TUTORIAL ONE – NEONATAL JAUNDICE

Introduction and Epidemiology

Jaundice is a disorder in which the skin, sclera, deeper tissues and excretions are stained a distinct yellow colour due to high plasma levels of bilirubin (a breakdown product of blood). While jaundice is a common physiological event, the possibility of pathology should always be a consideration.

1. 25-50% of full-term infants develop clinical jaundice (80-85μmol/L), but only 3% develop serum bilirubin levels higher than 210μmol/L
2. Risk factors for neonatal hyperbilirubinaemia include:
   a. Geography – East Asians, Native Americans, Greeks living in Greece, high altitudes
   b. Familial – siblings with neonatal jaundice, family history of relevant genetic disorders
   c. Maternal – diabetes, breast feeding, drugs (e.g. oxytocin in hypotonic solution)
   d. Neonatal - gestational age <37 weeks, low birth weight, low intake of breast milk

Physiology of Bilirubin Production

Bilirubin is produced in the reticuloendothelial system as the product of haem catabolism – 75% is derived from haemoglobin, but degradation of myoglobin, cytochromes and catalase also contribute.

1. Haem oxygenase (rate-limiting) degrades the haem moiety yielding biliverdin, iron and carbon monoxide (which can be measured in neonatal expiration as a marker for bilirubin production)
2. Biliverdin reductase reduces biliverdin (water-soluble) to bilirubin (practically insoluble)
   a. Unconjugated bilirubin is bound to albumin (increases in age, decreases in illness)
   b. A minute fraction is free in serum and is able to the blood-brain barrier (neurotoxicity)
3. Albumin-bound bilirubin then travels to the hepatocyte and is transported into the cell, where it partially binds to ligandin (increasing levels of this increases uptake of bilirubin)
   a. Ligandin levels are low at birth, but increase rapidly over the first few weeks of life
   b. Ligandin concentrations may also be increased with some drugs (e.g. phenobarbital)
4. Uridine diphosphoglucoronyltransferase in the endoplasmic reticulum catalyses binding of bilirubin to glucuronic acid (conjugation) making it water-soluble, able to be excreted in bile
   a. UDPGT activity is low at birth but increases to adult levels by age 4-8 weeks
   b. Activity is also increased by some drugs (phenobarbital, dexamethasone, clofibrate)
5. Once excreted, bilirubin is reduced to colourless tetrapyroles by colonic microbes
   a. β-glucuronidases in the brush border of the proximal small bowel deconjugate some bilirubin, which can then be reabsorbed into the circulation (enterohepatic circulation)
   b. Breast milk from certain mothers can also increase enterohepatic circulation

Aetiology

Physiological variation and pathology at any stage of bilirubin metabolism can lead to jaundice in the neonate. Causes are classified as indirect (<15% conjugated) and direct (>30-40% conjugated):

1. Indirect (unconjugated) hyperbilirubinaemia – note this can be physiologic due to increased bilirubin production (haemolysis of senescent red cells) and decreased excretory capacity
   a. Increased haemolysis:
      i. ABO or Rh incompatibility (fairly common if Rh prophylaxis available)
      ii. Abnormal red cells: spheroctosis, elliptocytosis, pyknocytosis, stomacytosis, glucose-6-phosphate dehydrogenase deficiency, pyruvate kinase deficiency
      iii. Others – sepsis ± DIC, swallowed maternal blood, birth trauma
   b. Decreased conjugation:
      i. Deficient hepatic uptake of bilirubin (Gilbert syndrome, incidence ~7%)
      ii. UDPGT deficiency (Crigler-Najjar II partial, Crigler-Najjar I complete)
   c. Others – hypothyroidism, maternal diabetes, Lucey-Driscoll syndrome (familial benign unconjugated hyperbilirubinaemia)
2. Direct (conjugated) hyperbilirubinaemia – generally comparatively rare in neonates
   a. Obstructed bile flow (± hepatocellular injury) – biliary atresia, choledochal cyst, Alagille syndrome (hypoplasia of interlobular bile duct), intestinal obstruction
   b. Hepatocellular injury with normal bile ducts
      i. Infection – viral (CMV, HBV, rubella, others), bacterial (Gram-negative sepsis, UTI or pylonephritis), parasitic (toxoplasmosis)
      ii. Metabolic – α1-antitrypsin deficiency, cystic fibrosis, carbohydrate diseases (galactosaemia, glycogen storage), lipid diseases (Gaucher’s disease)
      iii. Iatrogenic – parenteral nutrition, drugs (aspirin, sulfonamides, frusemide)
      iv. Idiopathic – hypopituitary, Dubin-Johnson & Rotor syndromes, Byler disease (progressive familial intrahepatic cholestasis), idiopathic neonatal hepatitis
Approach to Neonatal Jaundice

History and Examination:

1. Onset and duration may be useful to determine aetiology:
   a. Early (within 24 hours): always pathological, usually haemolytic (don't forget sepsis)
   b. After first day: most likely physiological (peaks 3-4 days, resolves by 1-2 weeks)
   c. Prolonged (after 7-10 days): exclude biliary atresia and hypothyroidism, further tests

2. Physical examination – not terribly useful, as most cases are just yellow ± drowsiness
   a. Neonatal jaundice is first seen in the face (“press the nose”) then gradually becomes visible
      in the chest/upper limbs, then pelvis and lower limbs (i.e. foot jaundice is bad)
   b. Hepatosplenomegaly, petechiae and microcephaly are suggestive of haemolytic anaemia,
      sepsis and congenital infections (which exacerbate neonatal jaundice)
   c. Neurological signs (altered tone, seizures, altered crying) in a significantly jaundiced infant
      are signs of early kernicterus (bilirubin >360µmol/L) which may progress:
      i. Stage I – sleepy, reduced suckling, lethargic feeding
      ii. Stage II – increased T°, odd mouth movement, lid retraction ('setting sun')
      iii. Stage III – latent phase
      iv. Stage IV – subsequent cerebral palsy, deafness, decreased IQ (later)

Investigations:

1. Serum bilirubin (total and direct) differentiates conjugated from unconjugated bilirubinaemia.
   Bilirubin can also be measured transcutaneously or via exhaled carbon monoxide
2. In most cases, the only other blood tests needed are blood type and group (mother and baby) and a
   direct Coombs test (Newman TB, Maisels MJ. Paediatrics 1992; 89:809-18)
3. However, in certain cases there may be increased risk for severe jaundice or there may be signs
   suggestive of an underlying illness warranting further investigation:
   a. Unconjugated – FBC + smear, blood culture, TFTs, Guthrie card tests
   b. Conjugated – LFTs + coags, titres for TORCHS, HbSAg, α1-antitrypsin level, sweat test for
      CF, RUQ ultrasound, radionucleotide biliary imaging, liver biopsy

Management of Neonatal Jaundice

Phototherapy is the primary treatment for neonates with unconjugated hyperbilirubinaemia. It works by
conversion of unconjugated bilirubin to water-soluble photo-isomers (mainly lumirubin) – note that these
cannot cross the blood-brain barrier, greatly reducing risk of neurotoxicity. Phototherapy should be stopped
when serum bilirubin falls 25-50µmol/L below initial levels – note that levels often rebound after treatment
has been stopped, so follow-up blood tests are taken 6-12 hours after discontinuation.

