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Serum Markers of Obstetric Complications

Markers of trisomy 21

Test	Trimester	Components	Diagnostic performance
Combined test	First trimester	Pregnancy-associated plasma protein A (PAPP-A), free beta human chorionic gonadotrophin (β-hCG) in combination with nuchal translucency (NT)	Sensitivity is 90% with a false positive rate of 5%
Triple test	Second trimester	Alpha fetoprotein (AFP), βhCG, unconjugated estriol (uE3)	Sensitivity is 70% with a false positive rate of 5%
Quadruple test	Second trimester	Alpha fetoprotein (AFP), βhCG, unconjugated estriol (uE3), and inhibin-A	Sensitivity is 75% with a false positive rate of 5%
Integrated test	First and second trimester	NT, PAPP-A in the first trimester, quadruple screen in the second trimester	Sensitivity is 95% with a false positive rate of 5%
Contingent test	First and second trimester	Results of first trimester screening determine subsequent second trimester assessment: - Low risk: No further action is required - Intermediate risk: second trimester screening offered - High risk: diagnostic testing is directly offered	Sensitivity is 88-94% with a false positive rate of 5%

S. A. Shazly, N. Eltaweel (eds.), *MRCOG Part 2*, https://doi.org/10.1007/978-3-030-78048-7_18

	AFP	uE3	hCG	Inhibin A
Trisomy 21 (Down syndrome)	Low	Low	High	High
Trisomy 18 (Edward syndrome)	Normal	Low	Very low	Normal
Trisomy 13 (Patau syndrome)	High	Normal	Normal	Normal
Turner syndrome	Low	Low	Very high	Very high

Markers of adverse obstetric events

First trimester markers

Low PAPP-A

- Spontaneous miscarriage
- Gestational hypertension
- Pre-eclampsia
- Low birthweight
- Preterm labour

Low hCG

- Spontaneous miscarriage
- Low birthweight

Second trimester markers

High AFP

- Foetal growth restriction
- Placental abruption
- Miscarriage.
- Foetal demise
- Preterm labour

High hCG

- Preterm delivery
- Gestational hypertension
- Pre-eclampsia
- Foetal demise
- Foetal growth restriction

High inhibin A

- Preterm labour
- Gestational hypertension
- Pre-eclampsia
- Foetal demise
- Foetal growth restriction

Low uE3

- Oligohydramnios
- Miscarriage
- Foetal demise
- Low birth weight

Noninvasive Prenatal Testing

Background

- Circulating cell free foetal DNA presents 10% of circulating DNA fragments in maternal plasma
- Assessment of circulating foetal DNA can be used for non-invasive prenatal screening (NIPS) of aneuploidy
- The test should be performed after 10 weeks of gestation

Accuracy

- The test has high sensitivity and specificity for trisomy 21 and trisomy 18 (99%)
- The test is less sensitive with trisomy 13 (90%) and monosomy X (93%)
- The test is less sensitive for trisomy 21 in twins (94%)

Advantages

- The test is associated with low risk compared to invasive testing. NIPS reduces need for amniocentesis by 53% and chorionic villus sampling by 77%
- Results are reported in 3-5 days (comparable to PCR invasive testing)

Disadvantages

- Incidence of non-conclusive results is 2-6%. If these results are repeated, incidence of NIPS failure is 20%
- Most common causes of non-conclusive or false results are:
    - Low foetal DNA fraction
    - Vanishing twin (false positive results)
    - Placental mosaicism (same issue with chorionic villous sampling)
    - Maternal cancers

Invasive Prenatal Testing

Introduction

- 5% of the pregnant population are offered invasive prenatal diagnostic tests
- Amniocentesis is the most common invasive prenatal diagnostic procedure in the UK

Timing

- Amniocenteses are performed to obtain amniotic fluid for karyotyping from 15 weeks (15^{+0}) onwards.
- Chorionic villus sampling (CVS) is usually performed between 11 (11^{+0}) and 13 (13^{+6}) weeks of gestation and involves aspiration or biopsy of placental villi

Complications

- **Miscarriage:**
  - Additional risk of miscarriage following amniocentesis is around 1%
  - Additional risk of miscarriage following chorionic villus sampling may be slightly higher than amniocentesis
- **Complications associated with improperly timed procedures:**
  - Early amniocentesis (before 14 week) is not recommended. It may be complicated by:
    - Higher fetal loss (1.3 times more)
    - Respiratory morbidity
    - Foetal talipes 5 times more and respiratory morbidity
  - Chorionic villous sampling should never be done before 10 weeks:
    - Technically more difficult
    - Risk of limb reduction defects
    - Risk of mandibular limb hyperplasia

Consenting

Invasive diagnostic test should be preceded by a written consent which include:

- risk of pregnancy loss (national and local)
- results (limitation, failure, timing, communication of results)
- need for anti D
- indications for seeking medical advice

Technique

- The procedure should always be done under ultrasound guidance
- Avoid Trans- placental passage whenever possible,
- Needle gauge size 0.9 millimeters (20 gauge) maximum, use local anesthetic if Transplacental

Continuous ultrasound guidance decreases blood staining from 2.4% to 0.8% (blood interferes with amniocyte culture)

Amniocentesis is comparable to venipuncture, so local anesthetic improves pain the angle of the needle insertion does not matter

If trans placental approach is inevitable, go through the thinnest part and avoid cord insertion (it does not increase miscarriage rate)

Needle size of CVS varies (18g, 20g, 17/19, 18/22), varies in aspiration (negative pressure by syringe, vacuum, biopsy forceps depending on preference)

Good practice

- Competency should be maintained by carrying out at least 30 ultrasound guided invasive procedures per annum
- Operator competence should be reviewed if loss 4% in amniocentesis or 8% for Chorionic villus sampling or 7% second insertion
- Competency is maintained by 30 ultrasound guided procedure per year. If more than 100/year is performed, the practitioner becomes very experienced with less loss. Continuous audit is needed

Multiple pregnancy consideration
• Invasive diagnostics in Twins need higher level of expertise in selective Termination of pregnancy required • Labelling of twins is greatly assisted if gender is different or in the presence of obvious fetal abnormality

Third trimester amniocentesis

- Women should be informed that third-trimester amniocentesis does not appear to be associated with a significant risk of emergency delivery.
- Multiple attempts and bloodstained fluid are more common in third trimester procedures.
- Risk of blood-stained amniotic fluid is 5-10% (10 times higher) and this increases the risk of culture failure (10%)

Risk of transmission of infection

Preventing transmission of infection	Source of infection	Important notes
• US probe sterile bag • Separate sterile gel • Screen for blood borne viruses: if declined, counsel the patient and document risk of vertical transmission • If HIV is positive: check viral load and treat (procedure is delayed till viral load is undetectable viral load. Start treatment if not previously treated) If HIV is inadequately treated or not treated, risk of transmission is 25%, Mono or double treatment only is associated with 6% risk of transmission) • If hepatitis B or C is positive: first and second trimester testing is allowed (very low risk of transmission)	• bowel puncture • skin contamination organism on gel or probe (risk of infection vs. degradation of the probe	• Risk of severe sepsis is 1:1000 • Anti-Dis indicated after all procedures

Genetic Disorders and Genetic Testing

Genetic disorders

Genetic disorders classification

Mitochondrial disorders	Chromosomal	Complex diseases	Monogenic disorders
• Incidence: 1:5000-8000. • Mostly commonly linked to inborn errors of metabolism.	Aneuploidy is the most common cause of spontaneous miscarriage and implantation failure	This refers to diseases that are precipitated by polygenic genetic and environmental factors	1. X-linked dominant 2. Y-linked disorder 3. Autosomal recessive 4. Autosomal dominant 5. X-linked recessive

Mitochondrial disorders	• Leigh syndrome and MELAS (mitochondrial encephalopathy, lactic acidosis, and stroke-like episodes) syndrome
X-lined dominant disorders	• Fragile X syndrome • Incontinentia Pigmenti
Y-linked disorders	• Some cases of Swyer syndrome and Y chromosome related infertility
Autosomal recessive disorders	• The most common disorder in Europe is cystic fibrosis. • The most common disorder in the UK is sickle cell disease (1 in 2,000). • The most common disorder worldwide is β-thalassemia.
Autosomal dominant disorders	• BRCA 1 and BRCA2 • Marfan and Huntington syndromes
X-linked recessive disorders	• Duchenne muscular dystrophy • Hemophilia

Preimplantation genetic diagnosis

Definition

- Preimplantation genetic diagnosis (PGD) refers to biopsy and genetic testing of products of conception prior to embryo transfer.

