever, lethargy, diarrhoea?</td>
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</tbody>
</table>

<table>
<thead>
<tr>
<th>Feeding and dietary history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amount/frequency (overfeeding)</td>
</tr>
<tr>
<td>Preparation of formula</td>
</tr>
<tr>
<td>Recent changes in feeding type or technique</td>
</tr>
<tr>
<td>Position during feeding</td>
</tr>
<tr>
<td>Burping</td>
</tr>
<tr>
<td>Behaviour during feeding</td>
</tr>
<tr>
<td>Choking, gagging, cough, arching, discomfort, food refusal</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medical history</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prematurity</td>
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<tr>
<td>Birthweight, growth and development</td>
</tr>
<tr>
<td>Past surgery, hospitalizations</td>
</tr>
<tr>
<td>Respiratory illnesses, especially croup, pneumonia, asthma</td>
</tr>
<tr>
<td>Other respiratory symptoms including hoarseness, hiccups, apnoea</td>
</tr>
<tr>
<td>Features of atopy</td>
</tr>
<tr>
<td>Other chronic conditions</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Medications</th>
</tr>
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<tbody>
<tr>
<td>Current, recent, prescription, non-prescription</td>
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</table>

<table>
<thead>
<tr>
<th>Family psychosocial history and family set-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sources of stress</td>
</tr>
<tr>
<td>Post-partum depression</td>
</tr>
<tr>
<td>Maternal or paternal drug use</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family medical history</th>
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</thead>
<tbody>
<tr>
<td>Significant illnesses</td>
</tr>
<tr>
<td>Family history of gastrointestinal disorders</td>
</tr>
<tr>
<td>Family history of atopy</td>
</tr>
</tbody>
</table>

| Growth chart including height, weight, and head circumference |

- Need to confirm the diagnosis
- Faltering growth
- Excessive vomiting
- Features suggestive of oesophagitis
- Abnormal electrolytes/acidosis
- Unexplained or difficult-to-control respiratory disease
HOW TO INVESTIGATE GOR?

Barium Radiology
Barium swallow assesses the patient over only a short period and can therefore either miss pathological reflux or overdiagnose physiological reflux. It is however an important test to rule out large hiatus hernia, oesophageal stricture or web, atypical pyloric stenosis, gastric web, duodenal web, malrotation, volvulus, or other anatomical causes of recurrent vomiting.

pH Study
This is considered by many to be the gold standard investigation test for acid reflux. It is a valid quantitative measure of oesophageal acid exposure, with established normal ranges.

Specific Indications for pH Study
- Diagnostic uncertainty
- Poor response to medical treatment
- If surgery is being considered
- Children in whom doing the test will lead to a change in management
- Symptoms suggesting occult reflux
- Unexplained or difficult-to-control respiratory disease

Physiological Basis and Technique of Using pH Probe
Acid reflux into the oesophagus occurs in all infants as a physiological phenomenon and is only significant when it occurs in excess. The pH probe is designed to measure acidity (ie, acid reflux) in the lower oesophagus. The test relies on the infant/child being off anti-reflux therapy in the 48–72-hour period running up to the test.

The pH probe is a microelectrode passed through the nose and down the back of the throat to sit above the lower oesophageal sphincter. An acid

Figure 1. This illustrates an example of a normal pH study with reflux index 3%. The study is over a period of 22.38 hours. There are minimal reflux episodes in the green area (supine) and some reflux in yellow area (meal times) which are physiological.
reflux episode is defined as an oesophageal pH of < 4 for a specified minimum duration, usually 15–30 seconds. A set period, usually 24 hours, is recorded, with a note made of the number of episodes, frequency of episodes, and the relationship of reflux to eating, position, sleeping or activity, and especially symptoms. The most sensitive marker of acid reflux on pH study is the reflux index, defined as the percentage of time that oesophageal pH is < 4. This has been validated in several studies. pH study reports are shown in Figures 1 and 2.

- The North American Society of Pediatric Gastroenterology, Hepatology and Nutrition consensus recommendation is that a reflux index > 7% is abnormal. In general, reflux index up to 10% is mild, 10–20% is moderate which is usually controlled by medical therapy and > 30% is severe which often requires surgical intervention.
- It is useful to correlate symptoms (eg, cough, chest pain) with acid reflux episodes and to select infants and children with wheezing or respiratory symptoms in whom GOR is a causative/aggravating factor.
- The sensitivity, specificity and clinical utility of pH monitoring in the diagnosis and management of possible extra oesophageal complications of GOR are not well established.

**Limitations of the Test**
There are several limitations to pH studies, as follows:
- pH studies are unable to detect anatomical abnormalities (eg, stricture, hiatus hernia or malrotation) or aspiration.
- Non-acid reflux will not be detected. This should be borne in mind with non-acidic feeds, such as infant formula, and, in particular, when infants are continuously fed.
- The changes in environment, diet and behav-
Reproducibility is poor.
There is potential for technical difficulties.
pH studies provide no objective measures of inflammation and thus are less useful than endoscopy and biopsies for the diagnosis and grading of oesophagitis.
The severity of pathologic acid reflux does not correlate consistently with symptom severity or demonstrable complications.

ALKALINE REFLUX

The pH study may be falsely negative in the presence of alkaline reflux (reflux of alkaline stomach contents, eg, during continuous feeding/duodenal contents). Either dual pH monitoring (electrode in stomach and oesophagus), oesophageal impedance or a radio-labelled milk scan is required to detect this.

MILK SCAN

This uses continuous evaluation for up to an hour after radio-labelled meal. It is independent of pH so it can detect alkaline reflux. It is performed over a period of up to an hour with a delayed 24-hour film to look for aspiration. The technique is useful for diagnosis of non-acid reflux. It also gives an assessment of gastric emptying which is a useful indicator of overall gut motility. Markedly delayed gastric emptying is common in children with cerebral palsy in whom vomiting may reflect an overall gut dysmotility rather than GORD. Sensitivity for detection of reflux is variable but can approach 95%.

IMPEDANCE

This measures the changes in the electrical impedance (resistance) between multiple electrodes located along an oesophageal catheter. Oesophageal impedance tracings are then analysed for the typical changes caused by liquid, solid, air or mixed bolus. The impedance changes suggestive of retrograde bolus movement indicate reflux. This test is superior to pH monitoring alone for the evaluation of the temporal relation between symptoms and GOR.

OESOPHAGEAL MANOMETRY

This measures the pressure inside the lower part of the oesophagus. It may be abnormal in patients with GORD, but the findings are not sufficiently
sensitive or specific to confirm the diagnosis, nor to predict response to medical or surgical therapy. It is useful to confirm a diagnosis of achalasia or other motor disorders of the oesophagus that may mimic GORD.

**OESOPHAGOSCOPY AND OESOPHAGEAL BIOPSY**

In children with suspected oesophagitis, upper gastrointestinal endoscopy is a useful investigation and should be considered in all children with severe symptomatic reflux. Biopsies need to be taken, as significant histological abnormality may not be obvious endoscopically. An eosinophilic infiltrate is a characteristic of reflux oesophagitis. However, an excess of eosinophils suggests cow’s milk allergic oesophagitis/EO.

Normal oesophageal histology does not exclude GOR.

In children with documented oesophagitis and normal pH study, other diagnoses should be considered.

**NON-REFLUX CAUSES OF OESOPHAGITIS**

- Cow’s milk allergic oesophagitis (see above)
- Eosinophilic oesophagitis
- Candidal oesophagitis
- Chemical oesophagitis from caustic ingestion
- Achalasia
- Crohn’s disease

**TREATMENT OF GOR**

Most patients with physiological gastro-oesophageal reflux are managed in primary care by the health visitor and general practitioner.

**Simple measures** are often effective, including:

- Explanation and reassurance about the natural history, particularly in the infant who is thriving.
- Review of feeding and feeding practice, eg, checking for overfeeding, trial of smaller more frequent feeds, and too small or too large a teat (both of which can cause air swallowing).
- Review of feeding posture – infants have significantly less reflux when placed in the prone position than in a supine position. However, prone position is associated with a higher rate of sudden infant death syndrome. In infants from birth to 12 months of age with reflux, the risk of sudden infant death syndrome generally outweighs the potential benefits of prone sleeping. In children > 1 year, it is likely that there is a benefit to right-side positioning during sleep and elevation of the head of the bed.
- Use of feed thickeners and use of anti-regurgitation milks – these are useful in reducing the symptoms of GOR and should be considered in children with persistent symptomatic reflux impacting on nutrient intake or through excessive vomiting on lifestyle. They should not be used for healthy children who regurgitate.
- Cow’s milk allergy is a potential differential and infants with persistent reflux may benefit from a 2–6 week trial of extensively hydrolysed formula. Soya formulae should not be used. There is a significant cross reactivity between cow’s milk and soya protein and because of the presence of phytoestrogens in soya milk, they are not recommended in infants < 6 months.

**Drug treatment** is indicated in children with severe symptomatic reflux or signs and symptoms suggestive of GORD.

The major pharmacological agents currently used for treating GORD in children are gastric acid–buffering agents, mucosal surface barriers,
Most children with gastro-oesophageal reflux disease will present in the first year.

and gastric anti-secretory agents. Acid suppressant agents are the mainstay of treatment for all but patients with occasional symptoms. The potential adverse effects of acid suppression, including increased risk of community-acquired pneumonias and gastrointestinal infections, need to be balanced against the benefits of therapy.

**STEP-UP APPROACH TO MEDICAL TREATMENT OF GOR**

Step 1 – lifestyle changes

Step 2 – thickeners/H₂ receptor blockers

Step 3 – prokinetics

Step 4 – proton pump inhibitors (PPIs)

Step 5 – consider change in feed/feed regimen

Step 6 – surgery

**Compound alginates** are effective symptomatic treatment for GOR. Infant aluminum hydroxide/magnesium trisilicate works by reacting with gastric acid to form a viscous gel. It comes in a dual sachet and each half is a dose. One dose for under 4.5 kg and two doses for over 4.5 kg are given for a maximum of six times a day. In infants, aluminium hydroxide/magnesium trisilicate can be added to feed or, for breast-fed infants, dissolved in cooled boiled water and given by spoon after a feed. Chronic use of alginates is not recommended for GORD because some have absorbable components that may have adverse effects with long-term use.

**Acid Suppression Agents**

**Histamine H₂ receptor blockers** are widely used in the management of reflux. They are safe and well tolerated and can be considered before any further investigation in children who are thriving and in whom the diagnosis is robust. Ranitidine is the most commonly used H₂ receptor blocker. Oral ranitidine provides symptomatic relief and endoscopic improvement of oesophagitis in children with GORD. Dose is 2–4 mg/kg twice daily; the syrup can be used (75 mg/5 mL).

