CHAPTER 1 Prenatal screening for aneuploidy and neural tube defects

- Multiple marker screening uses a combination of maternal age and 2 or more biochemical tests, with or without an USS, to produce a single result for risk of Down syndrome, trisomy 18, and open neural tube defects (ONTDs).
- A screen is positive when the risk of one or more of the screened disorders falls above a designated risk cut-off.
- **A risk cut-off** – The risk of the condition being present in the fetus at term or at mid-trimester. The risk for the latter will be higher, because 23% of fetuses with Down syndrome are lost between mid-trimester and term (risk cut-off of 1:350 at term would be similar to 1:280 at mid-trimester).

- Detection rate (DR) or sensitivity: The proportion of affected individuals with positive screening results.
- False-positive rate (FPR): The proportion of unaffected individuals with positive screening results. It is the complement of the specificity.
- As screening performance improves, the FPR decreases and/or the DR increases.
- Multiples of the median (MoM): The absolute value of the assayed marker (serum or NT) divided by the gestation-specific median value of the serum marker in the measuring laboratory or by using standard or sonographer-specific curves for NT. This allows direct comparison of results between programmes.

Maternal age

- In the past screening was offered only to women ≥35 years at the EDD. This was considered to be the point at which the risk of a pregnancy loss was less than the chance of identifying a pregnancy with a significant chromosomal abnormality.
- The probability of conceiving a fetus with a trisomy increases with maternal age. However, maternal age screening is inferior to the use of multiple biochemical markers ± a first trimester USS NT assessment. The latter provides a greatly reduced FPR with a substantially improved DR across all age groups.
- **Do not use maternal age alone for prenatal screening for aneuploidy.**
- Do not offer amniocentesis to women ≥40 years without prior screening, because with a negative screening result, their risk of a chromosomal abnormality remains <1/200.

Factors potentially affecting screening performance

Gestational dating – USS improves the precision of gestational age estimation, and reduces the error for each screening marker. This effect is greater for markers whose concentrations change most with gestational age. For all marker combinations, the FPR is lower by about 2% when gestational age is estimated using a scan.

Insulin-dependent diabetes mellitus – Some second trimester serum markers tend to be lower in women with IDDM. After weight correction, AFP is ~10% lower and uE3 is ~5% lower in diabetic women. NT measurement, free β-hCG, and PAPP-A are not affected.

Ethnic origin – Adjusting for ethnic origin slightly increases the DR for a given FPR. Statistically significant differences in NT measurement have been found between ethnic groups. However, these differences may be too small to warrant correction.

Maternal weight – There is a negative association between the levels of maternal serum markers and maternal weight. With second trimester screening, maternal weight adjustment increases DR by about 1% for a given FPR.

- Weight adjustment is beneficial if there is a marginally elevated AFP when screening for ONTD. Weight adjustment does not appear to be necessary for NT risk adjustment, because it increases by only a clinically insignificant amount with increasing maternal weight.

Assisted reproduction – In the first trimester, a lower value of PAPP-A has been reported in IVF pregnancies, but data on NT and first trimester free β-hCG remain inconsistent.

Invasive prenatal diagnosis

- Offer to women who are at increased risk of fetal aneuploidy:
  - Non-invasive screen result above the risk cut-off.
  - Ultrasound findings.
  - A history of a previous child or fetus with a chromosomal abnormality.
  - Woman/her partner is a carrier of a chromosome rearrangement that increases the risk of having a fetus with a chromosomal abnormality.
- In these scenarios, the risk of a chromosomal abnormality not detected by screening is high enough to offer invasive testing without prior screening.

Screening options

Screen should provide – A DR for Down syndrome of 75% with <3% FPR in the first trimester (UK and SOGC) and a DR of 75% with <5% FPR in the second trimester (SOGC).