Applications

- It may be offered to couples undergoing in-vitro fertilization (IVF).
- It is used to assess embryo prior to transfer in couples at high risk of transmitting a genetic disorder.

Invasive prenatal testing

- **Prevalence:**

  Prenatal diagnostic tests are offered to 5% of the pregnant population. The most common procedure is amniocentesis

- **Timing:**

  - Amniocentesis for karyotyping is performed at or beyond 15 weeks of gestation. Amniocentesis before 14 weeks (early amniocentesis) is not recommended
  - Chorionic villus sampling (CVS) is performed between 11+0 and 13+6 weeks of gestation

- **Risks and complications:**

Miscarriage	▪ Amniocentesis is associated with 1% additional risk of miscarriage ▪ Chorionic villus sampling is associated with slightly higher risk of miscarriage than amniocentesis ▪ Early amniocentesis is associated with 1.3 times higher risk of fetal loss
Fetal defects	▪ Early amniocentesis may be associated with respiratory morbidity, ▪ Early amniocentesis increases risk of fetal talipes by 5 times

	▪ CVS before 10 weeks may increase risk of limb reduction defects and mandibular limb hyperplasia
Vertical transmission of infection	Women should be screened for blood-borne viral infection: ▪ If a patient has HIV: viral load should be checked and treated accordingly. Procedure is delayed till viral load is undetectable *Risk of vertical transmission is 25% with no treatment, and 6% with inadequate treatment (monotherapy or double treatment)* ▪ If a patient has hepatitis B or C: risk of transmission in the first and second trimester is very low, and procedures can be performed ▪ If a patient declines testing, she should be counselled on risk of vertical transmission before the procedure is performed
Severe sepsis	▪ Incidence of severe sepsis is 1:1000 ▪ Infection may originate from bowel puncture, skin contamination, or contamination from the gel or ultrasound probe ▪ Measurements that can be taken to prevent infection include using ultrasound probe sterile bag and using separate sterile gel
Multiple attempts and blood-stained amniotic fluid	▪ This is more common with third trimester amniocentesis. The risk of blood-stained amniotic fluid is 5-10% (10 times higher than second trimester amniocentesis). This is associated with increased risk of culture failure (10%)* ▪ Third-trimester amniocentesis is not associate with risk of emergency delivery

* Blood staining of amniotic fluid interferes with amniocyte culture

- **Consenting:**

A written consent should be obtained before Invasive diagnostic test is performed. Consent form should include:

- Risk of pregnancy loss
- Test results (limitations and risk of culture failure, timing of testing and results, how results will be communicated)
- need for anti-D immunoglobulin after any procedure in Rh negative women
- Indications for seeking medical advice

- **Technical aspects of amniocentesis or CVS:**

  - The procedure is performed under ultrasound guidance
  - Maximum needle gauge size is 0.9 millimeters (20 gauge)
  - Local anesthetic can be used before entry if Trans placental
  - Avoid trans-placental passage whenever possible

  Continuous ultrasound guidance decreases incidence of blood-stained amniotic fluid from 2.4% to 0.8%

  CVS needle varies in size (18g, 20g, 17/19, 18/22). Sample is obtained by a syringe, vacuum, biopsy forceps (provider's preference)

  If trans-placental passage is inevitable, the needle should pass through the thinnest part and cord insertion should be avoided. Thereby, miscarriage rate is not increased

  Angle of the needle insertion has not significant impact on the procedure

- **Good practice:**
  - Maintenance of operator competency requires at least 30 ultrasound-guided invasive procedures yearly. A highly experienced level with less feta loss is achieved by performing at least 100 procedures/year
  - Operator competency should be reviewed if:
  - Incidence of fetal loss is 4% or more with amniocentesis or
  - Incidence of fetal loss is 8% or more with CVS or
  - Rate of second insertion is 7% or more

Fetal Growth Restriction

Background

Definition

Small-for-gestational age (SGA) fetus is a fetus that fails to reach a specific biometry or estimated weight threshold by a specific gestational age (the 10th centile for abdominal circumference and estimated birth weight is the commonly used parameter)

Causes

- Fetal growth restriction (FGR): 30-50%
- Fetuses that are constitutionally small: 50 – 70%

The lower the centile, the greater the possibility of FGR

Outcome

Immediate

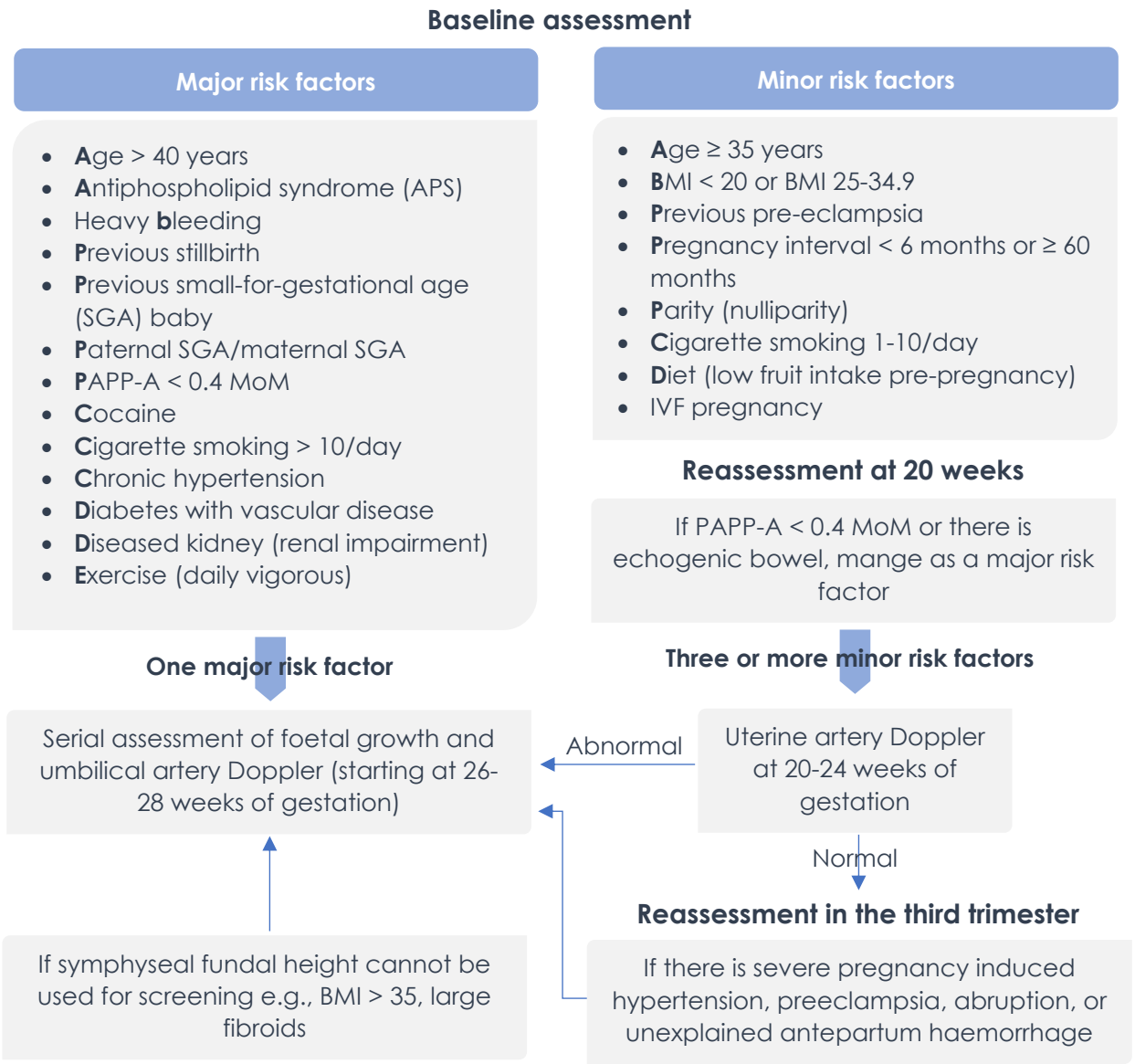
- Risk of stillbirth
- Risk of birth hypoxia
- Risk of neonatal complications & impaired neurodevelopment

Remote

- Type 2 (non-insulin-dependent) diabetes in adult life
- Hypertension in adult life