Exchange transfusion (directly removes bilirubin from intravascular compartment) was first line treatment
for neonatal jaundice until phototherapy was discovered in the 1950s, and currently is second-line therapy.
Prophylactic treatment of Rh-negative women with immunoglobulin has also significantly decreased the
incidence of neonates with severe Rh haemolytic disease. 180mL/kg is used, ~20mL at a time → ~90%
exchange of total blood volume.

American Academy of Paediatrics recommendations based on total serum bilirubin (µmol/L):

<table>
<thead>
<tr>
<th>Age (hours)</th>
<th>Consider phototherapy</th>
<th>Exchange transfusion if phototherapy fails</th>
<th>Exchange transfusion and intense phototherapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤24**</td>
<td>-</td>
<td>- (≥260µmol/L)</td>
<td>- (≥430µmol/L)</td>
</tr>
<tr>
<td>24-48</td>
<td>≥170µmol/L</td>
<td>≥260µmol/L*</td>
<td>≥430µmol/L*</td>
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<tr>
<td>49-72</td>
<td>≥260µmol/L</td>
<td>≥310µmol/L*</td>
<td>≥510µmol/L</td>
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<tr>
<td>&gt;72</td>
<td>≥290µmol/L</td>
<td>≥340µmol/L*</td>
<td>≥510µmol/L</td>
</tr>
</tbody>
</table>

* Failure of intensive phototherapy is defined as failure of bilirubin to fall 15-30µmol/L within 4-6 hours
** Infants ≤24 hrs old are excluded as jaundice is usually considered pathologic needing investigation

Other treatment modalities:

1. Phenobarbital can be used to enhance bilirubin metabolism but is generally only used in populations
   with high incidence of kernicterus (due to concerns about long-term effects)
2. IV immunoglobulin (500mg/kg) has been shown to significantly reduce the need for exchange
   transfusion in infants with isoimmune haemolytic disease (but probably not worth the risks)
3. Metal mesoporphyrins and protoporphyrins block the activity of haem oxygenase, allowing haem to
   be excreted directly in bile. These have not reached clinical use yet.
4. Treat the causes of conjugated hyperbilirubinaemia medically or surgically as required
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TUTORIAL TWO – NEONATAL HYPOGLYCAEMIA

• Introduction

Neonatal hypoglycaemia is difficult to define as there is no consensus on the blood glucose level appropriate for diagnosis. At National Women’s Hospital it is defined as serum glucose < 2.6mmol/L.

1. Risk factors:
   a. All infants with birth weight < 2.5kg or > 4.5 kg
   b. Important to remember preterm infants and those born to diabetic mothers
   c. Stresses – birth asphyxia, sepsis, haemolysis, respiratory distress, heart disease

• Physiology of Glucose Metabolism

There are three sources of glucose – dietary intake, release from liver and release from the kidney (fine-print stuff, only in prolonged starvation states). Serum levels are carefully maintained in a tight range by tight control of glucose homeostasis by insulin, glucagon, receptors and transporters.

In the fetus insulin concentrations are higher than in the adult – consequently both the insulin and glucagon response to acute changes in fetal plasma glucose are limited (defective cAMP activity).

1. Pre-birth:
   a. Placental glucose transport meets all requirements in the basal (non-stressed) state
   b. Stress results in catecholamine release which increases glucose and fatty acid levels

2. Post-birth:
   a. Serum glucagon and catecholamines increase 3-5x in response to cord-cutting
   b. Insulin levels fall and remain low for several days, and along with high glucagon and catecholamines supports glycogenolysis, lipolysis and gluconeogenesis
   c. Hepatic glucagon receptors increase in number, insulin receptors decrease and the cAMP response becomes functional
   d. Glycogen phosphorylase increases and glycogen synthetase decreases with time

• Aetiology

Limited hepatic glucose production:

1. Prematurity (transient)
   a. Functionally immature hepatocytes – poor gluconeogenic & glycogenolytic enzymes
   b. Fetal brain is proportionally larger and uses relatively more glucose when starved

2. Prenatal stress (transient)
   a. Hypoxia and acidosis lead to increased catecholamine activity ⇒ glycogenolysis
   b. Anaerobic metabolism of glucose with inefficient production of ATP

3. Inborn errors of metabolism (persistent)
   a. Enzyme deficiencies that affect glycogen metabolism – glucose-6-phosphatase, fructose-1,6-disphosphatase, phosphorylase
   b. Rarely amino acidopathies can affect gluconeogenesis

4. Starvation

Hyperinsulinism:

1. Infant of diabetic mother (transient)
   a. Impaired glucose production
   b. Persistent hyperinsulinaemia leads to marked and sustained hypoglycaemia

2. Rh incompatibility ⇒ erythroblastosis fetalis (persistent)

3. Beckwith-Weidemann syndrome (persistent)
   a. Exophthalmos, macroglossia, gigantism with macrosomia, neonatal hypoglycaemia
   b. Pancreatic β cell hypertrophy and hyperinsulinism

4. Others (persistent) – nesidioblastosis, islet cell adenoma and adenomatosis

Other conditions:

1. Sepsis (persistent) – increased BMR, lower gluconeogenesis, enhanced insulin sensitivity

2. Cold stress (transient) – increased glucose expenditure for thermoregulation

3. Hypothalamic, pituitary, adrenal disorders – 2° to effects on glycogenolysis/gluconeogenesis

4. Congenital heart disease – anaerobic utilisation of glucose (2° to hypoxaemia, hypotension)

5. Exchange transfusion – dextrose in stored blood products causes rebound hypoglycaemia

6. β-sympathomimetics to induce labour (transient) – may increase insulin secretion

7. High umbilical artery catheter with administration of glucose (transient) – hyperinsulinism
**Approach to Neonatal Hypoglycaemia**

**Symptoms** may include 'jitteriness', lethargy, feeding intolerance, apnoea, cyanosis, seizures, abnormal or high-pitched cry, coma, hypotonia, tremors, tachypnoea, cardiac arrest and hypothermia.