First trimester screening

Nuchal translucency (NT)

- NT – The subcutaneous layer of fluid behind the fetal neck and lower cranium visualized on ultrasound. It has a DR for Down syndrome ranging from 69 to 75%, with an FPR of 5–8%.
- Raised NT is also associated with numeric chromosome abnormalities, fetal anomalies such as cardiac defects, diaphragmatic hernia, and single gene disorders associated with decreased fetal movement.
- An NT >99th percentile has a sensitivity of 31% and specificity of 99% for major congenital heart defects when the fetal karyotype is normal. 1 in 33 fetuses with an NT >95th percentile and 1 in 16 with an NT >99th percentile have a major cardiac defect.
- Increased NT at 11–14 weeks with a normal fetal karyotype is an indication for a detailed USS at 18 to 20 weeks, to assess the fetal heart, including a 4-chamber view and view of the outflow tracts or a fetal echocardiogram.

First trimester combined (FTC)

- **Maternal age + NT + hCG + PAPP-A**
- 2 first trimester maternal serum biochemical markers: PAPP-A and hCG (total). PAPP-A is lower in Down syndrome pregnancies and hCG is higher.
- Combination of the maternal age-related risk, maternal serum PAPP-A, and free β-hCG provides a DR of 61% for Down syndrome, with a 5% FPR.
- Combination of the 2 first trimester biochemical markers with NT has a significant improvement over second trimester triple and quadruple screening.
- FTC detects 78% of cases with a 3% FPR using a term risk cut-off for Down syndrome of 1:300 (83% DR with a 5% FPR).
- FTC also screens for trisomies 13 and 18.

Nasal bone

- USS screening for delayed ossification of the fetal nasal bone in the first or second trimester.
- The first trimester USS, which determines the presence or absence of the nasal bone between 11 and 14 weeks of gestation, may be likely to be incorporated into other screening modalities. It detects 77% of Down syndrome cases.
- The difficulty in performing first trimester nasal bone sonography consistently in the general population might limit the usefulness of this screening technique.

Recommendations

- Given that timing is critical for serum analysis, accurate dating of the pregnancy is very important. Perform USS dating if menstrual or conception dating is unreliable. For any abnormal serum screen calculated on the basis of menstrual dating, perform an USS to confirm gestational age.
- Do not incorporate evaluation of the fetal nasal bone in the first trimester as a screening unless it is performed by sonographers trained and accredited for this service.
- For women who undertake first trimester screening, offer second trimester serum AFP screening and/or USS to screen for ONTDs.
- If local USS services are unable to provide a comprehensive screen for NTDs at 18 to 20 weeks' gestation, in patients undergoing first trimester screening for aneuploidy, offer MSAFP in the second trimester to screen for NTDs.

Second trimester screening

Triple marker testing

- Maternal age + MSAFP + unconjugated oestriol (uE3) + hCG measured between 15 and 20 weeks' gestation would detect 65% of fetuses with Down syndrome with a 5% FPR.
- Using a term risk cut-off of 1:385, the triple marker screening detects 72% of fetuses with Down syndrome with a 7% FPR.
- It also screens for ONTDs, other open fetal defects (e.g., gastroschisis, omphalocele), placental dysfunction, Smith–Lemli–Opitz syndrome, and trisomy.

Quadruple testing

- Maternal age + MSAFP + uE3 + hCG + **Inhibin A**
- Inhibin A will increase the DR of Down syndrome by 10%.
- With a risk cut-off of 1:230 at term, the DR is 75–80%, and the FPR is lowered to 3–5%.

Combined first and second trimester

Integrated prenatal screening (IPS)

- PAPP-A and NT in the first trimester and the quad screen in the second trimester, with results released when all the testing completed.
- DR of 85–87% with an FPR of 0.8–1.5%.
- When Inhibin A is excluded from the IPS, the FPR increases to ~2.5%.
- The benefit of IPS over FTS is the achievement of a lower FPR and reduction of the number of invasive diagnostic procedures needed. However it requires two visits and delays results.
- IPS also screens for ONTDs and trisomy 18.

Serum integrated prenatal screening

- PAPP-A in the first trimester and triple or quad screening in the second trimester.
- This has an 83% DR for Down syndrome for a 4% FPR.
- Alternatively, PAPP-A and free β-hCG can be offered in the first trimester, followed by AFP and uE3 in the second with the same performance. The FPR is 4.2% if PAPP-A is measured at 10 completed weeks, and the FPR is doubled (8.5%) if it is measured at 13 completed weeks.
- Serum IPS is a practical option for areas where there is limited or no access to NT screening.