Poor outcome is related to SGA fetuses caused by FGR rather than other cases

Assessment of high-risk population



Assessment of low-risk population

- **Symphyseal fundal height (SFH):**
  - SFH is used to screen foetal growth in all low-risk women during antenatal care visits
  - SFH should be plotted on a customized chart, rather than population-based chart, should be considered to improve prediction of SGA neonates
  - If SFH is below the 10th percentile or if it is slow or static over time, ultrasound is indicated
  - SFH may not be feasible in women with body mass index > 35, large fibroids, or polyhydramnios. In this case, foetal growth should be monitored with serial growth ultrasound

- **Ultrasound:**
  - If estimated foetal weight (EFW) or abdominal circumstance (AC) is less than the 10th percentile using customized charts, serial growth ultrasound with umbilical artery Doppler should be performed
  - If ultrasound is serially performed, EFW or AC should be measured at least 3 weeks apart
  - Uterine artery Doppler has a limited role in predicting perinatal outcomes in the third trimester

Investigations

- **Assessment of the cause:**

  Early onset foetal growth restriction (FGR) "before 23 weeks":
  - Refer to foetal medicine
  - Detailed anatomy scan to rule our structural abnormalities
  - Karyotyping should be considered if there is severe FGR in the presence of normal uterine Doppler
  - Serology testing of cytomegalovirus and toxoplasmosis (± malaria and syphilis in high-risk population) if FGR is severe

- **Foetal surveillance:**

Method	Assessment
Umbilical artery (UA) Doppler	▪ This is the primary tool to reduce perinatal morbidity and mortality in foetuses with FGR ▪ It is performed every 2 weeks (1 week if FGR is severe) ▪ If UA Doppler is abnormal (pulsatility index [PI] or resistance index [RI] > 2 standard deviations [SD]): □ Ductus venosus (DV) Doppler is performed to time delivery □ If end-diastolic flow is present, it should be repeated twice weekly □ If end-diastolic flow is absent/reversed, it should be repeated daily
Cardiotocography (CTG)	It is not used alone for foetal surveillance
Amniotic fluid (AF) assessment	It is not used alone for foetal surveillance. Deep vertical pocket (DVP) is measured
Biophysical profile (BPP)	Use of BPP is not recommended in women with preterm FGR
Middle cerebral artery (MCA) Doppler	▪ It has limited role in foetuses with preterm FGR ▪ In foetuses with term FGR, if UA Doppler is normal, MCA Doppler has moderate predictability of acidosis at birth if abnormal (< 5%) and is used to time delivery

Prevention

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- Low dose aspirin in women at high risk of preeclampsia may prevent SGA at or before 16 weeks of gestation
- Smoking cessation should be considered
- Anti-thrombotic therapy may yield promising results. However, there is insufficient evidence to support its use and it is associated with serious side effects
- There is no role for diet modifications, calcium or progesterone supplementation

Management

Symphyseal fundal height < 10th percentile or high risk for FGR

Foetal biometry

If AC or EFW is below the 10th percentile, or growth pattern is consistent with FGR

UA Doppler

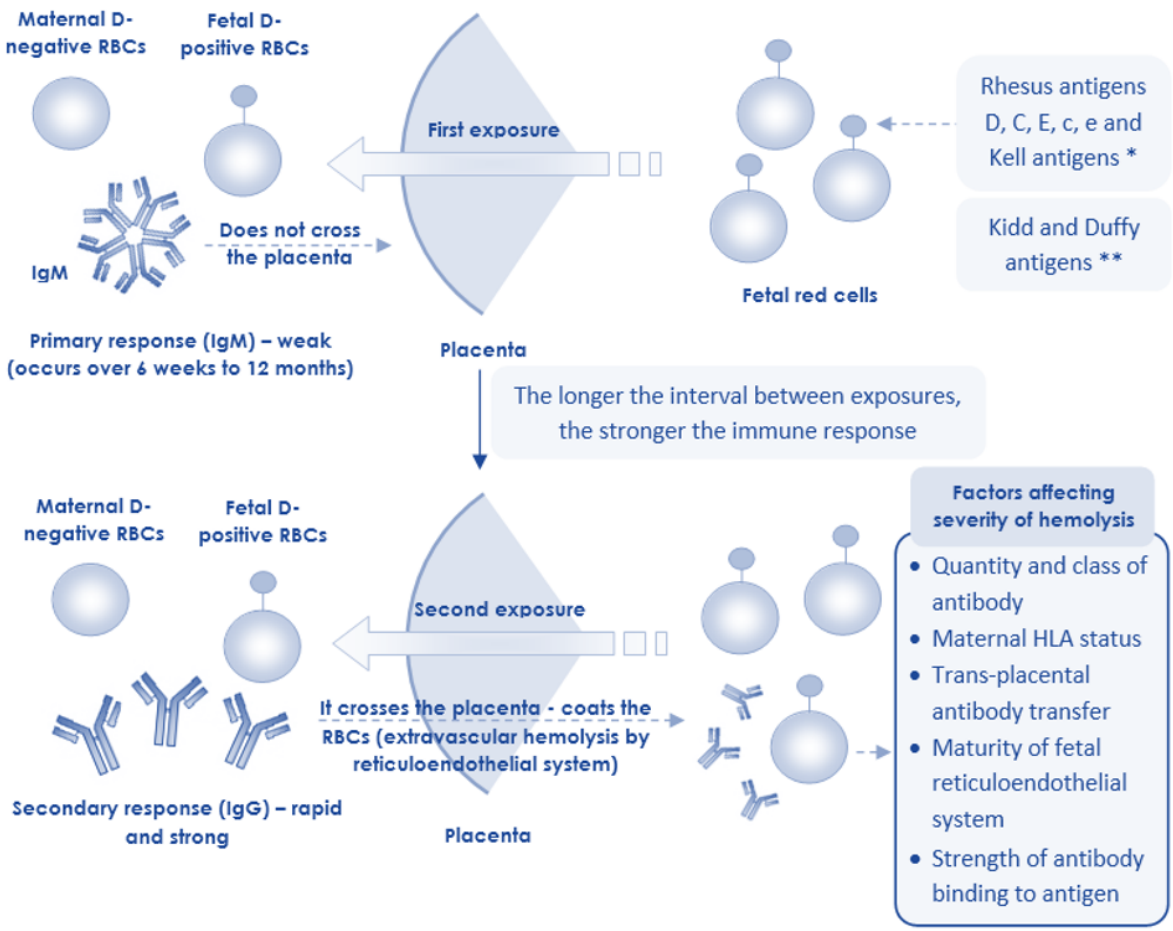
Normal	EDV present, PI or RI > 2 SDs	Absent or reversed EDV
Repeat ultrasound every 2 weeks including AC, EFW, UA Doppler, and MCA Doppler (after 32 weeks)	Repeat ultrasound every week including AC and EFW. Twice weekly UA Doppler	Repeat ultrasound every week including AC and EFW. Daily UA, DV Doppler and CTG
Delivery Offer delivery by 37 weeks (after involving a senior clinician) Recommend delivery at 37 weeks if MCA Doppler PI < 5th centile Consider delivery after 34 weeks if growth is static over 3 weeks Recommend steroids before CS	**Delivery** Recommend delivery at 37 weeks Consider delivery after 34 weeks if growth is static over 3 weeks Consider steroids before CS	**Delivery** Recommend delivery before 32 weeks after completion of steroid course (if gestational age is ≥ 24 weeks and EFW > 500 gram) Recommend delivery by 32 weeks Consider delivery at 30-32 weeks if DV is normal as well

EDV = End diastolic velocities, CS = Caesarean section

Red Cell Alloimmunization

Background

- Incidence of red cell antibodies is 1.2%. Incidence of significant antibodies is 0.4%
- There are no long-term complications to red cell alloimmunization in the mother
- Children to mothers with red cell alloimmunization are at risk of persistent anaemia for few weeks. Anaemia may be delayed in onset



Antenatal assessment

Women with red cell antibodies who are at risk of fetal anemia or who may have difficulty with availability of compatible blood in case transfusion is indicated

Pre-pregnancy counseling (but not screening)

Screen for alloantibodies at booking appointment and at 28 weeks

If maternal antibodies (D, C, c, E, e, K) are present

Non-invasive foetal genotype are tested. For other antigens, invasive testing is indicated if there is risk of foetal anaemia

OR

Test paternal genotype, if heterozygous, test foetal genotype, if homozygous, consider the foetus at risk

Non-invasive genotype (cell free foetal DNA) is done at 16 weeks for all antigens except K which is done at 20 weeks. If non-conclusive, management is either by repeating the test, considering invasive procedures or manage is as high risk

