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 affe screening results.
- False-positive rate (FPR): The proportion of unaffected i results. It is the complement of the specificity.
- As screening performance improves, the FPR decreases a
- Multiples of the median (MoM): The absolute value of t NT) divided by the gestation-specific median value of the laboratory or by using standard or sonographer-specific 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 screen

Gestational dating – USS improves the precision of gestation the error for each screening marker. This effect is greater for change most with gestational age. For all marker combinati when gestational age is estimated using a scan.

Insulin-dependent diabetes mellitus – Some second trimester in women with IDDM. After weight correction, AFP is ~10 diabetic women. NT measurement, free β-hCG, and PAPP-A

Ethnic origin – Adjusting for ethnic origin slightly increases t Statistically significant differences in NT measurement have groups. However, these differences may be too small to war

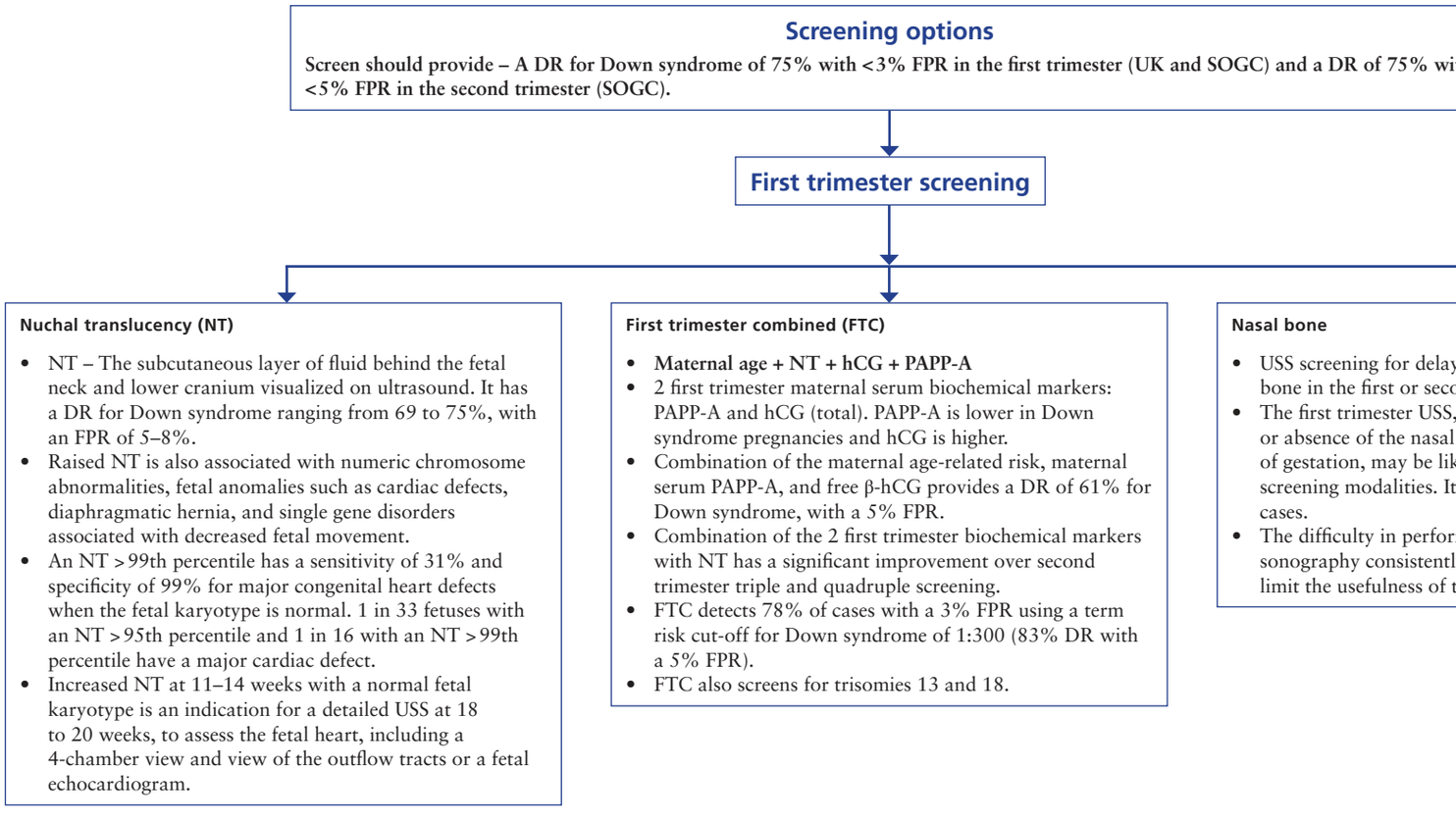
Maternal weight – There is a negative association between th markers and maternal weight. With second trimester screen increases DR by about 1% for a given FPR.