Other screening options

Contingent screening

- Majority of women receive their result after FTC. Women at high risk (risk > 1/50) are offered invasive testing, and women at low risk (risk < 1/1500) require no further testing. A proportion of women with a risk between the two cut-offs (1/50 and 1/1500) will go on to have second trimester screening and will receive a combined result.
- It is possible to select risk cut-offs that achieve performances similar to IPS, thus meeting the guideline recommendation, while achieving detection of a significant proportion of abnormal pregnancies by the end of the first trimester.
- It is suggested that contingent screening strategy had the best cost-effectiveness ratio, with fewer procedure-related euploid miscarriages and unnecessary terminations.
- However, the women in the intermediate risk group are likely to experience raised anxiety, and a proportion of them might wish to have an invasive test immediately.

Non-invasive prenatal testing (NIPT)

- Cell-free fetal DNA (cffDNA) comes from the placenta and can be detected from the first trimester of pregnancy onwards in maternal circulation. This technology is likely to become the primary screen for chromosomal abnormalities in pregnancy. This will enhance the information available to pregnant women while greatly reducing the loss of uncomplicated pregnancies as a result of miscarriage caused by unnecessary invasive procedures. NIPT is not considered diagnostic as yet. Results from an ongoing study will be used to assess the accuracy of NIPT in the lower-risk population, as the majority of previous studies have looked at high-risk women only. Further evaluation is being undertaken by the UK NSC before it considers whether to adopt NIPT in the NHS.

UK National Screening Committee (UKNSC) recommendations for Down syndrome screening programme

- Offer all women screening test(s) with an FPR of <3% and a DR of >75%.
- Screen in the time window of 10 weeks + 0 days to 20 weeks + 0 days' gestation.
- Preferred strategy is to complete screening by 13 weeks + 6 days' gestation.
- Presently there is insufficient evidence for screening strategies for Down syndrome prior to 10 weeks of pregnancy.

First trimester combined (FTC)

- **NT + hCG, PAPP-A (same time).**
- Early diagnosis; screening is completed in one stage; gives a risk before 14 weeks of pregnancy allowing earlier decision making.
- Biochemistry or USS alone before 13 weeks will not meet the 2007 recommendation for DR.

Integrated testing (IT)

- **NT + PAPP-A (1st trim.); hCG (all types), uE, and AFP (2nd trim.).**
- Woman needs to attend twice for screening and has to wait until both samples have been processed for a final result.

Serum integrated testing (SIT)

- **PAPP-A (1st trim.); hCG (all types), uE, and AFP (2nd trim.)**
- Requires two visits but does not include USS NT.
- Women need to wait for a final result.

Quadruple testing (QT)

- **hCG (all types), uE3, AFP, and Inhibin A.**
- Tests in the second trimester for those women who book late (around 15% of the pregnant population).
- The second trimester screening test that just meets the 2007 recommendation for DR and FPR is the quadruple test.

The full screening window for:

- First trimester PAPP-A test – 10 weeks + 0 days to 13 weeks + 6 days.
- NT measurement – 11 weeks + 0 days to 13 weeks + 6 days.
- Second trimester serum testing – 15 weeks + 0 days to 20 weeks + 0 days.
- The optimal time for the PAPP-A measurement is 9–10 weeks' gestation with the performance of PAPP-A decreasing between 10 and 13 weeks. The proportion of pregnancies in which a satisfactory NT measurement can be obtained is the highest at 11 to 13 weeks' gestation. First trimester measurements are usually carried out between 11 and 14 weeks' gestation as a compromise to make the timing favourable for NT and PAPP-A.

- Offer the 'First trimester combined test' between 11 weeks 0 days and 13 weeks 6 days. For women who book later in pregnancy, offer the most clinically and cost-effective serum screening test (triple or quadruple test) between 15 weeks 0 days and 20 weeks 0 days. (NICE, CGN 62; 2008).
- **Threshold levels for risk measurements** – Categorize individual results as higher or lower risk based on a cut-off of 1 in 200 at term for second trimester screening strategies and 1 in 150 at term for first trimester screening strategies.
- Offer a confirmatory diagnostic test for all screen positive results – amniocentesis/CVS.
- **Benchmark timeframe:**
  A DR for Down's syndrome of >75% with a FPR of <3% (April 2007 to April 2010).
  A DR of >90% with a FPR of <2% (by April 2010).