Invasive testing is not contraindicated if there is alloimmunization

High risk foetus

Check antibodies every 4 weeks till 28 weeks of gestation then every 2 weeks till delivery

- If anti-D titre:
  - Moderate risk > 4 - < 15 iu/ml
  - High risk > 15 iu/ml
- If anti-C titre:
  - Moderate risk > 7.5 - < 20 iu/ml
  - High risk >20 iu/ml
- If anti-K Abs:
  Refer immediately regardless of titre
- Anti-E potentiates anti-C:
  Therefore, refer at a lower titre

Refer to fetal medicine

- If there are ultrasound finding suggestive of foetal anaemia
- If there is a history of unexplained severe neonatal jaundice or neonatal anaemia requiring transfusion or exchange transfusion
- If there is a history of haemolytic disease of newborn, intrauterine transfusion, or a titre ≥32

Assessment of risk of haemolytic disease of the fetus and newborn (HDFN)

Assessment of risk of HDFN is determined by the cause of alloimmunization, past history and prior pregnancy outcomes

If antigens are present, antibody titre is high (see before), or anti-K antibodies are present

If there is history of alloimmunization if a prior pregnancy

Weekly middle cerebral artery peak systolic velocity (MCA-PSV) doppler and ultrasound

If MCA-PSV > 1.5 MOM or there are other signs of anaemia

Intervention (Foetal blood sampling and possible intrauterine transfusion)

Intrauterine transfusion

- Group O or identical blood group is used
- It should be negative for antigens that correspond to antibodies

Plasma is removed (increasing hematocrit to 0.7 -0.85)
Blood is irradiated

Foetal blood sampling is associated with 1-3% risk of foetal loss

Maternal care

Women with alloantibodies and at high risk of transfusion e.g. women with sickle cell anemia and placenta praevia

Blood Crossmatch at least every week

If blood is needed, transfuse blood of the same ABO and Rh group, K and CMV negative

Intrapartum management

- **Mode of delivery:**
  Mode of delivery is guided by obstetric indications

- **Timing of delivery:**
  It depends on antibody titre, foetal status and need for intervention. If antibody titre is stable with no complications, delivery is scheduled at 37-38 weeks

- **Place of delivery:**
  Women at high risk of transfusion should be delivered in specialized centres

- **Intrapartum measures:**
  - Continuous electronic foetal monitoring is indicated
  - In women with significant antibodies (e.g. anti-D, anti-c, anti-c + anti-E, anti-K) cord blood should be checked for haemoglobin, bilirubin and direct antiglobulin test is done
  - If women with red cell antibodies who need urgent blood transfusion, transfusion of ABO negative, Rh negative, and K-negative (without matching other antibodies) is considered after weighing risk and benefits of this decision

Neonatal management

- Observe/Follow-up anaemia (haemoglobin), jaundice (bilirubin), and neurobehavioral status
- Early discharge is not recommended
- Encourage breastfeeding (reduces dehydration and risk of jaundice)
- transfusion exchange or phototherapy is considered if bilirubin level becomes high or increasing

Neonatal exchange transfusion

Given blood should be:

- ABO compatible with the neonate and mother (cross-matched)
- CMV negative and K negative.
- Stored no more than 5 days
- Plasma reduced (Haematocrit is 0.5-0.6)

Neonatal small value transfusion

Given blood should be:

- ABO compatible with the neonate and mother
- Stored no more than 35 days
- No need to be irradiated (unless there is prior intrauterine transfusion)
- Plasma not reduced

Reduced Foetal Movements

Background

Definition

Fetal movements should be defined as maternal perception of any discrete kick, flutter, swish or roll.

Significance

- Normal perception of fetal movement ensures integrity of the central nervous and musculoskeletal systems.
- Abnormal perception of fetal movement (reduced or absent): may be a warning sign of fetal death (55%). This is significant up to and including the onset of labor.

Influencing factors

- **Maternal position:** women may perceive most fetal movements when lying down, fewer when sitting and fewest when standing.
- **Placental position**: an anterior placenta may decrease woman's perception of fetal movements (< 28 weeks).
- **Fetal position** (not presentation): women with anteriorly laid fetal spines may perceive fetal movement less (80% of cases of absent fetal movement despite good fetal movement during ultrasound exam).
- **Sedating drugs:** e.g. alcohol, benzodiazepines and other opioids (transient effect).
- **Blood glucose:** increase in fetal movements following the elevation of glucose concentration in maternal blood (controversial)
- **Carbon dioxide (smoking):** it may be associated with reduced fetal movement and influences fetal respiratory movements (after 30 weeks of gestation).
- **Antenatal corticosteroids:** they may decrease fetal movement and fetal heart rate variability over the 2 days following administration.
- **Major malformations:** e.g.
  - **Anencephaly:** normal or excessive fetal activity.
  - **CNS or musculo-skeletal abnormalities**: a lack of vigorous motion

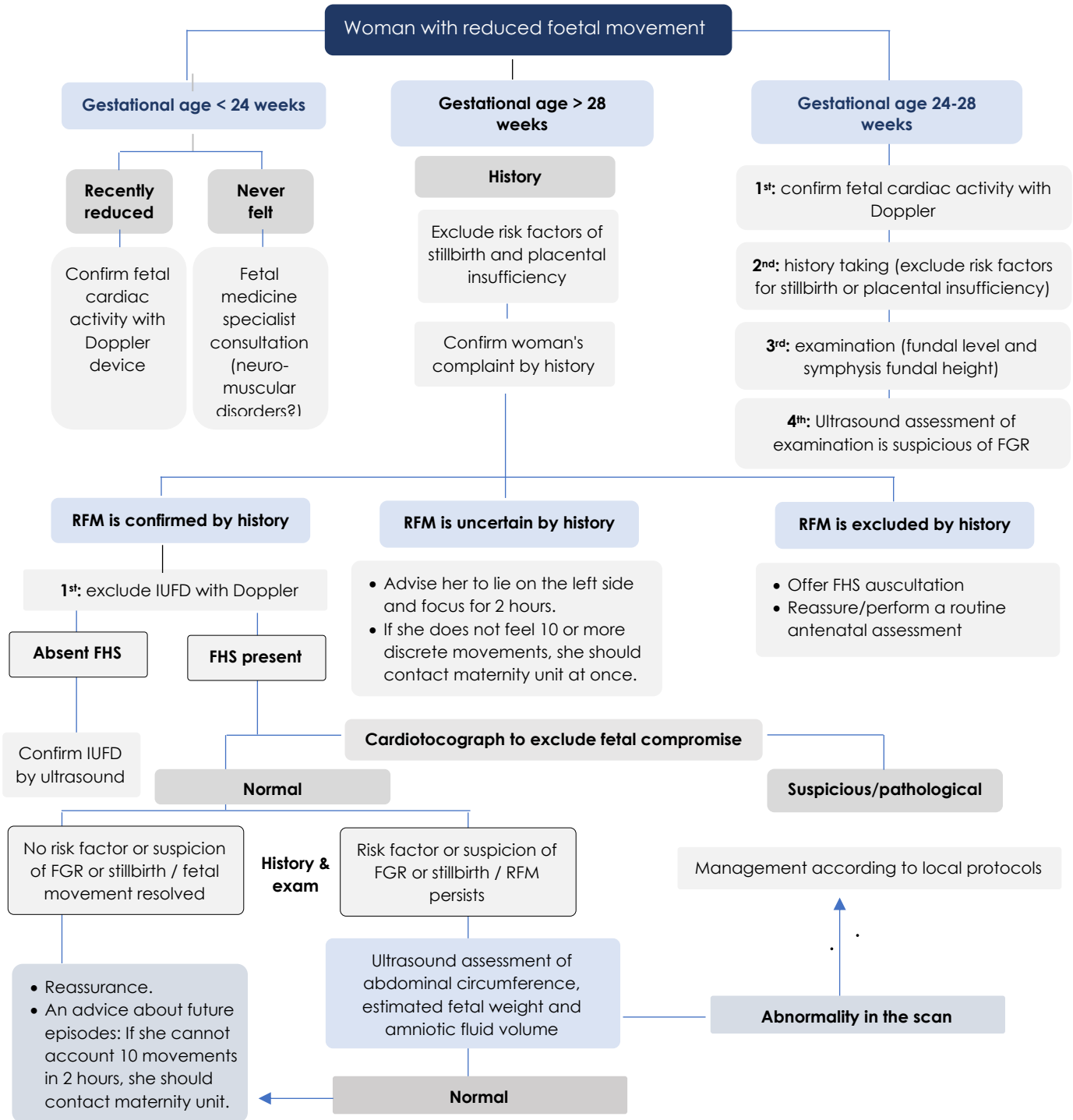
Normal pattern

- **Timing of first perception:** between 18 and 20 weeks of gestation (some multipara perceive as early as 16 weeks, some nullipara perceive after 20 weeks).
- **Progress of fetal movement:** The number tends to increase until the 32nd week then to plateau thereafter.
- **Frequency of fetal movement:**
  - The average number at term is 31 (16 - 45) per hour. The longest period between movements is 50 to 75 minutes.
  - The time for counting 10 movements varies between 21 minutes (focused counting) and 162 minutes (unfocused counting).