**Proton pump inhibitors** (e.g., omeprazole, lansoprazole) increase the pH of gastric content, decrease the total volume of secretions, and facilitate emptying. For healing of erosive oesophagitis and relief of symptoms, PPIs are superior to histamine receptor blockers. Omeprazole is the most commonly used PPI and is shown to be effective in children with GORD resistant to ranitidine. It is available as dispersible tablets or capsules given once daily. The tablet can be gently mixed or dis-
persed (not crushed), or the capsule can be broken for ease of administration in children. Dosage is 0.7–1.4 mg/kg per day although higher doses can be used, at up to 3 mg/kg. In practice, twice daily doses are often used. Lanzoprazole is available as dispersible tablets and given in the dose of 0.5–1 mg/kg once daily.

**PROKINETIC DRUGS**

These drugs increase lower oesophageal spincture pressure, improve oesophageal clearance, and promote gastric emptying. Efficacy data are limited. Examples include metoclopramide, domperidone, cisapride and erythromycin. Cisapride has been withdrawn from use because of concerns about cardiotoxicity. Although the effectiveness of domperidone in children is unproven, it is often used with no serious adverse effects at 0.3–0.6 mg/kg three times daily in children. It can occasionally exacerbate reflux.

**OTHER AGENTS**

Buffering agents (magnesium hydroxide and aluminium hydroxide) and sucralfate are useful for occasional heartburn. Buffering agents carry significant risk of toxicity and are not recommended for long-term use. Sucralfate binds to inflamed mucosa and forms a protective layer that resists further damage from gastric acid.

**CHILDREN WITH SEVERE REFUX RESISTANT TO MEDICAL MANAGEMENT MAY BENEFIT FROM:**

- Trial of hydrolysed protein formula feed
- Period of continuous feeding
- Trial of gastrostomy/gastro-jejunal feeding

**SURGERY**

**Indications**

- Failure of optimal medical therapy
- Dependence on long-term medical therapy
- Extra-oesophageal manifestations (asthma, cough, chest pain, recurrent pulmonary aspiration of refluxate)
- Complication of GORD (e.g., Barrett’s oesophagus, peptic stricture)

Surgery is usually fundoplication with consideration of a pyloroplasty if there is delayed gastric emptying. A gastrostomy for feeding is often done at the same time, particularly if there are feeding problems, e.g., neurodisability.

Most fundoplications are now done laparoscopically with good results in terms of reduced post-operative complications, reduced stay in hospital, and long-term outcome.

Children with underlying disorders predisposing to the most severe GORD are at the highest risk for operative morbidity and post-operative failure. Before surgery, it is essential to rule out non-GORD causes of symptoms and ensure that the diagnosis of chronic-relapsing GORD is firmly established. It is important to provide families with appropriate education and a realistic understanding of the potential complications of surgery, which include recurrence of reflux (10%), retching, bloating, dumping, and intestinal obstruction.

**Patient Groups at High Risk of Needing Surgery**

- Children with neurodisability
- Respiratory disease with intractable reflux (e.g., oesophageal atresia, bronchopulmonary dysplasia)
- Children with complication of oesophagitis such as stricture
- Tracheo-oesophageal fistula repair
- Barrett’s oesophagus
Barrett’s Oesophagus

- This refers to the presence of metaplastic columnar epithelium in the lower oesophagus thought to be a consequence of long-standing GORD.
- There is an increased risk of adenocarcinoma of the oesophagus.
- It is rare in childhood and requires aggressive medical treatment of the GOR and regular endoscopic surveillance.
- Surgery (fundoplication) is often considered.

GOR and Neurodisability

Children with cerebral palsy commonly suffer from feeding difficulties of which GOR is a component. Assessment of the contribution of GOR requires careful assessment.

There are many potential causes of feeding difficulties in children with neurodisability:
- Bulbar weakness with oesophageal incoordination
- Primary or secondary aspiration
- Reflux oesophagitis
- Widespread gut dysmotility
- Mobility and posture, degree of spasticity
- Poor nutritional state
- Constipation

Children require careful multidisciplinary assessment by a feeding team including dietitian, speech and language therapist, occupational therapist, and the neurodevelopmental paediatrician. A video barium assessment of the swallow is often indicated. GORD, if present, should be treated aggressively.

Attention to nutrition is of key importance, and many children with feeding difficulties benefit from a feeding gastrostomy. A fundoplication is required if reflux is severe, although in some cases, improved nutritional status will result in improvement of the reflux.

The motility of the gut is a key factor in feed tolerance in children with cerebral palsy who may have delayed gastric emptying which impact significantly on the ability to feed, particularly if nutrition is dependent upon nasogastric or gastrostomy feeding. It is important to recognize this as a separate condition from reflux. Abdominal pain, bloating and constipation are common features of gut dysmotility. Therapeutic strategies include explanation and reassurance, prokinetic agent such as domperidone, laxatives and, occasionally (if there is a need for distal gut deflation), suppositories. It may be necessary to give feeds by continuous infusion. It may also be necessary to consider gastro-jejunal feeding. A milk-free diet for a trial period of 2–4 weeks can be helpful. Hydrolysed protein formula feeds may be given as a milk substitute.

GOR and Respiratory Disease

GOR has been associated with significant symptoms in infants and children. There is a complex relationship between asthma and GOR, manifested...
by a bidirectional cause and effect.

One postulated mechanism for GOR-mediated airway disease involves micro-aspiration of gastric contents that leads to inflammation and bronchospasm. However, experimental evidence also supports the involvement of oesophageal acid–induced reflex bronchospasm, in the absence of frank aspiration. In such cases, GOR therapy using either H2 blockers or PPIs has been shown to benefit patients with steroid-dependent asthma, nocturnal cough, and reflux symptoms. Similarly, intrinsic lung disease may, through excessive coughing, result in reflux.

The association between GOR and apparent life-threatening events is somewhat controversial and probably only relevant if the infant vomits, chokes or turns blue during or immediately after feeds.

Eosinophilic Oesophagitis

In infants and young children, EO presents with symptoms similar to those of GORD but fails to respond to conventional acid blockade therapy. In older children, dysphagia and food impaction can occur.

EO is often seen in patients with atopy who have asthma, eczema or chronic rhinitis, or in those with family history of atopic disease. Multiple food antigens can also induce EO.

Endoscopy may reveal a ringed appearance or linear furrows. Standard biopsy findings reveal severe eosinophilic infiltration; more than 15–20 eosinophils per high-magnification microscopic field are necessary for diagnosis. In contrast to GORD, EO involves the mucosa, submucosa and, possibly, the muscularis.

EO is currently diagnosed based solely on endoscopic findings. Standardized skin prick testing and radioallergosorbent testing are not useful in the diagnosis of EO. About two-thirds of children with EO have an increased peripheral eosinophilic count. The exact pathophysiology of EO is unknown, but contact of the allergen with the oesophageal or intestinal mucosa is thought to be the initiating event.

Treatments include those for GOR, trial of dietary elimination, inhaled (swallowed) or oral steroids, anti-inflammatories, and immunosuppression. There is a natural history of relapse, remission and chronicity.

**CASE STUDY 1**

A 5-week-old, term, breast-fed baby presented unsettled in the evenings and at night. She was vomiting (not the whole feed), with episodes of arching. She has continued to gain weight appropriately. Mum was given advice on positioning and feeding, along with explanation and reassurance about the natural history of GOR. The symptoms, however, continued and infant aluminium hydroxide/magnesium trisilicate was started. She continued to thrive. Her reflux gradually improved with time. This infant presumably had functional GOR. There may have been a component of ‘infantile colic’. Infantile colic is poorly understood but, like reflux, generally improves. Symptoms may overlap and can cause considerable anxiety to parents.

**CASE STUDY 2**

A 3-month-old exclusively breast-fed baby was started on formula milk. He developed symptoms of retching (distress) with most feeds, constipation, and milk refusal. Cow’s milk allergy was considered. He was referred to a specialist clinic where he was started on extensively hydrolysed formula. Weaning was delayed to 6 months, after which he was started on dairy-
free weaning solids, with dietetic support. His symptoms improved rapidly and he showed good catch-up growth. Cow’s milk was gradually introduced in his diet from the age of 12 months, after a day case challenge, which he tolerated well. His diet was subsequently normalized. Cow’s milk allergy is the commonest food allergy in infancy and usually resolves by 2 years of life and almost always by 5 years of age. GOR can coexist, but poor response to anti-reflux therapy should prompt consideration of cow’s milk allergy.

**CASE STUDY 3**

A 2-year-old boy with spastic quadriplegia and intractable epilepsy presented to hospital repeatedly with aspiration pneumonia and poor weight gain. He was nasogastrically fed at home, and parents reported frequent retching and vomiting associated with feeds in spite of being on ranitidine and domperidone. His pH study confirmed severe reflux. He failed to respond to PPIs at good doses and trial of hydrolysed formula feed. He underwent fundoplication with feeding gastrostomy. Post-operatively, his admissions to hospital were reduced. Parents reported good weight gain and improved feed tolerance.

**CASE STUDY 4**

A 15-month-old baby presented with history of poor weight gain, recurrent vomiting and food refusal from very early age. She was born at term and there was no significant antenatal or medical history. She was particularly distressed at meal times as if she was in pain. Further investigations revealed significant reflux (reflux index 14%) and endoscopic findings of oesophagitis. She was treated with PPIs, with improvement in her symptoms. Her symptoms were secondary to acid reflux in response to gastric acid secretion associated with meal times. Her feeding improved with reflux treatment.

**FURTHER READING**


**About the Authors**

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INTRODUCTION

Antepartum haemorrhage can be defined as bleeding from the genital tract between 20 weeks’ gestation and term. It represents an important cause of maternal and fetal morbidity and mortality, complicating 2–5% of all pregnancies. The commonest causes include placenta praevia (31%) and placental abruption (22%), with other causes (including marginal sinus bleed, vasa praevia, cervicitis genital trauma, and infection) accounting for the remaining cases.

In the most recent Confidential Enquiry into Maternal and Child Health report (2006–2008), nine deaths were attributed to obstetric haemorrhage, producing an overall mortality of 0.39 per 100,000. Two of these maternal deaths were diagnosed with placenta accreta, the incidence of which is increasing in the presence of rising caesarean section rates. Successful management of placenta accreta and percreta remains a challenge and, if unrecognized, can be potentially life-threatening. A multidisciplinary team approach with senior obstetricians, anaesthetists and interventional radiologists improves outcome. Protocols for the management of massive antepartum haemorrhage, as well as simulation training, ensure both awareness and methodical management of this condition.

The cases outlined below illustrate the diagnostic and management challenges of two unique pregnancies complicated with placenta percreta and placental abruption.