This chapter is based on:
Prenatal Screening for Fetal Aneuploidy in Singleton Pregnancies; 2011; Joint SOGC–CCMG Clinical Practice Guidelines.
Screening for Down's syndrome: UK NSC Policy recommendations 2011–2014; Model of Best Practice; NHS Fetal Anomaly Screening Programme.
Antenatal Care – NICE Clinical Guideline 62; 2008.
Non-invasive prenatal testing for chromosomal abnormality using maternal plasma DNA. RCOG Scientific Impact – Paper No. 15; March 2014.
www. rapid.hhs.uk

CHAPTER 2 Routine fetal ultrasound screening

Use of first trimester USS

As part of prenatal screening, 11- to 14-week ultrasounds should be offered on a routine basis. (NICE CGN 62; 2008)

Indications/benefits

Accurate dating

- Crown–rump length (CRL) at 8–12 weeks is the most accurate method to date pregnancy; predicts the expected date of birth to within 5 days.
- It decreases the number of labour inductions for post-term pregnancy and helps to determine the timing of planned CSs to prevent iatrogenic prematurity.
- It is important to assess fetal growth and interpret maternal serum screening.
- First trimester USS is indicated when LMP date is uncertain.

First trimester TOP

- It is associated with lower maternal morbidity than second trimester termination procedures. An inaccurate estimation of gestational age can be avoided by ultrasound examination prior to procedure selection.

Diagnostic or therapeutic procedures

- **First trimester USS is recommended for suspected ectopic pregnancy, molar pregnancy, and suspected pelvic mass.**
- **First trimester USS is recommended during diagnostic or therapeutic procedures requiring visual guidance (e.g., CVS, amniocentesis) and prior to cervical cerclage placement.**

Multiple gestation

- USS examination should include number of fetuses, viability, CRLs, chorionicity or amnionicity, and NT assessment.
- Maternal serum screening for aneuploidy is not effective and an NT assessment of risk for each fetus is recommended.
- The accurate diagnosis of a chorionicity in twin pregnancy is important because it selects a subgroup of twin pregnancies at higher risk for twin-to-twin transfusion syndrome, congenital anomalies, FGR, and perinatal mortality.
- **First trimester USS is recommended for suspected multiple gestation to allow for reliable determination of chorionicity or amnionicity.**

Early fetal anomaly review

- Awareness of variations in anatomical appearance at different gestational ages is essential to avoid false-positive diagnoses of anomalies. In an unselected, low-risk population, first-trimester sonography can detect 63% of structural abnormalities.
- Although routine screening for fetal development at 11 to 14 weeks is not recommended, offer such screening to women at increased risk of fetal structural and genetic abnormalities.
- **Offer NT screening as part of a comprehensive prenatal screening and counselling programme.** (NICE CGN 62; 2008)

Fetal anomaly screening by USS

The purpose of the anomaly scan

- The main aims are:
  - To identify lethal abnormalities.
  - To plan appropriate management of the pregnancy and delivery. For serious abnormalities there are 4 possible pathways: incompatibility with prolonged life; association with serious morbidity; amenability to postnatal treatment with relatively low morbidity; antenatal treatment.
  - To offer a choice about whether or not to continue with a pregnancy with an abnormal baby.
  - To identify abnormalities for which there may be intrauterine treatments.
  - To identify abnormalities amenable to immediate neonatal treatment.
- About 33 conditions could be looked for by an ultrasound anomaly scan.

- Offer all pregnant women an USS to detect abnormalities in the fetus – NICE CGN 62; 2008; UKNSC.
- Dating scanning is recommended so that the risk for trisomy 21 can be accurately assessed. To some degree the early dating scan is progressing towards being an early anomaly scan that can detect major structural anomalies such as anencephaly and can screen early for trisomy 18 and 13.
- Timing of the fetal anomaly scan – should be undertaken at 18+0 to 20+6 weeks. This allows sufficient time for reassessment and investigation of suspected problems, counselling, and then decision making, before 24 weeks of pregnancy, after which by UK laws TOP needs to be carefully considered.