Diurnal Variations

- Diurnal variation is observed as early as 20 weeks of gestation. It is peak in the afternoon and evening periods (may be due to concentration).
- Fetal sleep cycles occur regularly throughout the whole day (20–40 minutes for each, rarely exceed 90 minutes).

Approach


Woman with reduced foetal movement
Gestational age < 24 weeks
Gestational age > 28 weeks
Gestational age 24-28 weeks
Recently reduced
Never felt
Confirm fetal cardiac activity with Doppler device
Fetal medicine specialist consultation (neuro-muscular disorders?)
History
Exclude risk factors of stillbirth and placental insufficiency
Confirm woman's complaint by history
1st: confirm fetal cardiac activity with Doppler
2nd: history taking (exclude risk factors for stillbirth or placental insufficiency)
3rd: examination (fundal level and symphysis fundal height)
4th: Ultrasound assessment of examination is suspicious of FGR
RFM is confirmed by history
RFM is uncertain by history
RFM is excluded by history
1st: exclude IUFD with Doppler
Absent FHS
FHS present
Confirm IUFD by ultrasound
Advise her to lie on the left side and focus for 2 hours.
If she does not feel 10 or more discrete movements, she should contact maternity unit at once.
Offer FHS auscultation
Reassure/perform a routine antenatal assessment
Cardiotocograph to exclude fetal compromise
Normal
Suspicious/pathological
No risk factor or suspicion of FGR or stillbirth / fetal movement resolved
History & exam
Risk factor or suspicion of FGR or stillbirth / RFM persists
Management according to local protocols
Reassurance.
An advice about future episodes: If she cannot account 10 movements in 2 hours, she should contact maternity unit.
Ultrasound assessment of abdominal circumference, estimated fetal weight and amniotic fluid volume
Abnormality in the scan
Normal

History

- **Analysis and confirmation of RFM:**
  - Is it reduced or absent?
  - The duration: for how long RFM is observed?
  - Is it the first occasion or recurrent?
- **Risk factors of stillbirth:**
  - Extremes of maternal age.
  - Primiparity.
  - Racial/ethnic factors.
  - Obesity and smoking.
  - Known FGR, hypertension, diabetes, placental insufficiency.
  - Recurrent RFM.
  - Congenital malformation.
  - Poor obstetric history (e.g.FGR and stillbirth).
  - Genetic factors.
- **Risk factors of fetal growth restriction**

Examination

- **Assessment of blood pressure (and proteinuria):** Pre-eclampsia is associated with placental dysfunction.
- **Auscultation of fetal heart:**
  - Auscultation of the fetal heart using a handheld Doppler device is made to exclude fetal death.
  - The fetal heartbeat is differentiated from the maternal heartbeat by the following:
    - The difference between the fetal heart rate and the maternal pulse rate.
    - Ultrasound assessment of fetal cardiac activity in case of doubt.
- **Assessment of fetal size (SGA):**
  - Clinical detection of SGA fetuses is done by:
    - Abdominal palpation.
    - Measurement of symphysis–fundal height (customized fundal height chart is recommended by RCOG).
    - Ultrasound biometry (particularly when clinical examination is difficult e.g. increased body mass index.

Investigations

- **Cardiotocograph (CTG):**
  - **Indication**: when history confirms RFM after 28 weeks and Doppler device confirms fetal viability.
  - **The procedure:** CTG monitoring is made initially for at least 20 minutes, computer systems for interpretation of CTG are more accurate than clinical experts.
  - **Normal findings:** The presence of a normal fetal heart rate pattern (fetal heart rate accelerations coinciding with fetal movements) indicates a healthy fetus.
  - **Abnormalities:** No acceleration for more than 80 minutes suggests fetal compromise.

- **Ultrasound assessment:**
  - ***Indication:*** Ultrasound scan assessment in indicated in women with RFM after 28 weeks of gestation if:
    - RFM persists despite a normal CTG or
    - Any additional risk factors for FGR/stillbirth.
  - ***Timing:*** If indicated, it should be performed within 24 hours of initial assessment.
  - ***Procedure:***
    - Assessment of abdominal circumference and/or estimated fetal weight to detect the SGA fetus.
    - Assessment of amniotic fluid volume.
    - Assessment of fetal morphology (if not previously performed). This should be accepted by the woman.

- ***Combined CTG and ultrasound*** are recommended within 2 hours (if women reported no fetal movements) and within 12 hours (if they reported RFM).

- **The biophysical profile (BPP):** the rule of BPP in these cases is controversial.

Recurrent DFM

Women with recurrent RFM episodes (2 or more) are at increased risk of a poor perinatal outcome (stillbirth, FGR or preterm birth). Ultrasound assessment is essential for evaluation of these cases.

Polyhydramnios

Background

- Polyhydramnios refers to the presence of excessive amniotic fluid
- Amniotic fluid increases gradually from the onset of pregnancy till 33 weeks, plateaus between 33 and 38 weeks and starts to decline thereafter
- 50-60% of cases have no identifiable cause. However, perineal mortality increases 2-5 times even if no cause is found

Causes

Maternal causes	Foetal causes	Placental causes
• Uncontrolled diabetes • Rh isoimmunization (causing foetal hydrops) • Drug exposure (lithium causes foetal nephrogenic diabetes insipidus)	• Structural anomalies e.g. oesophageal atresia • Chromosomal abnormalities • Infection e.g. parvo virus, TORCH infection • Foetal tumours e.g. cervical teratoma, neuroblastoma • Macrosomia	• Chorioangioma • Metastatic neuroblastoma

Assessment

- Diagnosis is made via ultrasound. Measurement of amniotic fluid is made by the deepest vertical pocket (DVP) if the 4 abdominal quarters. The pocket should be limb free and cord free to take an accurate measurement. Alternatively, amniotic fluid index (AFI) is measured
- Polyhydramnios is diagnosed if DVP is ≥ 8 cm or AFI is ≥ 25
- Once the diagnosis is made, further investigations are made to determine the cause

	Assessment	Action
Foetal causes	• Foetal anomalies • Foetal movement (ruling out arthrogryposis) • Foetal growth and weight	Urgent referral to foetal medicine if there is concern on foetal anomalies, aneuploidy infection, movement, or growth restriction
Maternal causes	• Red cell antibodies • TORCH infection, parvovirus • Fasting glucose, HBA1C, glucose tolerance test	Referral to foetal medicine

Classification

Mild	AFI equals 25 to 29.9 cm
Moderate	AFI equals 30 to 34.9 cm
Severe	AFI is ≥ 35 cm

Complications

- Preterm labour (cervical shortening is assessed, and antenatal steroids onsidered)
- Unstable lie and malpresentation
- Cord prolapse
- Antepartum haemorrhage
- Postpartum haemorrhage
- Higher risk of operative delivery

Antepartum management

Mild polyhydramnios likely resolves spontaneously and is not associated with higher risk of adverse outcomes except those related to associated macrosomia. Women with severe polyhydramnios may require further treatment

- **Amnioreduction:**
  - **Indications:**
    ① Relieving respiratory symptoms
    ② Reducing the risk of preterm labour if marked cervical shortening is observed
  - **Procedure:**
    - Slow technique (using 50 ml syringe)
    - Rapid technique (using vacuum assisted drainage system)
  - **Target:**
    The procedure should be stopped once symptoms are relieved and AFI is less than 25
  - **Complications: (1.5%)**
    - Preterm labour
    - Rupture of membranes
    - Chorioamnionitis
    - Placental abruption

- **Indomethacin (COX inhibitor) and sulindac (selective COX-2 inhibitor):**
  It should only be performed under strict specialist supervision. Risks associated with these medications are:
  - Gestational age dependent ductus arteriosus closure
  - Impairment of foetal renal function

Intrapartum management

- Polyhydramnios itself is not an indication of induction of labour
- Close monitoring and anticipation of shoulder dystocia should be considered given the associated risk of macrosomia
- Amniotomy is recommended in the theatre (controlled amniotomy)
- Immediately after delivery, postpartum haemorrhage should be anticipated and actively managed
- A thorough examination of the baby for anomalies should be considered. Upper gastrointestinal patency can be checked by passage of a nasogastric tube

Outcomes

- In the presence of structural anomalies, mortality risk is 60% versus 4% if no anomalies are detected
- Cases that have no aberrant anomalies may have undiagnosed disorders e.g. Bartter syndrome, West syndrome

Intrauterine Fetal Death

Definitions

- **Intrauterine foetal death (IUFD):** babies with no signs of life in utero.
- **Stillbirth:** a baby delivered with no signs of life and is died after 24 completed weeks of pregnancy. One third of stillbirths are small for gestational age fetuses and half are being unexplained.