CASE 1

A 38-year-old multiparous woman (gravida 2, para 1) and known Jehovah’s Witness presented at 28 weeks’ gestation with a significant, painless, unprovoked bleed of ap-
approximately 300 mL. The anomaly scan at 22 weeks demonstrated an anterior low-lying placenta. Her pregnancy had otherwise been uncomplicated. On examination, the uterus was soft, non-tender with no signs of active bleeding. Cardiotocography showed a satisfactory heart trace appropriate for gestation.

Placenta praevia is diagnosed when the placenta is inserted, wholly or in part, into the lower segment of the uterus. It has an incidence of 1 in 200 (0.4–0.8%). It is classified as minor (low-lying, but does not involve the internal cervical os) and major (covers the internal cervical os asymmetrically or symmetrically). A history of painless unprovoked vaginal bleeding in the presence of a high-presenting fetal part and absence of fetal compromise can be suggestive of a diagnosis of placenta praevia.

Although the exact aetiology of placenta praevia is unknown, various risk factors have been identified—these include higher parity, increasing maternal age, uterine abnormalities, multiple pregnancy, previous placenta praevia, history of previous caesarean section(s), smoking, cocaine abuse, and intrauterine surgery.

In our case, as the bleeding settled and the patient was haemodynamically stable, she was managed conservatively. A large bore intravenous cannula was sited, and blood samples were sent for a full blood count and coagulation screen. Intramuscular steroids were administered for fetal lung maturation. A repeat ultrasound scan showed a normally grown fetus in transverse lie, with major anterior placenta praevia. A multidisciplinary meeting was organized with specialist input from a consultant obstetrician, anaesthetist and haematologist, and the advanced directive for receiving blood or blood products was reviewed and signed with the patient refusing any kind of transfusion. The patient was managed conservatively and discharged 4 days later.

Management options when dealing with haemorrhage from placenta praevia include immediate delivery or expectant approach. In cases of continuous, severe and life-threatening bleeding, immediate caesarean section is recommended. If the bleeding is continuous but not profuse and the gestation is more than 34 weeks, then delivery is recommended after resuscitation of the patient.

Expectant management applies to women who experience bleeding that is either small or moderate and self-limiting. The aim is to achieve the maximum fetal maturity without compromising the maternal or fetal wellbeing. Prolonged hospitalization, although controversial, might be necessary for selected cases as it enables access to immediate resuscitation and prompt delivery as well as neonatal unit facilities.

Ultrasoundography remains the gold standard for identifying a low-lying placenta. The Royal College of Obstetricians and Gynaecologists (RCOG) supports placental localization during the routine 20-week anomaly scan. The earlier the ultrasound scan is performed, the more likely that the placenta will be found in the lower part of the uterus, owing to placenta migration in the second half of the pregnancy (28% of placentas are low-lying on ultrasound scan between 20 and 24 weeks of gestation, but less than 3% are low-lying at term). Transvaginal scanning has proved to be more accurate in terms of diagnosing placenta praevia, and if any doubt regarding localization of the placenta exists, a transvaginal scan should be offered. This is the case especially on follow-up scans at around 34 to 36 weeks of gestation. Magnetic resonance imaging does not appear to be a cost-effective method for diagnosing placenta praevia at present. However, it can be useful in equivocal cases to distinguish those women at specific risk of placenta accreta.

At 32 weeks’ gestation, the patient was admitted via ambulance following an episode of heavy
vaginal bleeding and abdominal pain. On this occasion, she lost approximately 500 mL of fresh red blood. She was admitted to the high dependency unit of the delivery suite where she was resuscitated and reviewed by a senior obstetrician. On examination, she was noted to have an irritable and tender uterus. Two large bore intravenous cannulas were sited, blood samples for full blood count, urea and electrolytes and coagulation screen were sent, and fluid resuscitation commenced. Cardiotocography revealed a normal fetal heart rate pattern. The patient continued to haemorrhage and decision was made for delivery via emergency caesarean section. The patient’s advanced directive was reviewed, and refusal for all blood products was confirmed. She agreed to receive therapeutic agents, including volume expanders (crystalloid and colloid) and recombinant clotting factors. Autologous blood transfusion via cell salvage was declined.

An emergency caesarean section under general anaesthetic was performed, and a live infant was delivered in good condition. Tranexamic acid infusion was commenced at induction of anaesthesia to reduce blood loss. Intra-operatively, the placenta was delivered with ease with subsequent bleeding from placental bed, controlled with haemostatic sutures. A retroplacental clot consistent with placental abruption was noted. The uterus remained atonic after administration of oxytocin/ergometrine maleate and a 40-unit oxytocin infusion was commenced. Haemostasis was achieved, and the total estimated blood loss was 3 L. The patient was transferred to the intensive care unit with postoperative haemoglobin of 6.2. She made an uneventful recovery and was discharged home 7 days later.

Placental abruption can coexist with placenta praevia in about 10% of cases. Placental abruption is defined as bleeding after premature separation of a normally cited placenta. The incidence ranges from 0.5% to 1.7%. It is concealed in approximately 30% of cases and revealed in approximately 70% of cases. There are four grades of placental abruption (Table 1). Risks of this condition affect both the mother and the fetus. Maternal risks include hypovolaemic shock, disseminated intravascular coagulopathy, acute renal failure, severe rhesus sensitization in rhesus-negative women and finally, a maternal mortality rate of 1%. Fetal risks include perinatal mortality (between 4% and 66% depending on neonatal facilities and gestational age), fetal growth restriction, congenital malformations (double compared with the general population), and fetal anaemia.

The diagnosis of placental abruption is clinical, and ultrasonography is often not necessary. The main symptoms are vaginal bleeding, abdominal pain, and uterine tenderness. In mild cases, the diagnosis is not made until after delivery, when a retroplacental clot is revealed. In severe cases, the patient may present with tachycardia, hypotension, a woody hard uterus, and fetal heart abnormalities. The Kleihauer test can prove useful in reaching the diagnosis in cases with abdominal pain without vaginal bleeding which may be suggestive of silent abruption.

Generally, the diagnosis of placenta praevia means delivery via caesarean section. The RCOG
recommends that if the placental edge is < 2 cm from the internal os in the third trimester, delivery via caesarean section is needed. However, when dealing with a minor degree of low-lying placenta and the fetal head is engaged and below the lower edge of the placenta, then vaginal delivery is appropriate. General anaesthesia was preferred in the past, but recently there is a tendency towards regional anaesthesia since increased safety and less intra-operative blood loss have been demonstrated.

According to the RCOG guidelines, delivery should be performed by a senior obstetrician. A multidisciplinary team of a senior anaesthetist, haematologist and interventional radiologist should be available in case of complications during or after the delivery.

Treatment of Jehovah’s Witnesses should adhere to strict guidelines. At booking, patients should be referred for consultant-led care. Additional or individual risk factors should be identified and anaemia should be corrected. Each individual case should be reviewed by a consultant haematologist, anaesthetist and obstetrician in a multidisciplinary meeting. Advanced directives should be reviewed, signed and clearly displayed in the obstetric notes. Use of specific blood products, substitutes and therapeutic agents should be explored, as well as personal choice, with regard to cell salvage in cases of life-threatening haemorrhage. Hyperbaric oxygen therapy has been described in the management of anaemia following severe blood loss.

**CASE 2**

A 39-year-old healthy Caucasian in her third pregnancy, with a history of two previous caesarean sections, was noted to have an anterior low-lying placenta at her 20-week anomaly scan. The patient remained asymptomatic until 28 weeks, when she presented with unprovoked vaginal bleeding which was managed conservatively. External fetal heart monitoring demonstrated a reactive trace. An ultrasound scan revealed an anterior placenta praevia, with signs suggestive of placenta percreta. Colour Doppler demonstrated hypervascularity of the serosa–bladder interface, with markedly dilated vessels over the peripheral subplacental zone. These findings were consistent with placental invasion into the posterior wall of the bladder, confirming placenta percreta (Figure 1).

Intramuscular steroids were administered to promote fetal lung maturation. In view of the diagnosis of placenta percreta, she was advised to remain as an inpatient until delivery, but she declined because of family commitments. The bleeding gradually settled, and she was discharged home after 4 days with the advice to return immediately should she experience any further bleeding.

At 32 weeks, she was readmitted with a further episode of unprovoked vaginal bleeding. On admission, her vital signs were normal. Blood tests revealed a haemoglobin of 10.5 g/dL with no evidence of coagulopathy. An ultrasound scan the next day confirmed a well-grown fetus with normal umbilical artery Doppler values. Mild intermittent
vaginal bleeding continued for 7 days, and hospital admission until delivery was again recommended. Six units of red cells were cross-matched, and neonatal unit facilities were available in case of an urgent delivery.

A detailed consultation followed; this involved the diagnosis of her condition and the available management options. A multidisciplinary joint meeting with the anaesthetist, haematologist, interventional radiologist, urologist and neonatologist was arranged and decision was made for delivery of the baby by classical caesarean section at 35 weeks of gestation. Intentional retention of the placenta to avoid bladder injury and minimize haemorrhage was considered in the pre-operative planning. The risks and benefits of the procedure were explained, and option for sterilization at time of caesarean was discussed. Informed consent was obtained, and as the patient had completed her family, she opted for tubal ligation.

Further episodes of bleeding at 33 and 34 weeks were managed expectantly. Regular haemoglobin checks showed no evidence of anaemia.

On the day of surgery, prophylactic uterine artery balloon catheters were introduced through the right and left femoral artery. In view of the risk of torrential bleeding, two blood infusion sets, in addition to cell salvage, were prepared. The haematologist and blood bank were informed of the possible need for blood products.

A healthy male infant weighing 3,100 g was delivered by classical caesarean section without causing separation of placenta at 35 weeks gestation under general anaesthesia. The placenta was left in situ, and oxytocics were avoided post-delivery to avoid unintended partial placental separation. The intraoperative blood loss was approximately 800 mL.

Following delivery, the uterine artery occlusion balloons were inflated to minimize the risk of bleeding and were subsequently deflated 4 hours post procedure, as there was no further bleeding. Prophylactic broad-spectrum antibiotics were administered. Her immediate post-operative recovery was uneventful. As the placenta was left in situ, weekly β human chorionic gonadotrophin estimations and serial ultrasound scans to ensure placental resolution were performed.

DISCUSSION

The incidence of morbidly adherent placentae, especially placenta percreta, is rising, most likely secondary to increasing caesarean section rates. It is believed that decidua basalis, a layer that prevents invasion of the trophoblast cells deeper into the myometrium, can be damaged owing to previous surgery. This results in the penetration of placenta into the superficial (placenta accreta) or deep (placenta increta) myometrium. In severe cases, the placental tissue penetrates through the entire myometrium and breaches the uterine serosal layer (placenta percreta). Once the serosal layer is breached, placental tissue can invade the surrounding areas (urinary bladder anteriorly, broad ligaments and ureters laterally and bowel posteriorly). Overall, maternal mortality of 7–10% has been reported with morbidly adherent placentae.