Detection rate

- Although it is used as a screening tool, it is difficult to establish the sensitivity and specificity rates of many conditions because of the paucity of literature. Also prevalence changes with gestational age due to miscarriage or preterm birth.
- However, it is recommended that to screen for a condition, the minimum number needed to be detected by screening should be no lower than 50%.
- Conditions screened for as a minimum in the NHS in England

Condition	Detection rate	Condition	Detection rate
Anencephaly	98%	Gastroschisis	98%
Trisomy 18	95%	Trisomy 13	95%
Open spina bifida	90%	Bilateral renal agenesis	84%
Exomphalos	80%	Diaphragmatic hernia	60%
Cleft lip	75%	Lethal skeletal dysplasia	60%
Serious cardiac abnormalities	50%		

Structures to be examined to constitute a minimum scan

- Head and neck – skull; neck skin fold (nuchal fold); brain; cavum septum pellucidum; ventricular atrium; cerebellum.
- Face – lips; chest – heart four-chamber view, outflow tracts, lungs.
- Abdomen – Stomach; short intrahepatic section of umbilical vein.
- Abdominal wall; bowel; renal pelvis; spine – vertebrae; skin covering.
- Limbs – femur length; hands; metacarpals (right and left) visible (not counted); feet metatarsals (right and left).
- Amniotic fluid volume; placenta.
- If these structures cannot be imaged sufficiently, refer to a diagnostic unit.
- Measure head circumference (HC), abdominal circumference (AC), and femur length (FL) to assess growth velocity in a pregnancy where the EDD has been assigned in line with nationally approved charts and tables. If the EDD has not been previously assigned then date the pregnancy by HC or FL.

The potential harm

- The anxiety of a false-positive result and the possibility of the loss of a normal fetus following invasive investigation based on false-positive result.
- Offering screening to women who would never choose TOP is also vital as they have a chance to benefit from other options such as fetal therapy (pleural–amniotic shunting for chylothorax or transfusion for anaemia), preparation for postnatal management (changing the place of delivery for cardiac and surgically correctable abnormalities), and psychological preparation in the event that there are no therapeutic options.
- Ultrasound normal variants (soft markers), e.g., choroid plexus cysts, two-vessel cords, and echogenic foci in the heart, can generate distress. The NHS FASP statement (January 2010) – soft markers (normal variants) should not be used to assess the risk for a chromosomal condition or as a screening tool.

Service provision

- All women with a suspected or confirmed fetal anomaly should be seen by an obstetric ultrasound specialist within 3 working days or seen by a FMU within 5 working days of the referral being made.
- All women should be offered a single further scan at 23 weeks of pregnancy to complete the screening examination if the image quality of the first examination is compromised by: increased BMI; uterine fibroids; abdominal scarring; or suboptimal fetal position.
- Where the first examination is suboptimal and the sonographer is suspicious of a possible fetal abnormality, a second opinion should be sought ASAP.

The Use Of First Trimester Ultrasound. SOGC Clinical Practice Guidelines; No. 135, October 2003.
Ward P, Soothill P. Fetal anomaly ultrasound scanning: the development of a national programme for England. The Obstetrician & Gynaecologist 2011;13:211–217.
NHS Fetal Anomaly Screening Programme in collaboration with the Royal College of Obstetricians and Gynaecologists, British Maternal and Fetal Medicine Society and the Society and College of Radiographers. 18+0 to 20+6 Weeks Fetal Anomaly Scan National Standards and Guidance for England. Author Donna Kirwan and The NHS Fetal Anomaly Screening Programme (NHS FASP); 2010.
Antenatal Care. NICE, Clinical Guidance Number 62; 2008.
www. screening.nhs.uk

CHAPTER 3 Amniocenteses and chorionic villus sampling

Approximately 5% of pregnant women (30 000 women/year in the UK) are offered invasive prenatal diagnostic tests (amniocentesis or CVS).