**Investigations:**
1. Blood glucose level via heel prick
2. If severe or persistent measure insulin, cortisol and growth hormone
3. Other investigations:
   a. Ammonia and acid-base status
   b. First void urine for ketones, organic acids and amino acids
   c. Guthrie card for MCAD or LCHAD DNA deletions (if low ketones with hypoglycaemia)

**Management:**
1. Monitor plasma glucose in at-risk infants
   a. Measure at 1-2 hours of age and at 4 hours, then 4 hourly (preferably before feeds)
   b. Monitor for 12 hours (or 12 hours from last hypoglycaemic level)
   c. If on dextrose monitor daily and with any decrease in infusion rate
2. Early intervention with oral or enteral feeding:
   a. Increase feed volume and feed rate (continuous if necessary)
   b. Increase glucose content of feeds using Polycose
   c. Supplement with 40% dextrose gel at 0.5mL/kg on buccal mucosa
   d. Others – IV infusion, glucagon if in trouble, hydrocortisone

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**TUTORIAL THREE – RESPIRATION AND THE NEONATE**

**Normal Lung Development and Function**

**Structural development** of the lungs is divided into four or five stages:
1. **Embryonic** (<5 weeks)
2. **Pseudoglandular** (5-16 weeks) – developing lung resembles an exocrine gland, all major elements are present except those involved in gas exchange (fetus not viable)
3. **Canalicular** (13-25 weeks) – characterised by vascularisation of lung tissue & differentiation of the cells. By the end of this stage respiratory bronchioles and alveolar ducts begin to form
4. **Terminal** (25-40 weeks) – continuing development of terminal sacs, epithelium becomes things, predominantly type I pneumocytes and some type II (surfactant-producing)
5. **Alveolar** (post natal, up to 8-10 years) – more respiratory bronchioles and primordial alveoli form. A term baby has only 1/5th of final alveoli, and preterm babies have no alveoli at all.

Note that only a small proportion (~8% vs. 100%) of blood returning to the fetal heart passes through the lungs as it bypasses via shunts (foramen ovale and ductus arteriosus). Consequently there is a very high pulmonary vascular resistance.

**Fetal lung fluid** fills the airways from early gestation until birth, where it clears and allows air breathing to occur. It has a role in fetal lung expansion, growth and maturation via lung expansion.
1. Different composition to amniotic fluid and plasma; produced by active transport mechanisms (primarily the transfer of C1 from plasma creating an osmotic gradient along which water follows)
2. Production is inhibited by adrenaline and vasopressin (especially in late gestation) – these increase cAMP causing activation of Na+ channels, reducing the osmotic gradient and leading to reabsorption. High hydrostatic pressure in apnoea and tracheal obstruction also contribute
3. By full term the alveoli contain ~30mL/kg of fetal lung fluid – it circulates by leaving via the trachea where it is either swallowed or enters the amniotic fluid

**Surfactant** reduces the surface tension at the air-liquid interface within the lung, reducing the work of breathing and allows small and large alveoli to co-exist.
1. Comprised of phospholipids, primary dipalmitoylphosphatidylcholine (DPPC) and proteins; produced and stored by type II alveolar epithelial cells
2. Type II cells and hence surfactant start appearing at about the 20th week of gestation, increasing slowly until a surge at 30-34 weeks of gestation where the lungs become mature
3. Surfactant can be increased by steroids (dexamethasone or betamethasone – cross the placenta, long half-life) with greatest benefit more than 48 hours and less than 7 days prior to delivery

At birth for gas exchange to occur there must be:
1. Clearance of liquid from airways:
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a. Reabsorption (90% vascular, 10% lymphatic) via reversal of osmotic gradient (mediated by stress hormones, corticosteroids, thyroid hormones)

b. Expulsion via the trachea due to changes in fetal posture (with uterine contractions)

2. Changes in pulmonary circulation (decreased pulmonary vascular resistance) due to increased blood $O_2$, onset of ventilation, lower lung volume and local vasodilators (NO, bradykinin, prostaglandins)

The first breath is a response to tactile, thermal, chemical (CNS, changes in blood gas) and mechanical stimuli. It requires an opening pressure of at least 20-60cm H$_2$O to overcome the surface tension of the air-liquid interface. Less pressure is needed for subsequent breaths as there is higher air volume in the lungs.

### Respiratory Diseases in the Neonate

**Respiratory distress syndrome** is a disease of lung immaturity, often due to surfactant deficiency (most common cause of morbidity and mortality in neonates). It is sometimes referred to as hyaline membrane disease as the lungs are under-inflated with alveoli filled with protein resembling a glassy membrane.

1. **Risk factors** – prematurity, perinatal asphyxia, maternal diabetes, caesarean section

2. **Clinical features** – onset in the first few hours of life, tachypnoea, grunt, flare and retraction ± pallor and cyanosis. Decreased breath sounds, hypotension and prolonged capillary refill on examination.

3. **CXR** – decreased lung volume, air bronchograms, reticulogranularity, lung opacification

4. **Management:**
   a. All women with threatened preterm delivery between 23 and 34 weeks gestation should be considered for antenatal steroids (glucocorticoids) which promote lung maturation
   b. Preterm babies of <30 weeks gestation should receive prophylactic surfactant (bolus injection, slow injection or nebuliser) ASAP, others as required or after diagnosis (‘rescue’)

**Transient tachypnoea of the neonate** (‘wet lung syndrome’) is characterised by delayed reabsorption of normal lung fluid which accumulates in peribronchiolar lymphatics and bronchovascular spaces. This results in high total ventilation and high respiratory rate but low tidal volume and a high dead space.

1. **Risk factors** – term or near-term infants, caesarean section, low Apgar scores, pulmonary artery hypertension, poor left ventricular volume, precipitous delivery

2. **Clinical features** – onset after 2-6 hours, mild to severe hypoxaemia & acidaemia

3. **CXR** – hyperexpansion, streaky infiltrates radiating from the hilum (interstitial fluid along the bronchovascular spaces), visible fluid in pulmonary fissures and cardiomegaly

4. **Management:**
   a. Usually resolves spontaneously within 72 hours via normal lymphatic clearance
   b. Supplemental $O_2$ (± CPAP), diuretics and normal supportive neonatal cares may help

**Meconium aspiration** causes problems by physical obstruction (→ atelectasis, air trapping, alveolar collapse and V/Q mismatch), inflammation (chemical pneumonitis), inhibition of surfactant function, and increased pulmonary vascular resistance (→ persistent pulmonary hypertension of the newborn)

1. **Risk factors** – term and post-term infants, fetal asphyxia, meconium-stained amniotic fluid (8-19%)

2. **Clinical features** – tachypnoea, rales, cyanosis → grunting, retraction, flare → profound cyanosis, pallor, irregular gasping, barrel chest (ball valve, gas trapping, alveolar over-distension)

3. **CXR** – air trapping, hyper-expansion and hyperinflation, bilateral diffuse coarse patchy infiltrates

4. **Management:**
   a. All infants at birth get suction at the perineum before the first breath is taken
   b. If symptomatic may need intubation, tracheal suction, oxygenation/ventilation and sedation

**Chronic lung disease** (bronchopulmonary dysplasia) is characterised by arrested lung development. It may be a complication of lung disease (RDS, oesophageal atresia, aspiration pneumonia, congenital heart disease, meconium aspiration), or iatrogenic from oxygen toxicity or barotrauma (pressure ventilation).