Causes

I. Causes of intrauterine death

Maternal

Maternal diseases e.g. pre-eclampsia and DM

Foetal

Chromosomal anomalies (6%)

Trans-placental infection

- Listeria.
- Cytomegalovirus, parvovirus B19, rubella, herpes simplex, coxsackie.
- Syphilis, leptospira, Q fever, and Lyme disease.
- Toxoplasmosis, malaria parasitemia

Congenital infection

Ascending infection

- Escherichia coli, Klebsiella.
- Hemophilus influenza.
- Group B Streptococcus, Enterococcus.
- Mycoplasma/ureaplasma
- Chlamydia

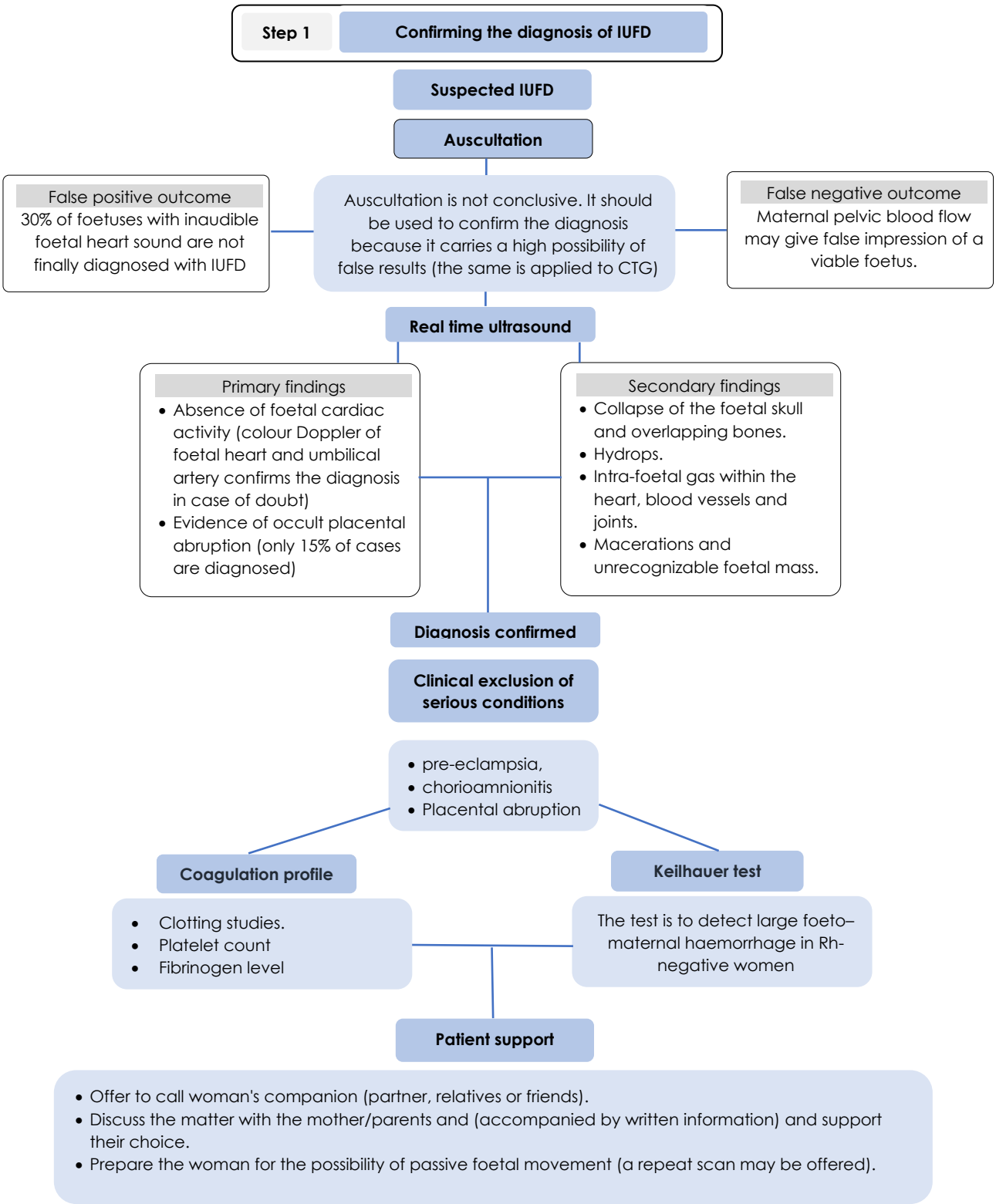
Combined

Foeto-maternal causes (antepartum haemorrhage)

II. Causes of intra-partum death

- Placental abruption
- Maternal and foetal infection.
- Cord prolapse
- Idiopathic hypoxia–acidosis.
- Uterine rupture.

Approach

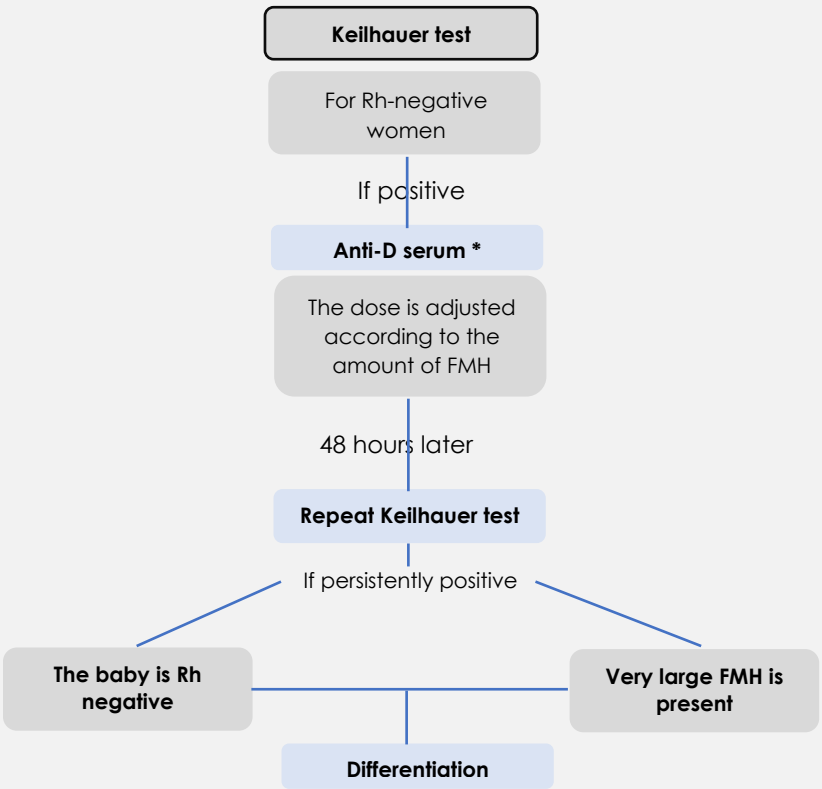

Step 1
Confirming the diagnosis of IUFD
Suspected IUFD
Auscultation
False positive outcome
30% of foetuses with inaudible foetal heart sound are not finally diagnosed with IUFD
Auscultation is not conclusive. It should be used to confirm the diagnosis because it carries a high possibility of false results (the same is applied to CTG)
False negative outcome
Maternal pelvic blood flow may give false impression of a viable foetus.
Real time ultrasound
Primary findings
• Absence of foetal cardiac activity (colour Doppler of foetal heart and umbilical artery confirms the diagnosis in case of doubt)
• Evidence of occult placental abruption (only 15% of cases are diagnosed)
Secondary findings
• Collapse of the foetal skull and overlapping bones.
• Hydrops.
• Intra-foetal gas within the heart, blood vessels and joints.
• Macerations and unrecognizable foetal mass.
Diagnosis confirmed
Clinical exclusion of serious conditions
• pre-eclampsia,
• chorioamnionitis
• Placental abruption
Coagulation profile
• Clotting studies.
• Platelet count
• Fibrinogen level
Keilhauer test
The test is to detect large foeto–maternal haemorrhage in Rh-negative women
Patient support
• Offer to call woman's companion (partner, relatives or friends).
• Discuss the matter with the mother/parents and (accompanied by written information) and support their choice.
• Prepare the woman for the possibility of passive foetal movement (a repeat scan may be offered).