Amniocenteses – to obtain amniotic fluid

- Perform after 15+0 weeks of gestation.
- Additional risk of miscarriage following amniocentesis is around 1%.
- Blood stained amniotic fluid – 0.5% of cases.
- Systematic review – Post-amniocentesis pregnancy loss (background and procedure related) is 2%.
- 'Early amniocentesis' – Amniocentesis performed before 15 completed weeks of gestation. It has increased pregnancy loss compared with second-trimester amniocentesis and has a higher incidence of talipes when compared with CVS. Therefore, do not offer early amniocentesis.

CVS – aspiration or biopsy of placental villi

- Usually performed between 11+0 and 13+6 weeks of gestation.
- Systematic review – The additional risk of miscarriage following CVS may be slightly higher than that of amniocentesis carried out after 15 weeks of gestation.
- Transabdominal or transcervical – Several RCTs show almost identical miscarriage rates.
- Early CVS – The association between CVS, oromandibular limb hypoplasia, and isolated limb disruption defects is debated. CVS before 11+0 weeks can be technically difficult to perform, owing to a smaller uterus and thinner placenta. Therefore, do not offer CVS before 10+0 weeks of gestation.

Procedure

- Use maximum outer needle gauge size of 0.9 mm (20-gauge).
- With 'USS guidance' visualize the position of the placenta and the umbilical cord insertion prior to amniocentesis and note a suitable entry point on the mother's abdomen. The use of real-time ultrasound allows the insertion of the needle under 'continuous ultrasound control' and is the technique of choice. It reduces blood staining from 2.4% to 0.8%, has greater success in obtaining amniotic fluid, and reduces the risk of maternal bowel injury.
- Avoid transplacental passage of the amniocentesis needle unless it provides the only safe access to an adequate pool of liquor. Under these circumstances, place the needle through the thinnest available part of the placenta. Ensure that the placental cord insertion is avoided. Penetration of the placenta may not be associated with increased complications where continuous USS guidance is used.
- Local anesthetic does not reduce pain scores.

Risk of transmission of infection

- Blood borne viruses present a risk of maternal–fetal transmission. Do not perform invasive prenatal procedures without reviewing blood borne virus screening tests.

  HIV –
- If no HIV test result is available, delay the test and perform a rapid HIV test.
- Review viral load and treatment regimens and consider delaying the procedure until there is no detectable viral load if the woman is already on treatment or consider antiretroviral therapy if women not yet on treatment for HIV.
- Testing earlier in pregnancy is safe provided that retroviral therapy is being used and the maternal viral load is low. There were no cases of transmission in women receiving HAART; however, there were significant rates of transmission where no treatment was in place (25%) and where mono or double therapy was used (6%). Whenever possible, delay procedures until treatment has optimized the maternal viral load.

  Hepatitis B or C – Invasive prenatal testing in the first or second trimester can be carried out as there is currently no evidence that transmission is increased following amniocentesis.
- Severe sepsis, including maternal death, has been reported following invasive prenatal procedures. The risk of severe sepsis is likely to be < 1/1000. Infection can be caused by inadvertent puncture of the bowel, skin contaminants, or organisms present on the ultrasound probe or gel.

Special circumstances

Multiple pregnancies

- CVS or amniocentesis needs to be performed by a specialist who has the expertise to subsequently perform a selective TOP if required. A high level of expertise in USS scanning is essential for operators because uterine contents have to be 'mapped' with great care. This is essential to ensure that separate samples are taken for each fetus.
- Most clinicians use two separate puncture sites.
- Miscarriage rate is likely to be higher than in singleton pregnancies (1.8%).
- The role of CVS in dichorionic placentas remains controversial because of a relatively high risk of cross-contamination of chorionic tissue, which may lead to false positive or false negative results. This risk may be minimized if two separate needles are used.

Third-trimester amniocentesis

- Most commonly indicated for late karyotyping and detection of suspected fetal infection in prelabour preterm rupture of the membranes.
- Does not appear to be associated with a significant risk of emergency delivery (0–0.7% for procedure-related delivery).
- Compared with mid-trimester procedures, complications including multiple attempts (over 5%) and blood-stained fluid (5–10%) are more common along with higher culture failure rates (9.7%). When carried out in the presence of PPROM, failure rates are higher.