1. **Risk factors** – prematurity, very low birth weight (<1500g), patent ductus arteriosus, poor nutrition, fluid overload, antioxidant deficiency, inflammation (→ iatrogenic causes), family history of asthma

2. **Clinical features** – tachypnoea, exercise intolerance, $O_2$ dependence, respiratory distress (retractions, nasal flaring, fine rales at bases or throughout)

3. **CXR** – depends on the stage of disease:
   a. Stage 1 – reticulogranular pattern and air bronchograms or RDS (first 3 days of life)
   b. Stage 2 – coarse granular infiltrates dense enough to obscure cardiac markings (3-10 days)
   c. Stage 3 – multiple small cysts within opaque lungs and visible heart border (10-20 days)
   d. Stage 4 – irregular large cysts alternating with areas of increased density (after 28 days)

4. **Management** aims to reduce factors that cause re-injury, allowing the lung to heal
   a. Adequate oxygenation and ventilation (allow permissive hypercapnia of 45-55mmHg $P_{aco_2}$)
   b. Adequate nutrition and fluid restriction
   c. Early ductus arteriosus closure (otherwise → oxygen toxicity, barotrauma)
d. Pharmacologic management:
   i. Bronchodilators (β₂ agonists, histamine inhibitors, methylxanthines; inhaled or systemic) relax bronchial smooth muscles to improve lung mechanics
   ii. Steroids (dexamethasone, beclomethasone; inhaled or systemic) improve survival, allow weaning from ventilators and decrease need for supplemental O₂
   iii. Diuretics improve lung mechanics, clinical respiratory status and allow weaning from mechanical ventilation

TUTORIAL FOUR – NEONATAL INFECTIONS

• Pathophysiology

Risk factors for neonatal infection include prematurity, low birth weight, hypothermia, prolonged rupture of membranes, and some congenital malformations (meningomyelocoele and abnormalities of the urinary tract). Potential sources and routes include:

1. Before birth – across the placenta (rubella, CMV, Toxoplasma, syphilis, TB, HIV) or ascending the birth canal (group B strep, E. coli, P. aeruginosa, Listeria monocytogenes, Mycoplasma hominis)
2. During delivery – organisms ascending the birth canal and gonococcus, HBV, Candida albicans, Coxsackie viruses and Chlamydia trachomatis
3. Within the first few days of life (often from caregivers, less frequently from mothers) – skin and umbilicus (Staphylococci), lower gut (E. coli), upper respiratory tract (Streptococci)

Protective mechanisms:

1. Immunoglobulins:
   a. Selective transfer of maternal IgG across the placenta in the last few weeks of pregnancy gives some protection against viral diseases (measles, mumps, chicken pox and rubella) but usually not bacteria (E. coli, group B Streptococci, H. influenza and S. pneumoniae)
   b. IgM or IgA cannot cross the placenta, but IgM can be produced in utero by 12-16 weeks and breast milk provides maternal IgA (absorbed whole by the neonatal intestinal mucosa)

2. Complement:
   a. Present in reduced amounts at birth
   b. Usually damages cell membranes of invading organisms, facilitating phagocytosis

3. Cellular immune systems:
   a. B lymphocytes (produce immunoglobulins) are immature at birth
   b. T lymphocytes (recognise foreign cells or cytotoxic) have limited function in the term infant
   c. Polymorphonuclear leucocytes move according to complement and phagocytose bacteria
      i. Migrate less effectively in the neonatal period but have fully mature killing capacity
      ii. Neutropenia may result with overwhelming infection (poor bone marrow response)

Colostrum contains IgA, lysozymes, lactoferrin and lymphocytes. Breast milk also reduces proliferation of organisms in the gut as the acidity produced by breakdown of lactose favours growth of harmless Lactobacilli, inhibiting growth of more pathogenic organisms such as E. coli.

• Serious Acute Neonatal Infections

Overview:

1. Incidence – 3 per 1000 live births
2. Clinical features – temperature instability, hypothermia, reluctance to feed, lethargy, vomiting, an anxious look, skin pallor, irritability, apnoea, jaundice, abdominal distension, collapse, failure to thrive
3. Investigations – FBC, blood cultures (1x 1mL sample), urine culture, lumbar puncture and CSF culture, CXR, swabs of obviously infected sites; electrolytes and blood gases if severely unwell
   a. Leukocytosis or leukopaenia, thrombocytopenia, left shift (increased immature neutrophils)
   b. Increased WBC in CSF (can be normal variant, so must culture), metabolic acidosis

Septicaemia may occur before, during or after birth.

1. Aetiology – group B Streptococci (most common in first 48 hours of life), E. coli, P. aeruginosa, Listeria monocytogenes, viruses less commonly
2. Complications – DIC → circulatory failure, haemorrhage
3. Management:
   a. Maintenance of temperature, fluids and electrolytes, blood glucose and nutrition
   b. Antibiotics – penicillin/ampicillin + gentamicin; or broad spectrum 2nd/3rd generation cephalosporins e.g. cefuroxime or cefotaxime
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Meningitis often follows an initial bout of septicaemia. Mortality rate is minimal with treatment, but 30-50% of infants who survive have permanent neurological handicap (e.g. deafness and blindness) secondary to complications such as hydrocephalus, subdural infusion and ventriculitis.

1. Aetiology – group B Streptococci (most commonly), E. coli; less commonly Listeria monocytogenes, P. aeruginosa and other Gram negatives
2. Clinical features – reluctance to feed, vomiting, pallor, temperature instability → fullness of anterior fontanelle, neck stiffness
3. Management:
   a. Lumbar puncture essential for all infants with septic signs
   b. Antibiotics as per septicaemia but continue until 10-14 days after negative CSF culture

Congenital pneumonia is generally part of an acute septic illness acquired prenatally, especially if membranes have been ruptured for >24 hours. It is rapidly fatal if not treated immediately.