Coagulation profile

- **Rationale:**
  The risk of DIC after IUFD is 10% within 4 weeks and up to 30% after 4 weeks. The risk is higher with maternal sepsis, placental abruption and pre-eclampsia (cause of IUFD).
- **Frequency:**
  Tests are repeated twice weekly if the patient is managed expectantly.

Keilhauer test

- **Rationale:**
  It is used to identify large foeto–maternal haemorrhage (FMH) either as a cause or because of IUFD.
- **The immunization approach:**



① Foetal blood grouping using foetal or cord blood

② Free foetal DNA (ffDNA) from maternal blood sample (should be taken shortly after birth)

*Anti-D serum should be given within 72 hours of FMH. However, it is still of some value up to 10 days of the accident. It should be considered that FMH may have occurred days before the diagnosis of IUFD.

Step 2 **Investigating the cause of IUFD**

I **Maternal investigations**

Standard laboratory tests

- **Haematology:** platelet count is particularly important in pre-eclampsia and DIC.
- **Chemistry:** it identifies end organ failure in women suffering from sepsis or haemorrhage.
- **Bile salt:** for diagnosis of obstetric cholestasis.

Keilhauer test

- **Rationale:** diagnosis of large FMH as a cause of IUFD.
- **Timing:** it should be before birth before foetal RBCs are cleared from the circulation.

Maternal bacteriology

- **Indications:**
  Indicated only if there is suspicion of chorioamnionitis including:
  - Maternal fever and flu-like symptoms.
  - Purulent offensive vaginal discharge.
  - Prolonged rupture of membranes before IUFD.
- **The tests:** Blood culture, midstream urine, cervico-vaginal swab.

Maternal serology

- **Indications:**
  Indicated for the diagnosis of occult maternal–foetal infection:
  - ***Routinely for all women:*** Parvovirus B19 (hydrops in not necessary), CMV, herpes simplex and Toxoplasma gondii.
  - **For women who are non-immune at booking:** screening for rubella.
  - **For women who are investigated for syphilis at booking:** Treponemal serology.
  - **For women who travelled to endemic areas e.g. Africa:** Malaria.

Maternal endocrinology

- **Diabetes mellitus:**
  - ***Maternal random blood glucose:*** for diagnosis of occult diabetes (gestational diabetes may be missed as blood glucose returns to normal few hours after IUFD)
  - ***Maternal HbA1c:*** for diagnosis of gestational diabetes mellitus (gestational diabetes can be also missed because most women have normal HbA1c).
- **Thyroid disease:**
  TSH, FT4 and FT3 are assessed for diagnosis of occult maternal thyroid disease.

Maternal thrombophilia

- **Indications:**
  Indicated if there is evidence of foetal growth restriction or placental disease.
  However, the association is weak and further considerations in next pregnancy are still doubtful.
- **Protocol:**
  If the tests are positive, it should be repeated after 6 weeks.

Maternal thrombophilia

Test	Indication	Conclusion
Anti-red cell antibody serology	If there is evidence of foetal hydrops	Diagnosis of immune haemolytic disease
Maternal anti-Ro and anti-La antibodies	If there is evidence of hydrops, endomyocardial fibro-elastosis or AV node calcification (post-mortem examination).	Diagnosis of occult maternal autoimmune disease
Maternal alloimmune antiplatelet antibodies	If foetal intracranial haemorrhage (post-mortem examination).	Diagnosis of alloimmune thrombocytopenia

Maternal urine (metabolites)

Maternal urine is examined for cocaine metabolites (after consent) if there is suggestive data of occult drug use.

II Parental investigations

Parental karyotyping

- **Indications:**
  - ***If post-mortem examination*** reveals foetal abnormality.
  - ***If foetal genetic testing*** reveals foetal unbalanced translocation or aneuploidy e.g. 45X (Turner syndrome).
  - ***If history is suggestive of aneuploidy (no or failed genetic testing):*** e.g. previous unexplained IUFD, recurrent miscarriage.
- **Conclusion:** Diagnosis of parental balanced translocation and parental mosaicism.

III Foetal/placental investigations

Foetal and placental microbiology

- Under clean conditions, cord or better cardiac blood (consent required) is obtained. Lithium heparin is added.
- This test is more informative than maternal serology in the diagnosis of viral infections.

Foetal and placental Karyotyping

Karyotyping helps to diagnose aneuploidy and single gene disorders. This helps in:
- Identification of the cause of IUFD.
- Testing in future pregnancies because some anomalies are possibly recurrent.

This can be achieved by: Tissue culture or QF-PCR

Post-mortem

- Parents should be offered post-mortem examination to possibly identify the cause of an IUFD, but they should never be persuaded.

Delivery

I Management of labour

Time of delivery

Immediate versus delayed delivery

Immediate

This is indicated in the following conditions:

- Sepsis.
- Preeclampsia.
- Placental abruption.
- Membrane rupture.
- Evidence of DIC.

Delayed

Short delay (48 hours)
This delay is acceptable. No harm is expected.

Prolonged delay
If the woman chooses to be managed conservatively, she should have a 24-hour contact number

Advantage
85% of women with IUFD delivers spontaneously within 3 weeks of IUFD

Disadvantages
The risk of DIC (see before).
The value of post-mortem is reduced.
Deterioration of foetal appearance.

These points should be covered clearly while counselling the woman for delivery.

Mode of delivery

Some women → **I. Caesarean section**

- There is an indication of CS.
- If requested, vaginal delivery of IUFD is emotionally stressful in 47% of women compared with 7% under normal circumstances.

Most women → **II. induction of labour**

90% of women deliver within 24 hours of induction of labour

Facilities for IUFD labour

- Facilities for emergency care.
- A special labour wardroom for uncomplicated IUFD (away from the sound of babies) with c nursing team trained to care with these women.
- A double bedroom for the woman and her companion.
- Delivery by experienced midwife

Intrapartum antibiotic therapy

- IV broad-spectrum antibiotic therapy (including Chlamydia) is indicated in sepsis.
- Antibiotics are not given routinely or in GBS colonized women.
- Pyrexia secondary to prostaglandin use should be considered and misinterpreted as infection.

Pain relief during labour

- Diamorphine is recommended (in preference to pethidine).
- Regional anaesthesia can be offered. However, sepsis and DIC should be excluded before the procedure is offered (sepsis is associated with epidural abscess, DIC is associated with epidural and subdural hematoma).

Induction regimens for women with IUFD

Women with unscarred uterus

Mifepristone 200mg single dose *
PLUS

< 26 weeks

100 µg 6 hourly of misoprostol

> 26 weeks

25–50 µg 4-hourly of misoprostol

Misoprostol vs. prostaglandin E2
Misoprostol is a better choice (less cost, equal safety and efficacy).
Intra-vaginal misoprostol vs. IV oxytocin
Misoprostol is more effective than oxytocin.
Vaginal versus oral misoprostol
Vaginal misoprostol yields the same efficacy but with less side effects (nausea, vomiting, diarrhea, pyrexia)

Women with previous 2 CS

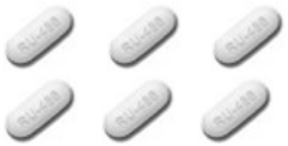
The risk of induction is slightly higher than in women with previous 1 CS

Women with > previous 2 CS

The safety of induction is unknown in these women

Women with previous CS should be monitored for the signs of scar dehiscence (maternal tachycardia, atypical pain, vaginal bleeding, haematuria, and maternal collapse). The decision of oxytocin augmentation is made by the consultant

Previous 1 lower segment caesarean section (CS)



Mifepristone 200mg 3 times for 2 days or 600mg once for 2days **

OR

Trans-cervical balloon catheter (restricted to clinical trials)

Advantages
- 79% of women achieve vaginal birth.
- Uterine rupture rate (0.58%) is lower than with prostaglandins (like spontaneous labour)

Disadvantages
- There is increased risk of ascending infection in the presence of IUFD.