Consent – amniocentesis

Discuss

- Explain the procedure – The procedure involves obtaining a sample of amniotic fluid from the pregnancy sac using a needle inserted through the woman's abdomen.
- Intended benefits – To provide information regarding the karyotype (chromosomal make-up) of fetus(es) and, less commonly, used to provide biochemical, metabolic or genetic information.
- Procedure – Involves the passage of a 20- or 22-gauge needle through the abdomen under direct ultrasound guidance into the amniotic sac followed by aspiration of 10–15 ml amniotic fluid.

Risks

Very common	1/1 to 1/10
Common	1/10 to 1/100
Uncommon	1/100 to 1/1000
Rare	1/1000 to 1/10 000
Very rare	< 1/10 000

- **Serious risks:**
  - Failure to obtain a sample of amniotic fluid – 6%.
  - Blood-stained samples – 0.8% with the use of continuous ultrasound guidance.
  - Miscarriage rate – 1% over the norm.
  - Fetal injury – rare.
  - Maternal bowel injury – rare.
  - Amniotic fluid leakage with the added risk of PTD.
  - Chorioamnionitis – Severe sepsis, including maternal death, has been reported but the risk of severe sepsis is likely to be <1/1000.
  - Failure of cell culture in the laboratory.
- **Frequent risks:**
  - Mild discomfort at needle insertion site.

- Check maternal RhD status in every case. Offer prophylaxis with anti-D immunoglobulin following each procedure in line with national recommendations.

Amniocentesis and Chorionic Villus Sampling. RCOG Green-top Guideline No. 8; June 2010.
Amniocentesis. RCOG Consent Advice No. 6; 2006.

CHAPTER 4 Non-immune fetal hydrops

Hydrops fetalis (HF) is an excessive fluid accumulation within the fetal extravascular compartments and body cavities, characterized by a generalized skin thickness of > 5 mm, placental enlargement, pericardial or pleural effusion, or ascites.

Immune – Rh alloimmunization
See Chapter 6 Fetal haemolytic disease

Non-immune fetal hydrops (NIFH) – 76–87% of cases of all fetal hydrops. Heterogeneous disorder, caused by a large number of underlying pathological processes.

Cardiovascular disorders

- Structural abnormalities and dysfunctioning (cardiac arrhythmias; myocardiopathies).
- High right atrial pressure or volume overload and right heart congestion, resulting in increased CVP and heart failure, or obstruction of venous or arterial blood flow which eventually leads to oedema.
- Inadequate diastolic ventricular filling occurring in rhythm disturbances or in cardiomyopathies leads to an increase in CVP.
- Hepatic venous congestion may complicate the clinical picture by decreasing hepatic function, thus leading to hypoalbuminaemia.

Chromosomal abnormalities

- Chromosomal causes are much higher in cases diagnosed prior to 20 weeks.
- Most common are trisomy 21 and Turner syndrome.

Hematological disorders

- Anaemia – resulting in cardiac failure
- Loss of oxygen-carrying capacity is the end stage. Rapidly generated anaemia usually causes immediate fetal death; hydrops occurs in the presence of slowly developing anaemia.
- Fetal anaemia can result from failure to manufacture normal haemoglobin (α-thalassaemia), fetal haemorrhage (intracranial bleeding), or haemolysis (glucose-6-phosphate dehydrogenase deficiency).

Lymphatic system

- Lymphatic drainage will be disturbed in lymph vessel dysplasias leading to liquid imbalance, thus producing hydrops.
- The central disturbance is a low output failure of the lymphatic system, that is, the overall lymphatic transport is reduced. This derangement occurs not only in lymphatic dysplasias but also in increased CVP, as this causes difficulties in draining the lymph into venous circulation.