1. Aetiology – group B Streptococci (most common); later onset from aspiration → Gram-negatives
2. Clinical features – respiratory distress ± septic features, fine rales on auscultation
3. Management:
   a. IV antibiotics – penicillin ± gentamicin (synergistic)
   b. Tilt head of cot upwards and move frequently to avoid local accumulation of secretions
   c. Humidified O_2 to maintain saturation, nasogastric tube for fluids and nutrients
   d. Prophylactic penicillin for neonate if group B Streptococci grown from maternal vaginal swab

Urinary tract infection is often missed as signs are very non-specific. However, progressive renal damage often begins in the neonatal period and ranges from mild vesico-ureteric reflux of infected urine to severe pyelonephritis with associated septicaemia.

1. Aetiology – E. coli (most common), less often other Gram negative organisms
2. Clinical features – reluctance to feed, drowsiness, vomiting, failure to thrive ± pyrexia
3. Management:
   a. Urine culture essential – clean-catch MSU, suprapubic aspiration or catheterisation
   b. Antibiotics (10-14 days) – empiric systemic Gentamicin → adjust when sensitivities available
   c. Post-treatment urine tests, renal tract USS or micturating cystogram; follow-up for 1 year

Listeriosis affects 1-15 per 100,000 pregnancies. Perinatal infection usually begins in the 2nd or 3rd trimester and can lead to miscarriage (recurrent), premature labour, stillbirth (20%) or infant mortality (30%).

1. Aetiology – usually via infected food e.g. unpasteurised milk, soft cheeses and pate
2. Clinical features – maternal features include fever, shivering, myalgia, headache, sore throat, cough, vomiting, diarrhoea, vaginitis; neonatal features include respiratory distress, (early) convulsions, hepatosplenomegaly, pustular or petechial rash, conjunctivitis, fever, leukopaenia and meningitis
3. Management
   a. Blood cultures on any women with unexplained fever for >48 hours; in neonate take cultures of blood, CSF, meconium and placenta
   b. Antibiotics – ampicillin/penicillin + gentamicin until 1 week after fever subsides

Varicella infection affects 3 per 1000 pregnancies. Maternal infection can lead to ARDS with a mortality rate of 35% if untreated; more commonly the mother gets shingles or goes into pre-term labour.

1. Clinical features:
   a. 1st 20 weeks – varicella syndrome (2%) with poor weight, eye lesions, undeveloped limbs, pigmented scars, cerebellar hypoplasia (microcephaly, convulsions, mental retardation)
   b. 3rd trimester can lead to neonatal infection (pneumonitis, hepatitis, DIC)
2. Management
   a. Acyclovir is mother becomes infected during pregnancy
   b. Immune globulin and acyclovir given to neonate at birth

Congenital Neonatal Infections

Congenital infections (“TORCHS”)

1. Toxoplasmosis is an infection by the protozoa Toxoplasma gondii found in dog/cat faeces and uncooked meat. It affects 1 in 500 pregnancies (often asymptomatic), with ~35% of fetuses infected.
   a. May cause glandular fever-type symptoms in the mother with fever and rash
   b. Causes microcephaly, hydrocephalus, hepatosplenomegaly, chorioretinitis and blindness
   c. Prevention – avoiding of raw meat, wearing gloves while gardening or disposing kitty litter
2. Rubella has become somewhat uncommon with the advent of vaccination and screening of pregnant women. Congenital infection is highly infectious and the virus can persist for up to a year.
   a. Infection in the first few weeks leads to micro-opthalmia, retinopathy and cataracts;
   b. Sensorineural deafness, heart defects (PFO, peripheral pulmonary stenosis), microcephaly
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b. Infection up to three months most commonly causes congenital deafness
c. Infection up to 20 weeks can cause non-specific problems including hepatosplenomegaly, jaundice, thrombocytopenia, growth retardation and rubella osteitis

3. Cytomegalovirus often originates from the urine of toddlers. It affects 5 per 1000 live births with greatest risk in the first 20 weeks. Note only 10% of neonates have signs at birth and maternal infection is usually mild (fever ± lymphadenopathy, sore throat) or asymptomatic → check antibodies.
   a. May cause spontaneous abortion, preterm labour, IUGR, mental retardation or fetal death
   b. Multisystem disease – early jaundice, purpura, haemolytic anaemia, hepatosplenomegaly, pneumonia; less commonly fits, rigidity, microcephaly, chorioretinitis and osteitis
c. Long-term complications include hepatitis (cirrhosis), progressive neurological disorders

4. Herpes simplex (usually type II but can be type I) infection can be transmitted if there are active maternal lesions at the time of delivery (50% transmission rate). Treatment is with acyclovir.
   a. Neonatal infection appears at 5-21 days with vesicular pustular lesions at the presenting part
   b. May be localised as an eye or mucous membrane infection, or may be generalised (fatal)
c. Jaundice, hepatosplenomegaly, meningoencephalitis or haemorrhage 2° to DIC can occur

5. Hepatitis B is transmitted vertically – women who are HBsAg positive are highly infectious with a 25% transmission rate, smaller risk in women who are HBsAg positive. Antenatal screening is crucial → treatment with HBV vaccine within 24 hours of birth and again at one and six months of age.
   a. Untreated infection can rarely lead to acute fulminant hepatitis (often fatal)
   b. More commonly leads to chronic carrier state → cirrhosis, hepatocellular carcinoma

6. HIV infection affects 25% of otherwise well women in sub-Saharan Africa, with 15% transmission by vaginal delivery (risk halved by caesarean section, maternal/neonatal AZT, bottle feeding). Serology for diagnosis is difficult as maternal antibodies can persist for up to 18 months in uninfected infants.
   a. Intrauterine infection is associated with prematurity and growth retardation
   b. Symptoms appear at 6 months with hepatosplenomegaly, failure to thrive, encephalopathy, recurrent fever, lymphadenopathy, Salmonella, Pneumocystis and CMV infection

7. Syphilis (Treponema pallidum) infection involves the placenta and doesn’t affect the fetus until after the 4th month of pregnancy (so treat before four months if positive serology). 1/3 of infected fetuses are stillborn, and ½ of infants that survive are infected. Treatment by penicillin IM for 10 days.
   a. Clinical features occur by 2-6 weeks with rhinitis, skin eruptions, hepatosplenomegaly (fatty infiltration cirrhosis), jaundice, anaemia, bone and CSF involvement.

TUTORIAL FIVE – CONGENITAL DEFORMITIES

- Cleft Lip and Palate

In New Zealand, cleft lip affects 11 out of every 10,000 European children and 7 out of every 10,000 Polynesian children. They may be single or double (with a protruding globular process), complete or incomplete. Unilateral cleft lips are more likely to affect the left side and bilateral clefts are more often found in boys than girls. Note that 85% of bilateral and 70% of unilateral cleft lips are found in combination with a cleft palate.