- Weight adjustment is beneficial if there is a marginally el ONTD. Weight adjustment does not appear to be necess because it increases by only a clinically insignificant amo weight.

Assisted reproduction – In the first trimester, a lower value o pregnancies, but data on NT and first trimester free β-hCG

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.



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 tr

Integrated prenatal screening (IPS)

- PAPP-A and NT in the first trimester and the quad scree
  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 incre
- The benefit of IPS over FTS is the achievement of a low
  number of invasive diagnostic procedures needed. How
  delays results.
- IPS also screens for ONTDs and trisomy 18.

Serum integrated prenatal screening

- PAPP-A in the first trimester and triple or quad screenin
- This has an 83% DR for Down syndrome for a 4% FPI
- Alternatively, PAPP-A and free β-hCG can be offered in
  AFP and uE3 in the second with the same performance.
  measured at 10 completed weeks, and the FPR is doubl
  completed weeks.
- Serum IPS is a practical option for areas where there is
  screening.

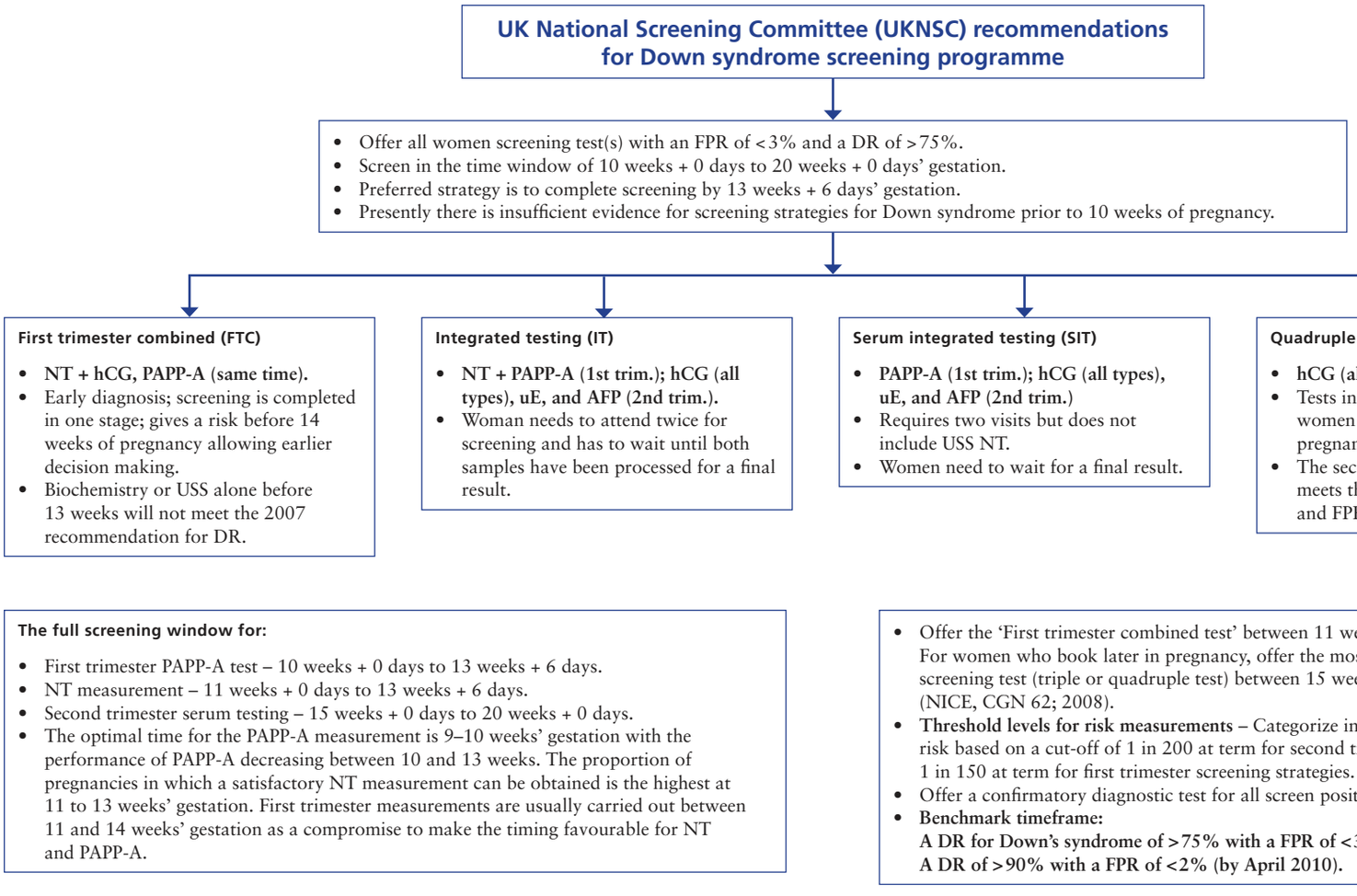
Other screening options

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
  first trimester of pregnancy onwards in maternal circula
  to become the primary screen for chromosomal abnorm
  enhance the information available to pregnant women
  of uncomplicated pregnancies as a result of miscarriage
  procedures. NIPT is not considered diagnostic as yet. R
  will be used to assess the accuracy of NIPT in the lower
  of previous studies have looked at high-risk women onl
  undertaken by the UK NSC before it considers whether



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 therapeuti

- **First trimester USS is ectopic pregnancy, m pelvic mass.**
- **First trimester USS is or therapeutic proced (e.g., CVS, amniocent 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 essential to avoid false-positive diagnoses of anom population, first-trimester sonography can detect 6
- Although routine screening for fetal development a recommended, offer such screening to women at ir genetic abnormalities.
- **Offer NT screening as part of a comprehensive pre 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 abn
  CGN 62; 2008; UKNSC.
- Dating scanning is recommended so that the ri
  assessed. To some degree the early dating scan
  an early anomaly scan that can detect major st
  anencephaly and can screen early for trisomy 1
- Timing of the fetal anomaly scan – should be u
  weeks. This allows sufficient time for reassessn
  problems, counselling, and then decision maki
  after which by UK laws TOP needs to be caref

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 constitu

- Head and neck – skull; neck skin fold (nuchal fold); bra
  ventricular atrium; cerebellum.
- Face – lips; chest – heart four-chamber view, outflow tra
- Abdomen – Stomach; short intrahepatic section of umb
- Abdominal wall; bowel; renal pelvis; spine – vertebrae;
- Limbs – femur length; hands; metacarpals (right and lef
  metatarsals (right and left).
- Amniotic fluid volume; placenta.