Infectious agents

- The main targets of infection include fetal bone marrow, myocardium, and vascular endothelium.
- Intrauterine congestive heart failure, anaemia, and fetal sepsis leading to anoxia, endothelial cell damage, and increased capillary permeability are the mechanisms.
- Causative organisms include syphilis, cytomegalovirus, parvovirus B19, toxoplasmosis, herpes simplex, rubella, and coxsackievirus. **Parvovirus** – See Chapter 20 Parvovirus infection in pregnancy.
- Fetal parvovirus B19 infection results in an aplastic crisis, which leads to profound anaemia and hydrops, the outcome of which may be either fetal death or spontaneous resolution without long term morbidity.

Congenital malformations

- Congenital cystic adenomatoid malformations and congenital diaphragmatic hernia form intrathoracic masses which can compress the heart and limit its function, and may reduce venous return because of increased intrathoracic pressure.
- Fetal thoracic tumors, including cystic hygromas of the neck and chest, and arteriovenous malformations may also have an intrathoracic mass effect.

Others

- Twin-to-twin transfusion syndrome – Linked to volume disturbances and a subsequent increase in CVP.
- Maternal systemic lupus erythematosus in which anticardiolipin crossing the placenta causes fetal heart dysfunction.
- Inborn errors of metabolism – Anaemia or liver failure leading to hydrops.
- Structural fetal malformations include skeletal dysplasias, which may be associated with thoracic compression, impairment of venous return, and subsequent hydrops.
- The association of other structural malformations with NIFH, such as gastrointestinal, genitourinary, and neurological abnormalities, may represent chance occurrences.

Non-immune fetal hydrops (NIFH)

Background and definition

- Definition – Presence of fetal subcutaneous oedema and abnormal fluid accumulations in one or more fetal compartments, with absence of antibodies against red-cell antigens in the mother.
- It represents an end-stage condition of different disease processes.
- The most common causes are cardiovascular pathology, chromosomal abnormalities, haematological disorders, and infections.
- An SR of the aetiology for NIFH has reported the causes of NIFH as: cardiovascular (21.7%), chromosomal (13.4%), haematological (10.4%), infections (6.7%), thoracic (6.0%), lymphatic dysplasia (5.7%), FFTS-placental (5.6%), syndromic (4.4%), urinary tract malformations (2.3%), inborn errors of metabolism (1.1%), extrathoracic tumors (0.7%), gastrointestinal (0.5%), miscellaneous (3.7%), and idiopathic (17.8%).

Prevalence and incidence

- Affects 1:1500 to 1:3750 pregnancies.
- PNM ranges from 55 to 98%.
- In a series of pre-screened populations:
  - The survival rate was up to 48% with PNM up to 40%.
  - Prenatal identification of cause was possible in up to 56% of cases.
  - Unexplained in 18% even after postnatal investigations.
- 61% of those that survive have no long-term morbidity.
- Parvovirus infection is associated with good prognosis.

Diagnosis – USS

- Detection of abnormal or increased fluid accumulation in fetal body cavities (pericardial effusion, pleural effusion, ascites), subcutaneous oedema, cystic hygroma, polyhydramnios, and placental thickening.
- Skin thickness of at least 5 mm is required to diagnose subcutaneous oedema, and a placental thickness of at least 6 cm is required to diagnose placentomegaly.

Exclude immune causes – Screen for antibodies associated with blood group incompatibility.

Referral to FMU

- MDT – Obstetricians, neonatologists, clinical geneticists, and other paediatric subspecialists.

Maternal history

- Age, parity, gestation, ethnicity.
- Previous scan findings in the current pregnancy.
- Past medical and obstetric history.
- Family history of any genetic disorders (e.g., metabolic disorders).
- Recent infections or contacts.

Maternal investigations

- Full blood count, blood group, and antibodies.
- Haemoglobin electrophoresis (α-thalassaemia carrier).
- Kleihauer–Betke stain (feto-maternal haemorrhage).
- Glucose-6-phosphate dehydrogenase deficiency screen.
- Infectious screen:
  - TORCH (toxoplasmosis, rubella, cytomegalovirus, and herpes simplex) titres.
  - Rapid plasma reagent test.
  - Parvovirus B19 IgG and IgM titres.
- Auto-antibody screen (SLE, anti Ro, and La).
- Oral GTT.