Cleft palate affects 7 out of every 10,000 European children and 18 out of every 10,000 Polynesian children. It may affect the hard palate and/or the soft palate (complete/incomplete) – it is important to beware the submucous cleft of the soft-palate (look for a bifid uvula) as this may affect feeding and speech and requires surgical correction. Cleft palate is generally more common in girls than boys. Only 27% of cleft palates occur with an intact lip.

Aetiology is unclear. In 60% of children there is no clear family history, though genetic factors may have some effects as risk is increased with a parental history (1 in 20) and family history (1 in 25). 10% are associated with other abnormalities e.g. trisomy 13 (Patau syndrome) and there are other obvious risks e.g. maternal anticonvulsants → craniofacial deformities.

Diagnosis can be made as early as 13-14 weeks gestation when the soft tissues of the face can be visualised via transabdominal or transvaginal ultrasound.

Management:

1. Feeding is the main problem – with an isolated cleft lip or small soft palate defect breast feeding may be possible, otherwise options include bottle feeding, special teats or fitted solid palatal prosthetics
2. Surgical – cleft lips are usually operated within 3 months of age (occasionally a few days after birth), while cleft palates are usually left until 6-9 months of age. Middle ear infections are common following closure, so grommet are usually inserted.
3. Additional therapy – cleft nurse specialist, SLT therapist, preventative/restorative dental care
The CNS begins to develop in the third week post-fertilisation from ectoderm, which folds to form a neural tube – when this closes (30th day post-fertilisation) it sinks into the embryo and is covered by a layer of skin around which the vertebrae form. In spina bifida, fusion fails usually in the lumbosacral region:

1. **Spina bifida occulta** is an incidental finding in up to 10% of the population; due to a limited defect of the vertebral arch with no protrusion of the cord and meninges. It usually occurs at the lumbosacral junction with a skin lesion (hairy patch, dermal sinus tract, dimple, haemangioma or lipoma).

2. **Spina bifida cystica** affects 1 in 1000 with a cyst-like sac protruding through a vertebral arch defect
   a. Meningocele (4%) – cystic swelling (dura and arachnoid) containing CSF protrudes through defect; spinal cord and roots are in the normal position and often there are no sequelae
   b. Myelomeningocele (96%) – sac (arachnoid laced with thin, fragile vessels) contains CSF, blood vessels, spinal cord and meninges; neurological deficit depends on lesion location and degree of damage to nerves, often accompanied by other anomalies e.g. hydrocephalus, Chiari II malformation, intestinal/cardiac/oesophageal malformation, urogenital abnormalities

**Aetiology** is a combination of hereditary (e.g. people of Celtic descent, family history) and environmental factors (e.g. folic acid, sodium valproate). Prenatal folic acid is recommended – 0.4mg/d if no previous family history of neural tube defects, 5mg/day if there is a positive family history for 2-3 months preconception until at least the 13th week of pregnancy. Note that folate metabolism is abnormal in many affected patients, suggesting it may be an inherited defect rather than a dietary deficiency.

**Clinical features:**
1. **Diagnostic features:**
   a. Prenatal – increased α-FP at 13-15 weeks; USS/amniocentesis confirmation at 15-18 weeks
   b. Radiologic – lamina defects, hemivertebrae, scoliosis, widening of interpedicular vertebrae
   c. Cutaneous – capillary haemangioma, caudal appendage, dermal sinus, hypertrichosis
   d. Orthopaedic – extreme asymmetry, foot deformities
   e. Neurological – leg weakness/atrophy/asymmetry, loss of sensation, hyperreflexia, back pain
   f. Urologic – neurogenic bladder, incontinence (90%)

2. **Complications:**
   a. Hydrocephalus (90% of myelomeningoceles) – requires ventriculoperitoneal shunting
   b. Chiari II malformation (90%) – downward displacement of the cerebellar vermis, 4th ventricle and brainstem below the foramen magnum into the cervical canal
   c. Tethering – traction on the spinal cord with subsequent neurologic deficits (progressive weakness and loss of muscle function, deterioration in gait, progressive scoliosis)
   d. Musculoskeletal – joint contractures, developmental deformities, osteopenia
   e. Urogenital issues – neurogenic bowel/bladder, incontinence → hydronephrosis, renal failure

**Management:**
1. **Assessment:**
   a. Site and level of lesion and associated motor/sensory level
   b. Presence of associated hydrocephalus or symptoms of hindbrain herniation
   c. Presence of associated orthopaedic deformity

2. **Treatment:**
   a. Surgery to close the defect is generally performed within 72 hours of birth to minimize infection risk and preserve existing cord function; VP shunting often done at the same time
   b. Decompression of the posterior fossa or cervical cord if there are symptoms of brainstem compression (e.g. stridor, apnoea, aspiration, dysphagia, hypotonia, strabismus, nystagmus)
   c. Others – bladder training ± medications, watch for potential hydronephrosis → renal failure; monitor weight and height; bracing to allow normal developmental progression

3. **Prognosis:**
   a. Aggressive treatment leads to survival in most cases, and aggressive use of VP shunting can lead to near-normal intelligence in most patients
   b. Ambulation depends on the neurological level involved (e.g. quadriceps strength) – patients with lumbosacral lesions walk with callipers by age 3; <20% of higher lesions ever walk

**Club Foot and Developmental Dysplasia of the Hip**

**Club foot** (congenital talipes equinovarus) is a congenital or neuromuscular deformity in which the hindfoot is fixed in equinus and varus, and the forefoot is fixed in varus and often cavus. It has an incidence of 1 in 1000 live births with a male to female ratio of 2:1. There is also higher incidence in Maori (50% bilateral) and Pacific Islanders (7x increased risk).

1. **Clinical features:**
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1. The neck of talus is congenitally short and rotated medially in a plantar direction – this may be prominent on the dorsolateral aspect with stretching of skin over the area
2. In unilateral cases the calf may be smaller and the foot shorter on the affected side. There may also be a prominent crease on the arch of the foot (indicaing a severe/rigid deformity)
3. Note that it is important to assess if the deformity is correctible (and degree of correction)

2. Management:
   a. Initial treatment is serial (weekly) passive manipulation with taping to maintain position – this should be done as soon as possible as elasticity decreases with age
   b. Casting is used when discharged from the neonatal nursery and changed 1-2 weekly – note that long-leg serial casting by the Ponseti technique has improved non-operative results
   c. Operative management is required in >90% of cases, with the aim being a pain-free plantar flexed foot. Referrals are generally made at 3 to 9 months of age.