Moreover, placenta percreta is also associated with increased maternal morbidity as surgical treatment might involve a difficult caesarean hysterectomy and, depending on the organs invaded, bladder resection or ureteric implantation, in addition to the implications of massive obstetric haemorrhage.

Placenta percreta poses a management dilemma for clinicians. Conservative management includes delivery of the baby through a classical (fundal) caesarean section without any attempt for placental separation, followed by monitoring for signs of infection and placental resolution. Howev-
er, such an approach is associated with immediate (sepsis, inadvertent partial separation of placenta leading to severe haemorrhage) as well as delayed (secondary postpartum haemorrhage and sepsis) complications. In addition, patient compliance is paramount because conservative management involves self-monitoring for signs of sepsis, bleeding, serial ultrasound scans and β human chorionic gonadotrophin estimations to ensure placental resolution.

ANTENATAL MANAGEMENT

Placenta praevia and percreta/accreta typically present with painless unprovoked bleeding. Bleeding may be self-limiting or may persist and can vary from mild spotting to catastrophic haemorrhage. Placenta percreta may present with persistent haematuria, and obstetricians should have a high index of suspicion when dealing with such cases.

Women with major placenta praevia should be counselled about the risk of preterm delivery and the need for possible hospital admission from 34 weeks’ gestation. There is still controversy regarding the management of asymptomatic women with major placenta praevia. If women are managed at home, certain safety precautions should be instigated, including easy access to hospital-based care and constant presence of a companion.

In cases of inpatient management, group-specific blood availability is imperative and thromboprophylactic measures should be considered. Mobility and good hydration should be encouraged and deterrent thromboembolic stockings are used. Prophylactic anticoagulation should be decided upon individual risk factors (reduced mobility, increased body mass index, personal or family history).

With regard to the use of tocolytics or cervical cerclage to prolong pregnancy in these cases, the evidence is insufficient. Decision regarding time of delivery should be based on achieving fetal maturity without compromising maternal well-being.

IMAGING EVALUATION

Routine ultrasound scanning at 20 weeks’ gestation should include placental localization. Transvaginal scanning can improve the accuracy of placental localization and a follow-up scan in the third trimester arranged in cases where the placenta covers or overlaps the cervical os. In asymptomatic women, the follow-up scan can be deferred until 36 weeks’ gestation. A distance of < 20 mm from the cervical os to the placental edge in the third trimester is an indication for delivery by caesarean section.

Women who have had a previous caesarean section with concurrent placenta praevia are at risk of placenta accreta, and appropriate imaging techniques should be arranged by 32 weeks’ gestation to allow planning for management in the third trimester.
Ultrasound imaging techniques including greyscale, colour Doppler and three-dimensional power Doppler may be used to confirm diagnosis (see Table 2). The role of magnetic resonance imaging in diagnosing placenta accreta is debatable, and studies have shown it to be comparable to ultrasonography. In equivocal cases, both imaging modalities may be used according to availability.

**USE OF BLOOD AND BLOOD COMPONENTS**

Management of severe antepartum haemorrhage requires the use of blood and blood components, adequate intravenous access, and consideration of surgical or radiological intervention to stop bleeding. Massive transfusion can be associated with dilutional coagulopathy secondary to tissue damage, hypoperfusion and consumption of clotting factors. Transfusion of red blood cells, plasma and platelets in appropriate proportions can minimize both hypovolaemia and coagulopathy.

In response to haemorrhage causing haemodynamic compromise, red blood cells should be administered, ideally group-specific and cross-matched. In a patient who is actively bleeding with evidence of coagulopathy (clinical or biochemically evident), it is reasonable to give blood components before coagulopathy deteriorates. Haematological advice should be sought and an initial dose of fresh frozen plasma (FFP) of 15 mL/kg is generally recommended at an early stage to avoid severe consumption coagulopathy. Cryoprecipitate may be indicated when there is bleeding with a fibrinogen concentration below 1 g/L. Platelet count is unlikely to fall below 50 x 10⁹/L until approximately two blood volumes have been replaced and the count should be maintained above 75 x 10⁹/L. Obstetric conditions such as placental abruption may predispose to development of dilution intravascular coagulation, resulting in factor V, factor VIII and factor XIII. If dilution intravascular coagulation is suspected, a transfusion of FFP should be considered prior to availability of results.

Large-volume transfusion can be associated with various complications; patients may develop hypothermia which can impair haemostasis by reducing red cell oxygen delivery to tissues. This can be further compounded by rapid transfusion of blood, which may further lower the patient’s core temperature.

When administrating FFP or platelets, the presence of citrate in the components can lower calcium levels. Coagulation defects may subsequently arise in the presence of hypocalcaemia (level of < 0.6–0.7 mmol/L). Large-volume transfusion can also

<table>
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<th>Table 2. Imaging modalities: criteria for diagnosis</th>
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<tbody>
<tr>
<td><strong>Greyscale:</strong></td>
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<tr>
<td>• Loss of retroplacental sonolucent zone</td>
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<tr>
<td>• Irregular retroplacental sonolucent zone</td>
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<td>• Thinning or disruption of the hyperechoic serosa–bladder interface</td>
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<td>• Presence of focal exophytic masses invading the urinary bladder</td>
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<tr>
<td>• Abnormal placental lacunae</td>
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<tr>
<td><strong>Colour Doppler:</strong></td>
</tr>
<tr>
<td>• Diffuse or focal lacunar flow</td>
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<tr>
<td>• Vascular lakes with turbulent flow</td>
</tr>
<tr>
<td>• Hypervascularity of serosa–bladder interface</td>
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<tr>
<td>• Markedly dilated vessels over peripheral subplacental zone</td>
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<tr>
<td><strong>Three-dimensional power Doppler:</strong></td>
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<tr>
<td>• Numerous coherent vessels involving the uterine serosa–bladder junction</td>
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<tr>
<td>• Hypervascularity</td>
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<tr>
<td>• Inseparable cotyledonal and intervillous circulations, chaotic branching</td>
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<td><strong>Magnetic resonance imaging:</strong></td>
</tr>
<tr>
<td>• Uterine bulging</td>
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<tr>
<td>• Heterogeneous signal intensity within the placenta</td>
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<tr>
<td>• Dark intraplacental bands on T2-weighted imaging</td>
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</tbody>
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**Practice points**

**Placental abruption**
- Typically present with vaginal bleeding and uterine tenderness
- Bleeding may not be evident (concealed abruption)
- Blood loss may be underestimated
- All obstetric units should have guidelines for the management of severe haemorrhage and for women who refuse blood products
- It is unlawful to administer a blood transfusion to a Jehovah’s Witness who has expressly forbidden it and may lead to referral to the UK’s General Medical Council, criminal and/or civil proceedings
- All maternity staff should have regular simulation training in managing major obstetric haemorrhage

**Placenta percreta**
- High index of suspicion in patients with low-lying placenta and a previous scar
- Doppler ultrasound and magnetic resonance imaging may aid in diagnosis
- Patients should be managed in a tertiary centre where interventional radiology, transfusion facilities and appropriate specialist care are available
- Appropriate informed consent should be obtained and risk of hysterectomy is discussed
- Intentional retention of the placenta can minimize risk of bleeding and injury to involved organs
- Pelvic artery embolization is safe and effective treatment in cases of persistent intra-pelvic bleeding despite surgical measures

**FURTHER READING**


**About the Authors**

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Clinical Case
Nipple Soreness and Swelling During Breastfeeding
Gayle Fischer, MBBS, MD, FACD

CASE SCENARIO
Anna, a 30-year-old mother, was breastfeeding her 6-week-old son. Soon after she started breastfeeding, she developed swelling and irritation of the skin at the periphery of her nipple areolae. The area was constantly swollen, weeping and sticky, and very uncomfortable, especially when her baby started sucking. She had breastfed her two other children with no problems.

Anna was in the habit of giving her baby ranitidine just prior to each feed, but the problem persisted even when she changed the timing of the ranitidine.

What has happened and what can be done to help Anna?

(Answers on p. 211)
INTRODUCTION

Cardiovascular disease remains the commonest cause of mortality and morbidity in the UK. Treatment of lipid disorders in adults has had a significant impact in reducing the overall burden of cardiovascular disease, particularly in individuals who have sustained a cardiovascular event such as myocardial infarction or stroke (secondary prevention). There is increasing focus on primary prevention of cardiovascular disease, including consideration of the cardiovascular health of children. It is lifetime exposure to vascular risk factors, such as low-density lipoprotein (LDL) cholesterol (LDL-C), that appears to be of importance. This is particularly so for monogenic causes of hyperlipidaemia, the archetype of which is familial hypercholesterolaemia (FH) where an affected individual is exposed to high levels of LDL-C from birth. Secondary causes of hyperlipidaemia are of increasing relevance in childhood owing to the burgeoning obesity epidemic and its association with type 2 diabetes mellitus. In this review, we provide an overview of lipid metabolism and discuss both secondary and primary causes of dyslipidaemia in childhood, with particular focus on FH. Current treatment options will also be appraised.

OVERVIEW OF LIPID METABOLISM

Two pathways of lipid metabolism are recognized: the exogenous and endogenous pathways (Figure 1). The exogenous pathway functions to distribute triglycerides and cholesterol absorbed from the diet to peripheral tissues for use or storage. It is characterized by the formation of chylomicrons, large lipoproteins that are particularly triglyceride-rich. Once deplete of triglycerides, the particle is known as the chylomicron remnant, which is cleared by the liver.
The endogenous pathway functions in the fasted state to deliver lipids to peripheral tissues. This is achieved by the formation of very low-density lipoprotein (VLDL) in the liver, a triglyceride-rich lipoprotein which also contains cholesterol. Triglycerides are delivered peripherally, and the particle reduces in size and increases in density; these are sequentially known as intermediate-density lipoprotein (IDL) and, finally, LDL. These contain proportionally more cholesterol, and LDL, in particular, delivers cholesterol to tissues. Any that remains is cleared by the liver via the LDL-receptor (LDL-R); this is the defective step in FH. The sequence of events in LDL-R synthesis and in binding and processing of LDL is shown in Figure 2.

A further pathway also exists, known as reverse cholesterol transport. High-density lipoprotein (HDL) is the major lipoprotein involved. It is produced by the liver in a cholesterol-deplete state and acquires cholesterol from tissues. A complex interplay then occurs between HDL and other lipoproteins such that excess cholesterol is returned to the liver via HDL and apolipoproteins are redistributed.

It is important to note that when cholesterol is measured by a clinical laboratory, it is derived from all the lipoproteins mentioned above. HDL cholesterol measurements isolate the cholesterol specifically from this fraction, but LDL-C concentration is often a calculated estimate based on an assumption of the ratio of triglyceride to cholesterol in VLDL. This may not always be applicable, for example, when chylomicrons are present in the non-fasted state or where IDL is the predominant non-HDL/non-LDL fraction.