- If these structures cannot be imaged sufficiently, refer to
- Measure head circumference (HC), abdominal circumfe
  to assess growth velocity in a pregnancy where the EDD
  nationally approved charts and tables. If the EDD has n
  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
  obstetric ultrasound specialist within 3 workin
  working days of the referral being made.
- All women should be offered a single further s
  complete the screening examination if the imag
  is compromised by: increased BMI; uterine fibr
  suboptimal fetal position.
- Where the first examination is suboptimal and
  possible fetal abnormality, a second opinion sh

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 Societ
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
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 ge
- Systematic review – The additional risk of miscarriage f higher than that of amniocentesis carried out after 15 w
- Transabdominal or transcervical – Several RCTs show a
- Early CVS – The association between CVS, oromandibu limb disruption defects is debated. CVS before 11+0 we to perform, owing to a smaller uterus and thinner place 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 in

- Blood borne viruses present a risk of maternal–fetal tra prenatal procedures without reviewing blood borne viru

HIV –

- If no HIV test result is available, delay the test and perf
- Review viral load and treatment regimens and consider is no detectable viral load if the woman is already on tr therapy if women not yet on treatment for HIV.
- Testing earlier in pregnancy is safe provided that retrovi the maternal viral load is low. There were no cases of tr HAART; however, there were significant rates of transm place (25%) and where mono or double therapy was us procedures until treatment has optimized the maternal v

Hepatitis B or C – Invasive prenatal testing in the first or as there is currently no evidence that transmission is inc

- Severe sepsis, including maternal death, has been report procedures. The risk of severe sepsis is likely to be < 1/1 by inadvertent puncture of the bowel, skin contaminant 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 detec prelabour preterm rupture of the membranes.
- Does not appear to be associated with a significant risk o procedure-related delivery).
- Compared with mid-trimester procedures, complications 5%) and blood-stained fluid (5–10%) are more common rates (9.7%). When carried out in the presence of PPRO

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 statu with anti-D immunoglobu line with national recomm

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 o
Heterogeneous disorder, caused by a large number of u
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

- Lympha lymph v imbalan
- The cen failure the ove This de lympha CVP, as the lym

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 sync disturbances and a subsequen
- Maternal systemic lupus eryth crossing the placenta causes f
- Inborn errors of metabolism - to hydrops.
- Structural fetal malformations may be associated with thorac venous return, and subsequen
- The association of other struc such as gastrointestinal, genit abnormalities, may represent