Developmental dysplasia of the hip comprises a spectrum of congenital disorders ranging from mild acetabular dysplasia to full dislocation of the femoral head from the acetabulum. It has an incidence of 10 in 1000 live births with a male to female ratio of 1:6. Note that children with risk factors should have a hip examination at each visit until 1 year of age with a single AP x-ray of the pelvis and hips at 3 months of age.

1. Aetiology:
   a. Genetic factors – female, family history (20%), certain ethnic groups
   b. Mechanical – breech presentation, oligohydramnios, packing phenomenon (e.g. first child), post-natal positioning (e.g. swaddling in extension/adduction), generalised ligamentous laxity

2. Pathophysiology:
   a. The hips develop from a single block of cartilage that separates into femoral and acetabular components at 7 to 8 weeks gestation.
   b. At birth the acetabulum has a relatively small bony component and large cartilaginous component – the percentage of the femoral head covered by the acetabulum is the lowest
   c. The first six weeks of life are critical to hip development as it is particularly susceptible to modelling – adequate contact and normal positioning is crucial for normal development

3. Clinical features:
   a. Classification:
      i. Type 1 – Ortolani positive (clunk when hip is pulled anteriorly and relocated)
      ii. Type 2 – Barlow’s positive (femoral head can be dislocated posteriorly)
      iii. Type 3 – unstable hip, usually resolves spontaneously in first three weeks
   b. Imaging:
      i. X-ray is not reliable in neonates as the pelvis is still radiolucent – the earliest age at which it is useful is ~6 weeks. Findings include proximal lateral migration of the femoral neck, delayed ossification of the ossific nucleus and a shallow acetabulum
      ii. Ultrasound can determine hip laxity, subluxation, dislocation, reducibility, presence of interposed tissue and status of the acetabulum, though less useful than X-ray after 6 months due to ossification of the femoral head

4. Management:
   a. Triple nappies are no longer considered effective treatment and are expensive for parents
   b. Pavlik harness worn 24 hours a day is ~95% effective if used prior to 6 months of age – check at 2-3 weeks to confirm reduction, adjust 3-weekly and reassess after 6 weeks, wean if hip stable. Complications – AVN of proximal femur, femoral nerve palsy, skin irritation.
   c. Closed or open reduction for patients who present after 6 months of age
   d. Follow up all children until maturity with X-ray every 2-3 years – 17% can develop acetabular dysplasia in a 12-year average follow-up period

TUTORIAL SIX – CONGENITAL HEART DISEASE

Congenital heart disease affects around 1% of live births (more males than females). They are associated with a number of factors including maternal rubella infection, alcohol abuse, drug treatment, radiation and genetic or chromosomal abnormalities.

1. Clinical features:
   a. Often involve shunting of blood between the pulmonary and systemic circulation – as pressures are higher in the systemic circulation, the shunt will initially be left to right:
      i. Exposure of the pulmonary circulation to higher pressures leads to pulmonary hypertension, characterised by symptoms such as dyspnoea and fatigue.
      ii. If this continues, the right heart and vessels undergo hypertrophy resulting in a right-to-left shunt – the pulmonary circulation receives less blood → central cyanosis
Neonatal Tutorials

b. Other symptoms include growth retardation, episodes of syncope (particularly on exertion), finger clubbing, embolism from systemic veins to systemic arteries and abnormal posture (squatting obstructs venous return and increases peripheral resistance → reduces shunting)

2. **Long-term sequelae:**
   a. Atrial and ventricular arrhythmias are common and resistant to treatment
   b. Sudden cardiac death is possible
   c. End-stage heart failure may need heart or heart-lung treatment

**Ventricular septal defects** are the most common congenital heart condition, affecting 1 in 500 live births. As the systemic and pulmonary circulations are connected, and there is a left to right shunt, the pulmonary circulation is exposed to left ventricular pressure resulting in pulmonary hypertension.

1. **Clinical features:**
   a. Loud ejection systolic murmur ± symptoms (fatigue, dyspnoea, cyanosis) depending on size
   b. CXR may show cardiac and pulmonary artery enlargement; Eisenmenger syndrome (normal heart size with prominent central pulmonary arteries and decreased peripheral markings)
   c. Doppler USS can assess the degree of the defect

2. **Management:**
   a. Small defects may require no intervention (except SBE prophylaxis as required)
   b. Moderate to large defects may need aggressive medical management if signs of congestive heart failure develop – digoxin, diuretics, increased caloric intake and close follow-up
   c. Perimembranous and muscular defects may reduce or close spontaneously – repair should be done early if there is evidence of heart failure, failure to thrive or pulmonary hypertension; otherwise reassess and repair before 2 years if there is shunting/pulmonary hypertension
   d. Conoseptal hypoplasia and malalignment defects do not close spontaneously and surgical closure is indicated in infancy

**Atrial septal defects** account for 6-10% of all congenital cardiac anomalies (more common in females than males). There are four major types – ostium primum (beneath the atrioventricular valves, associated with a cleft mitral valve), ostium secundum (mid-septal), sinus venosus and coronary sinus. A left-to-right shunt results in right atrial and ventricular volume overload and eventually pulmonary hypertension (at ~30 yrs).

1. **Clinical features:**
   a. Most infants and even older children with moderate left-to-right shunts are asymptomatic, though children with larger shunts may complain of progressive fatigue and dyspnoea
   b. Growth failure is uncommon, though children are more prone to pulmonary infections and may present with recurrent illness. Older patients may also present with atrial arrhythmias
   c. Wide and fixed splitting of the second heart sounds is due to a delay in emptying of the right ventricle; there may also be a systolic ejection murmur due to increased blood flow across the pulmonary valve and a diastolic murmur due to increased flow across the tricuspid valve
   d. CXR shows cardiomegaly, increased pulmonary vascular markings and a dilated pulmonary trunk in patients with significant left-to-right shunts; ECG may show a RBBB and/or right axis deviation; Doppler USS reveals the location, size and associated defects

2. **Management:**
   a. Infants with congestive heart failure should be treated with digoxin and diuretics
   b. Elective repair is indicated if there is large left-to-right shunting, cardiomegaly, symptoms or prophylaxis against paradoxical emboli or refractory supraventricular arrhythmias
   c. Sinus venosum and ostium primum defects require repair regardless of the defect size, typically done at 3-4 years of age – mortality for an uncomplicated defect is close to 0%

**Patent ductus arteriosus** has an incidence of 1 in 2,000 live births (more common in females than males) with incidence proportional to prematurity. It is defined as the persistence of the normal fetal vascular conduit between the central pulmonary and systemic arterial systems. Normally, this closes functionally by 18 hours of life and structurally by the third week – if it remains open beyond 3 months of age it is considered abnormal and is unlikely to close spontaneously (<0.6% per year). Risk factors include prematurity, maternal rubella infection in the first trimester, high altitude and genetic or familial factors.