Cholesterol concentrations also vary with age. In children, they show a slight rise until age 10–11, and then dip during puberty before rising to adult levels. A steady rise then occurs throughout adulthood.
The assessment of global cardiovascular risk is well established in adults. Calculation of cardiovascular risk is commonly used to target therapies for primary prevention. Several tools may be used, many of which use data from the Framingham study, a long-term ongoing study of cardiovascular risk. These take into account variables such as total cholesterol, HDL cholesterol (HDL-C), age, and systolic blood pressure. The output from such risk factor calculators is usually expressed as percentage risk of developing cardiovascular disease over a 10-year period. There is limited data to support the use of these tools in paediatric practice, and the cardiovascular risk of a child over the next 10 years will always be low owing to the influence of young age. Post-mortem studies, such as the Pathobiological Determinants of Atherosclerosis in Youth study, demonstrate that atherosclerosis, with the formation of fatty streaks, begins in childhood, and calculation of lifetime cardiovascular risk may therefore be more applicable in the paediatric population. However, such calculators for children are not yet in widespread use. The American Academy of Pediatrics therefore recommends assessment of lipid status in overweight and obese children, and in those with diabetes mellitus or hypertension, as well as smokers, and those with a family history of dyslipidaemia or premature cardiovascular disease. For individuals with FH, the use of cardiovascular risk assessment tools based upon Framingham data are inappropriate as they tend to underestimate cardiovascular risk in untreated FH.

SECONDARY CAUSES OF HYPERLIPIDAEMIA

When interpreting a lipid profile, it is important to recall that a number of conditions can be associated with dyslipidaemia. Treatment of the underlying disease will often completely correct this. Several biochemical tests should therefore be requested as part of the assessment of a lipid disorder (Table 1).

Diabetes Mellitus
Type 1 and type 2 diabetes mellitus are both associated with an increased lifetime risk of cardiovascular disease. However, well-controlled type 1 diabetes mellitus is not typically associated with significant dyslipidaemia. The obesity epidemic has driven the rate of development of type 2 diabetes mellitus, with increasing number of cases diagnosed in childhood. Type 2 diabetes mellitus is often associated with characteristic lipid abnormalities, typically an increase in total cholesterol and triglycerides, and a reduction in HDL-C. There is currently no evidence to support lipid-lowering therapy for the vast majority of children with diabetes mellitus. However, given the increased lifetime cardiovascular risk attributable to the disease, treatment should be considered particularly when there are multiple risk factors present, such as obesity, smoking and hypertension.

Thyroid Disease
Untreated hypothyroidism may be associated with
increased total and LDL cholesterol. This is probably due to decreased receptor-mediated LDL catabolism. Treatment of the hypothyroidism almost invariably results in resolution of hypercholesterolaemia. Use of statins in untreated hypothyroidism is associated with an increased risk of myopathy.

Renal Disease
Nephrotic syndrome is associated with increased total and LDL cholesterol and to a lesser extent, reduction in HDL-C. The degree of dyslipidaemia appears to be inversely related to the serum albumin concentration. An increase in hepatic VLDL production subsequently results in an increase in circulating LDL-C. Evaluation of urinary protein is easily overlooked in a patient who is referred for evaluation of FH and should be a mandatory part of the evaluation.

Liver Disease
Obstructive jaundice is associated with an increase in total cholesterol due to an increase in lipoprotein particles similar to LDL. Hepatocellular disease is more often associated with hypertriglyceridaemia. The latter is a predominant feature of non-alcoholic fatty liver disease which has a strong association with obesity and insulin resistance.

Alcohol
Excess alcohol ingestion may be associated with hypertriglyceridaemia because of increased hepatic triglyceride production, which subsequently leads to an increase in hepatic VLDL secretion. Enquiry regarding alcohol consumption is therefore important in the assessment of dyslipidaemia in older children.

Anorexia Nervosa
Hypercholesterolaemia is a recognized feature of eating disorders. It appears to be particularly associated with the bulimic subtype of anorexia nervosa. Multiple mechanisms are responsible, including endocrine changes secondary to loss of adipose tissue, and increased absorption of dietary cholesterol during high-fat binging episodes. The relevance of this to cardiovascular risk is not clear, and tackling dyslipidaemia as an isolated issue is usually not productive unless there are other concerns with regard to cardiovascular risk or there is a family history of FH.

Drugs Causing Hyperlipidaemia
Several classes of drugs used in paediatric practice may be associated with dyslipidaemia (Table 2). In some cases, it may be possible to switch to an alternative drug, for example, agents used for the treatment of hypertension. If a drug which causes dyslipidaemia is not likely to be used for long-term therapy, such as a course of an oral retinoic acid derivative, a transient dyslipidaemia is likely to be clinically acceptable. Otherwise, an assessment of overall cardiovascular risk should be made to help decide if treatment of the dyslipidaemia is required.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Triglycerides</th>
<th>LDL cholesterol</th>
<th>HDL cholesterol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Thiazides</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>β-Blockers</td>
<td>↑</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Oestrogens</td>
<td>↑</td>
<td>–</td>
<td>↑</td>
</tr>
<tr>
<td>Retinoic acid derivatives</td>
<td>↑</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Protease inhibitors</td>
<td>↑</td>
<td>↑</td>
<td>–</td>
</tr>
<tr>
<td>Ciclosporin</td>
<td>–</td>
<td>↑</td>
<td>–</td>
</tr>
</tbody>
</table>

HDL = high-density lipoprotein; LDL = low-density lipoprotein.
PRIMARY CAUSES OF HYPERLIPIDAEMIA

Familial Hypercholesterolaemia

Autosomal co-dominant FH is the most common monogenic cause of coronary heart disease (CHD). Most cases are caused by mutations in the LDL-R, which results in high circulating LDL-C. The estimated prevalence of heterozygous FH is 1 in 500 in Europe and North America. Untreated, it carries a risk of premature coronary disease of >50% in men and >30% in women by the age of 60 years.

Homoyzygous FH has an estimated prevalence of 1 in 1,000,000 and is associated with circulating LDL-C levels in excess of 10 mmol/L. CHD in homozygous FH presents from the second decade of life. The risk of cardiovascular mortality and morbidity is linked to extensive atherogenesis affecting the proximal aorta, aortic valve, and coronary arteries. Florid physical signs are often present, such as tendon and subcutaneous xanthomata.

Diagnosis of FH

The diagnosis of FH involves a personal and family history, physical examination, measurement of total and LDL cholesterol in serum, and the use of DNA diagnostics. In the UK, the Simon Broome criteria (Table 3) are used as they were developed using a UK population and are straightforward to employ in the clinic. However, all clinical diagnostic criteria lack specificity and sensitivity, particularly in less severe presentations when cholesterol concentrations may not reach the diagnostic thresholds. This is a particular issue in children and younger people owing to the variation of cholesterol concentrations with age, and diagnostic physical stigmata, particularly tendon xanthomata, that are often absent in children. For these reasons, there is

Table 3. Simon Broome register criteria for diagnosis of familial hypercholesterolaemia

<table>
<thead>
<tr>
<th>Lipid criteria</th>
<th>Other criteria required for diagnosis</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Definite FH</strong></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 16 years: total cholesterol &gt; 6.7 mmol/L or LDL-C &gt; 4.0 mmol/L</td>
<td>Tendon xanthomata in patient or in first-degree relative (parent, sibling or child) or in second-degree relative (grandparent, uncle or aunt) OR DNA evidence of a mutation in LDL-R, apolipoprotein B&lt;sub&gt;100&lt;/sub&gt; or PCSK9 genes</td>
</tr>
<tr>
<td>Age &gt; 16 years: total cholesterol &gt; 7.5 mmol/L or LDL-C &gt; 4.9 mmol/L</td>
<td></td>
</tr>
<tr>
<td><strong>Possible FH</strong></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 16 years: total cholesterol &gt; 6.7 mmol/L or LDL-C &gt; 4.0 mmol/L</td>
<td>At least one of the following: Family history of myocardial infarction in first-degree relative aged &lt; 60 years or second-degree relative aged &lt; 50 years OR Family history of raised total cholesterol: &gt; 7.5 mmol/L in adult first- or second-degree relative or &gt; 6.7 mmol/L in child or sibling aged &lt; 16 years</td>
</tr>
<tr>
<td>Age &gt; 16 years: total cholesterol &gt; 7.5 mmol/L or LDL-C &gt; 4.9 mmol/L</td>
<td></td>
</tr>
</tbody>
</table>

FH = familial hypercholesterolaemia; LDL-C = low-density lipoprotein cholesterol; LDL-R = low-density lipoprotein cholesterol receptor; PCSK9 = proprotein convertase subtilisin/kexin type 9.
an increasing role for a DNA diagnosis in suspected FH in paediatric practice.

**Genetics of FH**

Familial hypercholesterolaemia is most commonly caused by mutations in the LDL-R gene, with a smaller number of cases due to mutations in the apolipoprotein (apo) B100 and PCSK9 genes. There is a higher risk of CHD in individuals with an LDL-R mutation, compared with those who are mutation-negative. Mutations may be identified in up to 90% of individuals with ‘definite’ FH (with tendon xanthomata), and genetic testing in patients with ‘possible’ FH can help clarify the diagnosis. Current National Institute for Health and Clinical Excellence clinical guidelines support early identification of FH in children from age 10 years, and a DNA diagnosis can provide conclusive evidence of a diagnosis to parents and their doctors. However, the absence of a detectable DNA mutation does not exclude the diagnosis of FH, and an individual with a clinical diagnosis of FH, who does not have a demonstrable DNA mutation, should still be considered at high risk and treated accordingly.

**Cascade Testing for FH**

In the UK, it is estimated that 85% of the estimated 120,000 people who are affected by FH have not been diagnosed. Cascade testing is the preferred strategy for identifying these individuals. The most efficient and cost-effective approach is to use DNA testing for families with a known mutation or cholesterol testing in families in whom a mutation cannot be found. Cascade testing commenced across Wales in 2010, with extension to the rest of UK anticipated in the next few years. One consequence of this approach is that there will be an increase in the number of children and young people identified with FH who will need advice and treatment.

**Polygenic Hypercholesterolaemia**

Polygenic hypercholesterolaemia is much more...
Polygenic hypercholesterolaemia is more commonly identified in adults, and the risk of premature CHD is much lower than for FH with a documented DNA mutation.

Familial Combined Hyperlipidaemia

Familial combined hyperlipidaemia is an important disorder but is much less clearly defined than FH. It is likely that several genes are responsible and lifestyle factors may also be important. Typically, the total and LDL-C are elevated, as well as serum triglycerides, although there does seem to be significant heterogeneity in the lipid profiles of families with familial combined hyperlipidaemia. The abnormal lipid profile probably occurs owing to overproduction of VLDL.

Hypertriglyceridaemia

Hypertriglyceridaemia may be seen in childhood, usually due to a precipitating factor in a susceptible individual. Genetic forms also exist, such as the rare familial lipoprotein lipase deficiency, which may result in severe hypertriglyceridaemia. Presentation with this disorder may be with eruptive xanthomata or acute abdominal pain, which may be recurrent. Acute pancreatitis may occur when the triglycerides exceed 10–15 mmol/L and may occasionally

There is an increasing role for a DNA diagnosis in children and younger people with suspected familial hypercholesterolaemia.
exceed 100 mmol/L. In childhood, this results from the failure to clear chylomicrons, although in the teenage and adult years, VLDL may also accumulate. Treatment for a primary hypertriglyceridaemia thus focuses on restriction of fat intake.

**TREATMENT**

**Lifestyle Interventions**

Lifestyle therapies are an important component in the treatment of hyperlipidaemia and involve avoidance of smoking, and dietary and exercise interventions. Such interventions are important for general long-term cardiovascular health and the prevention and treatment of obesity. Lifestyle intervention alone is usually not effective for the prevention of cardiovascular disease in inherited dyslipidaemias. The role of nutritional supplements containing plant stanols and sterols is not clear in children, but beneficial effects appear to be similar to those seen in adults.

**Drug Therapy**

**Statins**

They are the most commonly used class of drugs to treat hyperlipidaemia in both children and adults. They work by inhibiting the rate-determining step of the cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A reductase, and effectively reduce total and LDL cholesterol. They have limited effects upon triglyceride and HDL-C metabolism. There are few randomized placebo controlled trials of statins in paediatric FH, but a wealth of data has confirmed the beneficial effects of statins in the reduction of cardiovascular mortality and morbidity in non-FH adults. There are no outcome studies in children, and most have used surrogate markers, such as measures of endothelial function and carotid intima media thickness. These have indicated an improvement in surrogate markers with statins in the FH population. Previous concerns that statins may not be safe in children appear to be unfounded, as data now confirm that statins do not have detrimental effects upon growth and development and are generally well tolerated. Therapy should

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**Practice points**

- Assessment of serum lipids should be carried out in children with a family history of premature cardiovascular disease or dyslipidaemia
- Assessment of serum lipids may also be useful in children with other cardiovascular risk factors
- Screening investigations should be used to exclude secondary causes of dyslipidaemia
- Familial hypercholesterolaemia is the commonest inherited monogenic cause of premature cardiovascular disease
- Statins are effective and safe in children aged 10 years or older
be considered in an individual child based on LDL-C concentrations and the age of onset of cardiovascular disease in family members. Treatment with a statin should be considered in FH from the age of 10. In the UK, currently, atorvastatin is licensed in children over the age of 10 years up to a dose of 20 mg per day and pravastatin is licensed at a dose of 10–20 mg per day in children aged 8–14 years and up to 40 mg in older children.

Other Drug Therapy
Ezetemibe decreases intestinal absorption of cholesterol and may be used in children. Its main use is in combination therapy with statins, in particular for children with homozygous FH. It can also be used in monotherapy, for instance, if statin therapy is not tolerated.

Fibrates reduce hepatic triglyceride production and peripheral lipolysis and have been used in children. Their main use is in the treatment of hypertriglyceridaemia, and they have a limited effect in reducing LDL-C.

Bile acid sequestrants and nicotinic acid are also licensed for use in hyperlipidaemia but are not widely used in children.

LDL Apheresis
LDL apheresis is a treatment similar to renal dialysis. Patients usually attend fortnightly. LDL-C is removed from the patient and absorbed onto a specific LDL absorption column and blood then returned to the patient. This invasive procedure effectively reduces LDL-C in conjunction with drug therapy, and its use should be considered in all children with homozygous FH.

General Issues
The majority of children and young people are currently managed in specialist centres for inherited metabolic disease where advice can be obtained. With cascade testing and an increase in the number of children and young people identified with FH, new strategies for secondary care will need to be considered to advise and treat these patients.

FURTHER READING

Clinical Case
Nipple Soreness and Swelling During Breastfeeding
Gayle Fischer, MBBS, MD, FACD

Answer:

COMMENTARY

Diagnosis
Many women experience discomfort, irritation, and fissuring of the nipples when they are establishing breastfeeding; however, true eczema of the nipple can also occur. The inflammation of eczema results in raw areas, itch, and fissuring, which is painful. This leads to compromise of the epidermal barrier, which in turn may result in infection.

Anna’s symptoms are typical of infected eczema with swelling, weeping, and soreness. During lactation, this is usually secondary to the physical action of suckling; however, a reaction to allergens in the baby’s mouth is a possibility. If her baby is prone to reflux, traces of medication in the baby’s stomach could still come into contact with the nipple well after ingestion.

Ranitidine, an H2-antagonist, is a very uncommon cause of allergy and is unlikely to have played a role here; however, to rule out this possible source, it would be necessary to cease it completely rather than change the timing of giving it. As it is such an unlikely cause, this would only be necessary if other measures have failed. Other causes should be addressed first.

Anna may not have mentioned potential irritants and allergens that she could be applying herself. Creams, topical medications, and nipple shields could all be playing a role and are much more likely than ranitidine to cause these symptoms. Topical medications may contain lanolin, tea tree oil, and local anaesthetics, which are all potential allergens.

Many women develop eczema of the nipple that is atopic. Another relevant question is whether the patient is asthmatic or has had eczema on other parts of her skin in the past.
Psoriasis may also involve the nipple. This condition tends to occur in areas of skin that are exposed to chronic friction and trauma – this is known as the Koebner phenomenon – this is known as the Koebner phenomenon. GPs should look for any signs of psoriasis on the rest of the patient’s skin.

*Candida albicans*, found in the baby’s mouth, can be cultured from inflamed nipples. This may not represent true infection. *Candida*, as a cause of breast symptoms, is controversial; however, it is not unreasonable to give a trial of topical antifungal cream if there is a positive culture.

True mastitis during breastfeeding is seen in about 2% of lactating women. It seems to be more common in women aged 30 years and older and where there has been obstruction of a duct. The infective organism is usually either *Staphylococcus aureus* or Group A *Streptococcus*, which gain entry via cracks in the nipple. Mastitis is acutely painful and patients may be unwell and febrile.

### Differential Diagnoses

The most feared condition in the differential diagnosis of any sort of inflammation of the nipple is Paget’s disease. This presents with a unilateral, well-demarcated, erythematous scaly plaque involving the nipple and areola. It frequently erodes and weeps.

The clue to this patient’s condition being something much less sinister, apart from her age, is that both nipples are involved. A rapid response to appropriate treatment is all that is required to rule out Paget’s disease of the nipple. Papillary adenoma of the nipple is a benign condition; however, it can mimic Paget’s disease with an erosive, crusted rash and bloodstained nipple discharge.

Raynaud’s phenomenon can cause pain during breastfeeding. The clue to this diagnosis is that the nipple blanches during breastfeeding, with the typical triphasic colour change seen in Raynaud’s of the fingers precipitated by exposure to cold.

### Treatment

GPs should ensure that patients with this condition are not using any potential irritants or allergens, including soap, and take a skin swab to rule out bacterial and fungal infection. A finding of *S. aureus* or Group A *Streptococcus* should be treated with oral antibiotics. If there is true cellulitis of the breast with spreading erythema and fever, oral antibiotics should be commenced immediately. Group A *Streptococcus* cannot always be isolated from skin cultures. A finding of *C. albicans* can be treated with topical antifungal cream.

The eczema will settle with regular use of a simple greasy emollient such as white soft paraffin or emulsifying ointment applied after every feed and a topical corticosteroid ointment. A potent non-fluorinated preparation, preferably in an ointment base, such as methylprednisolone aceponate 0.1% or mometasone furoate 0.1%, will produce rapid results in a few days, after which the weaker hydrocortisone 1% can be used immediately for any recurrences. The patient may be anxious about her baby being exposed to the ointment; however, the more potent ones only have to be applied once per day and hydrocortisone twice a day. This should be done directly after a feed.

Anna should continue to breastfeed, providing it is not too uncomfortable for her. Pain relief is important, and paracetamol can be given while breastfeeding. She can be reassured strongly that this is a common and harmless condition. The patient may feel more confident if she speaks with a lactation consultant at an early childhood health centre.

### SUMMARY

Irritation of the nipple during breastfeeding is usually due to mechanical trauma; however, if inflammation and weeping occurs, then mastitis and bacterial superinfection may be present. This is benign and usually responds rapidly to use of topical corticosteroids, bland moisturisers, and antibiotics.

### FURTHER READING


### About the Author

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Male Infertility
VCY Lee, MRCOG, FHKAM(OG); EHY Ng, MD, FRCOG; PC Ho, MD, FRCOG

EPIDEMIOLOGY
Infertility generally affects one in seven couples and is a growing problem worldwide.1,2 This is illustrated by the increase in the number of assisted reproductive technology (ART) treatment cycles worldwide in 2009–2010, ranging from an increase of 5.9% to over 100%.3–5 Male subfertility is one of the major causes, as a sole factor accounting for 29.7% and as a contributor for another 10.3–29.7% in the United Kingdom and Hong Kong.3,5 There is some evidence suggesting that there might be a decline in semen concentration of men born in the 1930's to 1980's.6–8

DEFINITION
In the investigation of an infertile couple, semen analysis has all along been performed for the assessment of the fertility status of the male partner. The World Health Organization manual for examination and processing of human semen has been recognized as the global standard for semen analysis. The most recent World Health Organization manual for semen analysis was published in 2010 and set the lower ‘reference’ limits of semen parameters according to the fifth centile of men, whose partners had a time-to-pregnancy of 12 months or less, worldwide (Tables 1 and 2).9 Therefore, men with semen parameters below the lower reference limits (other than those with azoospermia) are not necessarily infertile. It is recommended that semen samples should be collected by masturbation after 2–7 days of sexual abstinence without the use of lubricants. The process of analysis should be carried out within 1 hour of collection, and two or more samples are required especially for abnormal results.

AETIOLOGY
The aetiology of male infertility can be classified as pre-testicular, testicular, and post-testicular (Table 3).10,11 The management of male infertility should be based on the aetiology if it is known. However, the exact aetiology is often not known.