1. **Clinical features** depend on the clinical condition associated with the PDA, the magnitude of the left-to-right shunt, individual anatomic/physiologic features and reaction to raised pulmonary blood flow
   a. Premature infants may be completely asymptomatic or present with complete cardiovascular collapse; older infants may have CHF, failure to thrive or recurrent pulmonary infections
   b. The typical murmur is a pansystolic murmur loudest at the left upper or midsternal border (may become continuous as pulmonary vascular resistance decreases), associated with an hyperdynamic precordium and bounding pulse (wide pulse pressure)
   c. X-ray and ECG may show changes consistent with minor degrees of left atrial and ventricular hypertrophy; Doppler USS is diagnostic and may establish pulmonary pressures
Coarctation of the aorta accounts for 6-8% of all congenital cardiac anomalies (more common in males than females) and refers to a stenosis of the upper thoracic aorta, usually just opposite the site of insertion of the ductus arteriosus. This results in decreased systemic blood flow after ductal closure, with increased resistance to left ventricular outflow resulting in systolic hypertension and left ventricular hypertrophy. There is some link with Turner syndrome (35% of these patients) and other genetic/chromosomal abnormalities.

1. Clinical features:
   a. Bicuspid aortic valve occurs in 85% of patients; other associated lesions include PDA, VSD, aortic stenosis, mitral stenosis, renal artery stenosis, berry aneurysm of the circle of Willis
   b. Coarctation may present clinically as congestive heart failure or shock 2 to ductus closure (poor feeding, dyspnoea, diaphoresis, poor weight gain, oliguria) or may be asymptomatic with systolic hypertension and/or a heart murmur (claudication, headaches and epistaxis)
   c. Radiofemoral delay is the classic sign but does not occur until after the collateral circulation has developed; there may be a mid-to-late systolic murmur over the upper precordium or the back with an ejection click (bicuspid aortic valve) and/or bruits over the intercostals
   d. CXR may show a dilated aorta indented at the site of the coarctation; ECG shows left ventricular hypertrophy and aortography can demonstrate the lesion

2. Management:
   a. Severe congestive heart failure or shock can be managed with prostaglandin infusion, inotropic support and diuretics for pulmonary hypertension or oedema
   b. Repair of the defect and associated anomalies can be done in infancy (5-15% mortality) or delayed in asymptomatic children (but higher risk of hypertension/atherosclerosis)
   c. Complications include bleeding, mesenteric arteritis, paradoxical hypertension, spinal cord ischaemia, chylothorax, diaphragm paralysis, subclavian steal & aortic aneurysm/dissection. PTCA has been suggested but may lead to recurrent stenosis and aneurysm formation.

Tetralogy of Fallot accounts for 3.5-8% of all congenital cardiac anomalies and is due to anterior misalignment of the infundibular septum, resulting in an over-riding aorta, pulmonary stenosis (right ventricular outflow tract obstruction), ventricular septal defect and resultant right ventricular hypertrophy. It may be associated with a chromosome 22q11 microdeletion or linked to other syndromes including Down, fetal alcohol and a variety of limb abnormality syndromes.

1. Clinical features:
   a. Pulmonary stenosis leads to various degrees of cyanosis that may present at birth or appear during infancy or childhood; there may be finger clubbing or polycythaemia after 12 months
   b. S2 may be louder due to the more anteriorly located aorta, and there may be a systolic ejection murmur at the left upper sternal border due to pulmonary stenosis
   c. ECG may show right axis deviation or right ventricular hypertrophy; CXR shows a right aortic arch, boot-shaped heart (‘coeur en sabot’) with a concave main pulmonary artery segment; echo shows discontinuity between the aorta and anterior wall of the ventricular septum

2. Management:
   a. A Blalock-Taussig shunt between a subclavian artery and a pulmonary artery can be used palliatively to keep the infant alive until they grow sufficiently to permit further surgery
   b. Complete surgical correction (VSD patch closure and right ventricular outflow tract reconstruction) is possible in infants or children though residual problems are common

TUTORIAL SEVEN – DOWN SYNDROME

Down syndrome is a syndrome of multiple abnormalities including hypotonia, flat facies, up-slanting palpebral fissures, large mouth and small ears. It was first described by John Langdon Down in 1866 and the majority of cases are due to trisomy of chromosome 21 – incidence is between 1:600 and 1:800 live births (increasing with maternal age) – note that >50% of fetuses are spontaneously aborted.

1. 94-97% are due to maternal chromosomal nondisjunction, <5% are due to paternal nondisjunction, 2.4% are due to trisomy 21/normal mosaicism; others are due to sporadic/balanced translocations
2. Risk factors include advanced maternal age (note slight increase in risk in very young mothers) and maternal Down syndrome; there is also a 1-2% recurrence rate in subsequent children

Clinical features include:
1. Congenital heart disease (40-50%) – atrioventricular canal, ventricular septal defect, patent ductus arteriosus, atrial septal defect, aberrant subclavian artery, tetralogy of Fallot
2. Gastrointestinal atresia (12%), Meckel diverticulum, Hirschsprung disease, imperforate anus, renal malformations, hypospadias (5%), cryptorchidism (5-50%), germ cell tumours, infertility
3. Thyroid disease (15%), transient myeloproliferative disorders, neonatal polycythaemia, leukaemia (10-30x baseline risk), obesity, alopecia areata (10-15%), dry hyperkeratotic skin (75%)
4. Hearing loss (66-75%), strabismus (33-45%), nystagmus (15-35%), fine lens opacities (59%), cataracts (1-15%), refractive errors (50%), seizures (5-10%), Alzheimer disease, mental retardation

Antenatal screening:
1. Maternal serum (triple) test – low α-FP, high β-HCG and low unconjugated oestriol suggestive of Down syndrome (60% sensitive, 95% specific); adding inhibin-A increases sensitivity to ~75%
2. Nuchal translucency – specific but not sensitive alone, but combined with maternal age and absence of fetal nasal bone at 11-14 weeks is 85% sensitive and 99% specific
3. Prenatal karyotyping – via amniocentesis (15-17 weeks gestation) or chorionic villus sampling (11-14 weeks gestation) is usually offered to women >35 years of age; note there is 1% risk of miscarriage

Prognosis:
1. Complications include serous otitis media, recurrent conjunctivitis/sinusitis, tonsillar and adenoidal hypertrophy leading to obstructive sleep apnoea, obstructive bowel disease and/or constipation, subluxation of the hips and atlantoaxial instability (2° to ligamentous laxity, worse under age 10)
2. Median age of death was 49 years in 1997, with mortality usually associated with congenital heart defects, dementia (20x baseline rate) and leukaemia (1.6x baseline rate)