Pre-testicular causes include hypogonadotrophic hypogonadism due to Kallmann syndrome (with anosmia), brain tumours, radiotherapy for brain tumours, gene mutations (such as luteinizing hormone receptor mutation), and idiopathic hypogonadotrophic hypogonadism. Post-testicular causes are mostly obstructive, which include iatrogenic obstruction (vasectomy), congenital bilateral absence of the vas deferens (CBAVD), and post-inflammation or infection. Testicular causes include genetic causes, infection, systemic diseases, and trauma. Coital dysfunction in the form of erectile and ejaculatory dysfunction is another possible cause of infertility. Retrograde ejaculation can be due to anatomical causes including bladder neck surgery and posterior urethral valves, neurogenic causes including diabetes mellitus and spinal cord injury, and drug-induced like alpha-receptor blockers and antipsychotics.12

CLINICAL WORKUPS
History and Physical Examinations
When infertile couples first attend the
infertility clinic, semen analysis reports should preferably be available for review. A detailed clinical history and clinical examination of the men should be conducted, and further investigations would be dependent on the severity of abnormal parameters. Clinical history includes history of torsion, trauma and infection/inflammation of the testicles (which may damage the testis), drug history like chemotherapy/radiotherapy, surgical history such as orchidopexy for cryptorchidism, and social history especially smoking history, sauna habit and occupation. Physical examination should include the size and consistency of the testes (which are indicators for testicular function), any distension of the epididymis (which may indicate obstructive causes), and the absence of vas deferens (which is indicative of CBAVD).

Genetic Tests
Genetic tests, including karyotype and Y chromosome microdeletion test, should be arranged if there is severe oligozoospermia or azoospermia. Karyotype abnormality and Y microdeletion account for about 15–21% and 8.5–10% of non-obstructive azoospermia (NOA), respectively. Klinefelter syndrome (KS), including 80% non-mosaic type and 20% mosaic type, is the major cause of karyotype abnormality. Most Y chromosome microdeletions occur on the long arm (q) and are subdivided into three azoospermia factor (AZF) regions: AZFa, AZFb, and AZFc. There is evidence that the prevalence of karyotype anomalies and AZF deletions increases with decrease in semen concentrations. The prevalence of karyotype anomalies in oligozoospermic men with semen concentration below 5 million/mL is 8%, which increases to 15% in azoospermic men, while the prevalence of AZF deletion also increases from 5% to 10%. Based on the prevalence of abnormalities of karyotype and Y microdeletion in 295 oligozoospermic or azoospermic men from Hong Kong with different sperm concentrations, we recommend performing a karyotype and Y microdeletion test only if the semen concentration is below 2 million/mL.

Screening for cystic fibrosis genetic mutation should be done in men with CBAVD. The prevalence of cystic fibrosis transmembrane conductance regulator (CFTR) gene in Caucasian men with CBAVD is high, ranging from 71% to 87% in different Western countries, and it warrants proper testing followed by screening of the female partner if a mutation is present. However, the prevalence of cystic fibrosis and the carrier rate of CFTR gene mutation in the Chinese population are very low. As

### Table 1. Semen parameters according to the World Health Organization (2010)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Lower reference limits (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semen volume, mL</td>
<td>1.5 (1.4–1.7)</td>
</tr>
<tr>
<td>Total sperm number, × 10⁶ per ejaculate</td>
<td>39 (33–46)</td>
</tr>
<tr>
<td>Sperm concentration, × 10⁶/mL</td>
<td>15 (12–16)</td>
</tr>
<tr>
<td>PR, %</td>
<td>32 (31–34)</td>
</tr>
<tr>
<td>Total motility (PR + NP), %</td>
<td>40 (38–42)</td>
</tr>
<tr>
<td>Sperm morphology (normal forms), %</td>
<td>4 (3.0–4.0)</td>
</tr>
<tr>
<td>Vitality (live spermatozoa), %</td>
<td>58 (55–63)</td>
</tr>
</tbody>
</table>

NP = non-progressive motility; PR = progressive motility.

### Table 2. Nomenclatures of abnormal semen parameters according to the World Health Organization (2010)

<table>
<thead>
<tr>
<th>Abnormality</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Oligozoospermia</td>
<td>Sperm concentration &lt; 15 × 10⁶/mL or total sperm count &lt; 39 × 10⁶/mL</td>
</tr>
<tr>
<td>Asthenozoospermia</td>
<td>&lt; 32% progressive motility or &lt; 40% total motility</td>
</tr>
<tr>
<td>Teratozoospermia</td>
<td>Normal sperm morphology &lt; 4%</td>
</tr>
<tr>
<td>Azoospermia</td>
<td>No spermatozoa found in ejaculate</td>
</tr>
<tr>
<td>Cryptozoospermia</td>
<td>Spermatozoa absent from fresh preparations but observed in a centrifuged pellet</td>
</tr>
<tr>
<td>Aspermia</td>
<td>Absence of ejaculate (either no ejaculate or retrograde ejaculation)</td>
</tr>
</tbody>
</table>

Any combinations of oligozoospermia, asthenozoospermia and teratozoospermia mean the combination of abnormal parameters shown in semen analysis.
the main aim of genetic testing is to avoid full-blown cystic fibrosis in the offspring by prenatal diagnosis or preimplantation genetic diagnosis if the partner is also a carrier of the mutation, the tests for the mutation would not be necessary in the Chinese.

Hormonal Tests
Hormonal tests, including those for follicle-stimulating hormone (FSH) and testosterone, should be considered in azoospermic men. High gonadotrophin and normal/low testosterone levels (hypergonadotrophic hypogonadism) indicate gonadal failure, and low gonadotrophin and low testosterone levels indicate hypogonadotrophic hypogonadism. Hormonal tests are likely to be normal in azoospermia of obstructive aetiology. The treatment would be completely different. However, there is controversy over the use of hormonal levels and other factors like inhibin B and anti-mullerian hormone to predict the success in surgical retrieval of sperm in men with gonadal failure, and there is no consensus on the cut-off value of these tests in the prediction.18–21 The association of hyperprolactinaemia with or without pituitary adenoma and male infertility is not clearly defined, yet hypogonadism caused by hyperprolactinaemia (resulting in erectile dysfunction) may be a contributing factor.25 Dopamine agonists, such as bromocriptine, can normalize the prolactin level. However, they would not improve the infertility problem in terms of hormonal profiles, semen parameters and pregnancy outcome in hyperprolactinaemic patients or idiopathic infertile men.22,23

Table 3. Aetiology of male infertility

<table>
<thead>
<tr>
<th>Pre-testicular causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Idiopathic (~50%) (idiopathic hypogonadotrophic hypogonadism)</td>
</tr>
<tr>
<td>• Hypothalamic-pituitary-gonadal axis problems (Kallmann syndrome; gene mutations, eg, luteinizing hormone receptor mutation; brain abnormality, eg, pituitary tumour)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Testicular causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital including anorchia and cryptorchidism</td>
</tr>
<tr>
<td>• Genetic diseases (chromosomal including Klinefelter syndrome and balanced translocation; Y microdeletion)</td>
</tr>
<tr>
<td>• Infection/inflammation (eg, tuberculosis, prostatitis)</td>
</tr>
<tr>
<td>• Systemic diseases or medical therapy including chemotherapy and radiotherapy</td>
</tr>
<tr>
<td>• Trauma to testicles or torsion</td>
</tr>
<tr>
<td>• Varicocele</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Post-testicular causes</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Congenital bilateral absence of the vas deferens (with or without cystic fibrosis mutation)</td>
</tr>
<tr>
<td>• Iatrogenic (post-vasectomy)</td>
</tr>
<tr>
<td>• Post-inflammation (epididymitis)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Coital dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Erectile or ejaculatory problem</td>
</tr>
<tr>
<td>• Retrograde ejaculation (anatomical causes, eg, surgery to prostate and bladder neck, and posterior urethral valves; neurogenic causes, eg, diabetes mellitus and spinal cord injury; drug-induced, eg, alpha receptor blockers for benign prostate hyperplasia and antipsychotics)</td>
</tr>
</tbody>
</table>

Miscellaneous
Transrectal ultrasound scanning is used to confirm the diagnosis of obstructive causes and also to delineate the extent of obstruction to see if reconstructive surgery is feasible.24

Tests on sperm DNA integrity and fragmentation are some of the most controversial investigations in male infertility. It has been shown that fertilization and subsequent embryo development depend in part on the inherent integrity of the sperm DNA, and there seems to be a threshold of sperm DNA damage in terms of DNA fragmentation, abnormal chromatin packaging and protamine deficiency.
resulting in impaired embryo development.\(^{25,26}\) The American Society for Reproductive Medicine recommends that there is no proven role for routine DNA integrity testing as the results do not predict pregnancy outcomes in spontaneous conception and ART treatment cycles and there is no effective treatment available for abnormal DNA integrity.\(^{27}\) Therefore, tests for DNA fragmentation should not be used routinely for infertility investigations.

**TREATMENT**

Treatment would depend on the aetiology of the male factor, the severity of abnormalities in semen parameters, and the presence of female factors such tubal status and woman’s age. In men with mildly abnormal semen parameters to severe oligoasthenoteratozoospermia, intrauterine insemination (IUI) and in vitro fertilization (IVF) with or without intracytoplasmic sperm injection (ICSI) can improve the pregnancy rate. In men with azoospermia, treatment would be dependent on the underlying reasons. The algorithm is shown in Figure 1.

**Azoospermia**

Azoospermia can be classified as NOA and obstructive azoospermia (OA). NOA can further be classified as due to gonadal failure or hypogonadotropic hypogonadism. Surgical retrieval of sperm is the treatment for OA and gonadal failure. There are different techniques including percutaneous epididymal sperm aspiration (PESA), microsurgical epididymal sperm aspiration (MESA), testicular sperm aspiration (TESA)/testicular sperm extraction (TESE), and microscopic or microdissection testicular sperm extraction (mTESE).

**Obstructive azoospermia.** PESA and MESA are used in OA to retrieve epididymal sperm from distended tubules in the epididymis. PESA can be done under local anaesthesia. It involves percutaneous puncture of the scrotal skin into the epididymis using a fine needle (eg, 26-gauge), and aspiration can be repeated in multiple sites.\(^{28}\) MESA involves an open operation under an operating microscopy and is able to retrieve greater number of sperm and minimize contamination of the sample with blood. Some urologists advocate MESA over PESA in patients with OA who would consider more than one IVF cycle, as MESA typically results in sperm with adequate motility for effective cryopreservation for multiple treatment cycles.\(^{29}\) There is so far no direct comparison between MESA and PESA. A Cochrane review commented that there is only scarce evidence on the choice of surgical technique in sperm retrieval.\(^{30}\) So, the choice of surgical technique would mainly depend on personal preference and surgical expertise. If no sperm is obtained from the epididymis, direct retrieval of sperm from the testicles can be performed in the same setting.\(^{28}\) MESA can be combined with reconstructive surgery in selected cases.\(^{31}\)

**NOA – gonadal failure.** Surgical retrieval of testicular sperm is the mainstay of treatment for hypergonadotropic hypogonadism. TESE/ TESA involves retrieval of sperm directly from the testicles using different techniques. mTESE requires an operation under microscopy and helps in visualization of the larger, more opaque, whitish tubules, presumably containing more intratubular germ cells with active spermatogenesis. A higher retrieval rate was reported with mTESE than with conventional TESE.\(^{32,33}\) The successful retrieval rate in NOA patients is typically quoted as less than 50%, although a higher retrieval rate may be possible with mTESE.

The use of TESE or mTESE, together with ICSI in IVF treatment cycles, is the only option for KS men to bear their own genetically linked children, and the success rate of surgical retrieval of sperm was reported to be similar with other NOA men with no karyotype abnormality.\(^{34,35}\) One group reported a higher retrieval rate of 68% and 72% in KS men using mTESE or conventional TESE, respectively.\(^{36,37}\) Not only is karyotype abnormality a predictor of the success of retrieval, the presence of AZF microdeletions on the Y chromosome is also a good predictor. Men with AZFc microdeletions alone have a similar success rate of surgical sperm retrieval on TESE, while those with AZFa or AZFb microdeletions will almost definitely have no sperm retrieved for ICSI.\(^{15,38}\) Therefore, genetic tests would be extremely useful in counselling before the surgical retrieval of sperm and for examining the inheritance of the mutation in the next generation.

**NOA – hypogonadotropic hypogonadism.** Induction of spermatogenesis with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins, ie, human chorionic gonadotrophin (hCG) or FSH, is the treatment of choice for men with hypogonadotropic hypogonadism.\(^{39}\) Both treatments have been shown to in-
duce spermatogenesis successfully.\textsuperscript{39–41} Although some investigators showed that the use of pulsatile GnRH was related to a greater testicular growth and faster induction of spermatogenesis, the ‘take-off’ for this kind of treatment is limited by the high cost of the drug and the difficulty in handling the pump system. The high success rate of gonadotrophins, ranging from 53\% to 78\%, implies that it is the treatment of choice in some localities.\textsuperscript{42,43} The usual recommended treatment consists of twice weekly injection of hCG 1,500 IU to 2,000 IU, with further dosage increment after review of the hormonal levels in 4 to 6 weeks’ time. In men suffering from hypogonadotropic hypogonadism after puberty, hCG alone is usually sufficient.
for induction of spermatogenesis, with the median sperm count of 8 million/mL, when their partners get pregnant.43 Whereas in men suffering prepubertal hypogonadism, the treatment usually requires FSH together with hCG injection in order to induce spermatogenesis.42,43 Prior androgen administration was shown to be related to a slower induction of spermatogenesis. The average treatment duration may be up to 25 to 30 months before the men can impregnate their partners.43

Abnormal Semen Parameters
The treatment would be dependent on the severity of abnormal semen parameters, after taking into consideration the woman’s age and tubal status. IUI and IVF can be offered.

Artificial insemination using husband’s semen may be performed with intravaginal insemination, intracervical insemination, or IUI. IUI is currently the most commonly performed method in the management of male infertility. It is used in men with 2–5 million total motile spermatozoa after processing. The criteria differ in various clinics, with the lowest threshold of 1 million total motile spermatozoa in the inseminate.44 Sperm morphology (strict criteria) seems to be predictive of the success rate of IUI, with a significantly higher pregnancy rate when the morphology is ≥ 4%.45 However, different centres should have their own criteria for recruitment for IUI. There is contradicting evidence on the protocol of IUI. It was suggested that IUI has no significant benefit over timed intercourse and ovarian stimulation does not improve the outcome.46 However, it was shown that gonadotrophin for ovarian stimulation offers a significantly better pregnancy outcome than does anti-oestrogen, while there was no difference between anti-oestrogen and aromatase inhibitor. There was also no benefit in using either GnRH agonist or antagonist in IUI in terms of pregnancy rate. Low-dose gonadotrophin was suggested, as doubling the dose would only increase the complication rate, namely multiple pregnancy rate and ovarian hyperstimulation syndrome, but not the pregnancy rate.47 As there is no robust evidence, further properly designed trials are needed to confirm the present suggestions.

In vitro fertilization consists of follicular development with various ovarian stimulation protocols, oocyte retrieval, fertilization inside laboratory environment, and transfer of embryos to the uterine cavity. Since the first report of the use of ICSI in human that resulted in a pregnancy, ICSI has become the routine practice for severe male infertility.48 ICSI is the procedure of injecting a single sperm directly into an oocyte. Although sperm morphology was reported to be more relevant to fertilization failure,49 the prediction of fertilization failure by morphology or other parameters is still poor50 and so different centres have their own set of criteria for using ICSI. The development after fertilization including the blastulation rate was shown to be not affected by sperm morphology.51 A study showed that the use of ICSI in non-male infertility was associated with a lower implantation rate when compared with conventional insemination; thus, ICSI should be reserved for severe male factor infertility. As shown by a recent review, there is a slight increase in de novo chromosomal abnormalities and the major congenital malformation rate is similar for IVF and ICSI (~3–4%).53

Miscellaneous therapies. (a) Antioxidant. There is evidence suggesting that reactive oxygen species (ROS)-mediated damage to sperm is a significant contributing pathology in 30–80% of male factor infertility. There are two principal mechanisms of ROS-related infertility. Firstly, ROS damage the sperm membrane, impairing the sperm’s motility and ability to fuse with the oocyte. Secondly, ROS causes sperm DNA damage, compromising the paternal genomic contribution to the embryo.54 Raised ROS levels are usually associated with smoking, genital tract or systemic infections, and varicocele.55,56 It has been shown that embryos formed from fertilization with sperm having high DNA damage are of poorer quality and have a decreased cleavage rate.57

As antioxidants (namely vitamins C and E, folate, zinc, selenium, carnitine, and carotenoids) are scavengers of ROS, they have been studied in male factor infertility. A Cochrane review indicated that the use of antioxidants, such as vitamin C and zinc, may improve the pregnancy outcome in ART cycles based on evidence from small randomized trials, and larger trials are needed to confirm the results.58 There is also evidence of improvement of sperm parameters and spontaneous conceptions. However, the trials were all small and had significant methodological and clinical heterogeneity. Drawing a conclusion from these trials may not be appropriate,59 and so antioxidants should not be recommended routinely.
(b) Treatment of varicocele. There is a hot controversy on the effectiveness of varicocele treatment (including surgical and radiological methods) on semen parameters and pregnancy outcomes. Some investigators reported no improvement\textsuperscript{60,61} while others showed significant improvement in spontaneous conceptions.\textsuperscript{52–64} According to the recommendation of the American Society for Reproductive Medicine, treatment of varicocele should be considered if all of the following conditions are met: (1) the varicocele is palpable on physical examination of the scrotum; (2) the couple has known infertility; (3) the female partner has normal fertility or a potentially treatable cause of infertility; and (4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Moreover, it explicitly expressed that varicocele treatment for infertility is not indicated in patients with normal semen qualities and a subclinical varicocele.\textsuperscript{65} As some trials included men with subclinical varicocele, the outcome in men with clinical varicocele would be difficult to interpret. Nevertheless, the evidences come from the comparison between expectant management and varicocele treatment in spontaneous conception while there is no evidence of the effectiveness in ART cycles including IUI and IVF cycles. Different surgical approaches were compared in one randomized trial, which revealed that subinguinal microsurgical varicocelectomy had better outcomes than open inguinal and laparoscopic varicocelectomy.\textsuperscript{66}

(c) Lifestyle modification. Tobacco smoking is associated with male factor infertility, probably related to the increase in ROS and DNA damage. There are many studies showing poorer semen quality in smokers compared with non-smoking counterparts.\textsuperscript{67,68} However, there is no evidence showing that quitting smoking may improve semen parameters.\textsuperscript{69} Nonetheless, smoking has been shown to reduce significantly the pregnancy rate in IVF treatment cycles.\textsuperscript{69} It would be sensible to advise both partners to quit smoking before commencement of treatment cycles, not only for the ART cycles but also for their general health.

Coital Dysfunction

Psychosexual counselling is the mainstay of treatment for coital dysfunction. The use of phosphodiesterase inhibitors, such as sildenafil and vardenafil, should be considered in men with erectile dysfunction after excluding contraindications.\textsuperscript{70} If these first-line treatment methods fail, intra-penile injections, vacuum constriction devices and implantation of a penile prosthesis for the treatment of their erectile dysfunction can be considered.\textsuperscript{71} If the couple fails to conceive naturally after these measures or if the semen quality is not good, ART like IUI or IVF may also help.

For retrograde ejaculation, treatment of the underlying causes is needed. Drug treatment is the first-line treatment, including alpha agonistic drugs and parasympathomimetics. If the drug therapy fails, penile electrovibration stimulation and sperm retrieval from the urine with oral sodium bicarbonate a few hours before collection of urine can be offered.\textsuperscript{12}

Other Options

In men who have NOA and no sperm retrieved from surgery, or men with AZFa or AZFb deletion, use of donor sperm should be counselled. Couples should be fully counselled on the implications of the use of donor gametes. The couple also needs to understand the regulation of the law and the code of practice in different countries and regions, like the Human Fertilisation and Embryology Authority in the United Kingdom and the Council on Human Reproductive Technology in Hong Kong. Adoption and childlessness are the other two options.

CONCLUSION

Semen analysis is the most common method for assessment of fertility status of the male partner, although its prognostic value is limited except in the case of azoospermia. The management of male infertility should be based on the aetiology if it is known. For male infertility with unknown cause, empirical treatment methods such as IUI, IVF and ICSI can be offered. The development of these methods offers hope for couples suffering from male infertility, even for those with severe sperm problems or azoospermia.

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A complete list of references can be obtained upon request to the editor.
CME Questions

This continuing medical education service is brought to you by the Medical Progress Institute, an institute dedicated to CME learning. Read the article ‘Male Infertility’ and answer the following questions. This JPOG article has been accredited for CME by the Hong Kong College of Obstetricians and Gynaecologists.

CME Article

Male Infertility

Answer True or False to the questions below.

1. Male factor infertility accounts for 10% of subfertility problems.
2. Klinefelter syndrome is a major chromosomal abnormality found in patients with non-obstructive azoospermia.
3. Tests for CFTR gene mutation should not be offered to men with congenital bilateral absence of the vas deferens in various Caucasian populations.
4. Tests for Y chromosome microdeletion in the AZF region have prognostic value in the success of surgical retrieval of sperm.
5. Bromocriptine can improve semen parameters and pregnancy outcomes in men with hyperprolactinaemia.
6. Tests for DNA fragmentation should not be used routinely in the investigation of infertility.
7. Non-obstructive azoospermia can be classified as due to gonadal failure or hypogonadotrophic hypogonadism.
8. Induction of spermatogenesis with pulsatile gonadotrophin-releasing hormone (GnRH) or gonadotrophins is the treatment of choice for men with hypogonadotrophic hypogonadism.
10. Antioxidant treatment can clearly improve the sperm parameters.

Name in BLOCK CAPITALS: ________________________________

Signature: ________________________________

Date: ________________________________

Please mail your completed answer sheet back to: The Secretariat
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