OR

Misoprostol

NICE recommends the use of lower doses (25–50 µg) for previous CS

Positives
No evidence of an increased rate of hysterectomy or maternal death.
Foetal distress risk is of no rule here

Negatives
Higher risk of endometritis, blood transfusion and scar dehiscence and rupture (0.7%)

* Mifepristone (when added to misoprostol) reduces the time interval for labour by about 7 hours.
** This regimen increases the chance of labour within 72

II Postpartum management

Hospital stay

- Unless there is associated critical condition that necessitates special care e.g. pre-eclampsia, sepsis, DIC, a woman can return home immediately.
- If a woman does not want to return home immediately, adequate privacy should be provided to the woman with complete separation from the maternity unit.

Thrombo-prophylaxis

- IUFD is not a risk factor for thromboembolism. However, many causative conditions (e.g. infection, maternal disease) are themselves risk factors. Assessment of risk should be done according to the usual guidelines.
- Haematological consultation may be necessary if heparin thromboprophylaxis is indicated in a patient with DIC.

Suppression of lactation

- **Dopamine agonists:** (90% effective).
  - ***Bromocriptine:*** 2.5 mg twice daily for 14 days.
  - ***Cabergoline:*** 1 mg (a simpler regimen, less rebound activity and side effects than bromocriptine).

  NEVER give these drugs to women with hypertension (including pre-eclampsia) because they may increase blood pressure and may be associated with intracerebral haemorrhage.
- **Other options:** non-pharmacological methods (e.g. support brassière, ice packs and analgesics) and oestrogen are not proper choices for their uncertain effectiveness and adverse effects.

Fertility - contraception

- The woman should be counselled about future fertility and contraception choice before leaving the hospital.
- As a health care provider, you should be aware of these 2 points:
  - Early conception following foetal loss experience may predispose to psychological problems.
  - In these women, ovulation may return rapidly (as early as 18 days) due to suppression of lactation and they may conceive before their first menstrual period.

Psychological support

- The psychological impact of these women greatly varies but they are generally liable to postnatal depression and post-traumatic stress disorder. There is also 40% higher risk of parental relationship dissolving.
- Accordingly, offer counselling to the woman, her partner and consider family members in this counselling. Advise couples about support groups.

Follow up

Time and frequency of visits

There is optimal schedule, but the results of different investigations should be available (usually 6-8 weeks)

Follow up (cont.)

Place of visits

Generally, home visits are not superior to clinical visits. However, it should be offered if possible when the woman finds it distressing to return to the place where she delivered.

Content of visits

- **First:** Discuss the results of previous investigations and the possible cause of IUFD. Give information about the chance of recurrence and if applicable, how to avoid further loss.
- **Second:** Discuss delay of conception. The parents should be advised that delaying conception can give time for possible psychological sequences of IUFD to recover. However, both early pregnancy and delayed pregnancy can evoke anxiety.
- **Third:** Offer a pre-pregnancy advice regarding smoke cessation and optimization of body mass index (BMI). A documented plan for the next pregnancy should be agreed in this set.

III Management in next pregnancy

During pregnancy

- Clear documentation of risk (previous IUFD).
- Women with a previous unexplained IUFD should be offered:
  - Obstetric antenatal care.
  - Screening for gestational diabetes.
- Women with previous IUFD (apparently normal but SGA) should be offered serial ultrasound assessment of growth.

During labour

- Woman with previous unexplained IUFD should deliver in specialist maternity unit.
- Woman with previous nonrecurrent cause of IUFD requires individual evaluation to choose for the place of birth.
- Scheduled birth should consider the gestational age of the previous IUFD, previous intrapartum events and induction of labor safety.

After labour

- After birth, women are at risk of depression. Risk factors for depression include:
  - Depression in the third trimester (risk extends up to 1 year after birth).
  - Women who conceive within < 12 months from a previous IUFD.
- Maternal bonding can be adversely affected.

Pregnancy following unexplained stillbirth

Women with a history of stillbirth (as a single risk) have:

- A 12-fold increased risk of intrapartum stillbirth.
- An increased risk of pre-eclampsia and placental abruption.
- An increased risk of gestational diabetes (four times).
- An increased risk of ischemic placental disease, foetal distress, chorioamnionitis, extreme preterm birth and early neonatal mortality.

Appendix - I Foetal and placental karyotyping

Written consent

It is necessary for any foetal samples

I. Tissue

1. Tissue sampling is taken from the deep foetal skin, cartilage and the placenta. Obtain several specimens to minimize the risk of failure.
2. Preserve in a culture fluid that contains antibiotics to reduce the risk of bacterial contamination (culture failure).
3. Keep culture bottles in the refrigerator away from formalin preservation bottles. They should be thawed slowly before examination.
4. Genetic material should be stored if a single-gene syndrome is suspected.

Amniocentesis

A sample from the amniotic fluid may be used in women managed expectantly.

Disadvantages
Culture failure rate is ~60% (twice that of other tissues).

Placental biopsy

Technique
Take approximately 1 cm from the foetal surface near cord insertion (to avoid maternal tissues).

Advantages
Placenta is the most viable tissue. It supplies rapid growing cells for tissue culture.

Disadvantages
Maternal contamination
Placental pseudo mosaicism

Cartilage sample

It is the second choice. However, it is difficult to sample e.g. patella

Skin sample

Technique
Skin biopsy is taken deep to include underlying muscle (about 1 cm from the upper fleshy part of the thigh).

If culture fails

II. QF-PCR

Quantitative fluorescent polymerase chain reaction (QF-PCR) can be performed on extracted DNA.

Tissue culture versus QF-PCR

Tissue culture	QF-PCR
Culture rovides wide range of genetic information (trisomies, monosomies, translocations, major deletions and marker chromosomes). Microdeletions are requested specifically based on postmortem examination findings.	It is reliable (<0.01% failure rate), efficient and cheap for aneuploidies. However, it is unreliable for the detection of translocations and marker chromosomes.

Appendix - II Postmortem examination

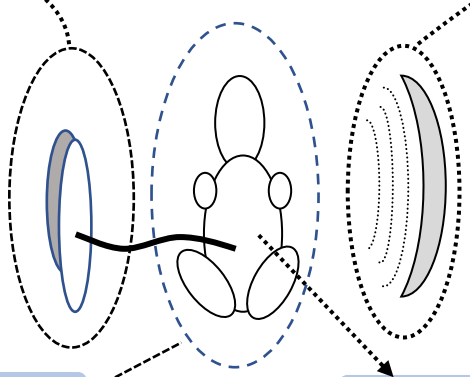
The consent (cover the following)

- The purpose of examination.
- The procedure and its extent.
- Possible organ/tissue retention and purpose.

Methods of postmortem examination

Placenta/cord

Pathological examination of the cord/placenta and membranes is recommended (even if not requested).



Medical

- **Skeletal X-rays:** can show skeletal defects.
- **MRI:** for the brain and spinal cord (24% adds new information).
- **Ultrasound:** for internal organs (the value is not yet evaluated).

External examination

Examiner should report any apparent abnormalities, Weight and height should be reported (consider IUGR).

Autopsy/microscopy

Microscopic examination of relevant tissues should be performed (after parent's consent).

Levels of postmortem examination

The level of postmortem examination goes down according to parent's request. However, the lower the level, the less conclusive the examination.

Full postmortem examination
The classic examination in the diagram

Limited postmortem examination
Restricted conventional postmortem examination

Limited postmortem examination
Minimally invasive examination

Disadvantages

- Its value is limited unless there is a specific suspicious organ that the parents agree to be examined.
- It is technically difficult and may need more aggressive dissection than expected by the parents e.g. examination of the heart indicates removal of the lung and the thymus.

Approach

- **Minimally invasive surgical methods:** such as transcutaneous tissue biopsy, body-cavity aspiration (less informative).
- **Medical imaging:** ultrasound and magnetic resonance imaging (MRI) are an adjuvant rather than a substitute for conventional postmortem.

Antenatal Care of Multiple Pregnancy

Booking visit

First trimester ultrasound should be offered to women with multiple pregnancy for:

- Assessment of viability
- Assessment of gestational age (gestational age is determined by the largest foetus)
- Assessment of chorionicity and amnionicity
- Assignment of nomenclature (assign foetuses as left and right, or upper and lower for consistency)

Methods of determination of chorionicity and amnionicity

- The number of placental masses
- The presence of amniotic membrane(s) and membrane thickness
- Lambda or T-sign
- Discordant fetal sex (if gestational age is beyond 14 weeks)

Dichorionic diamniotic (DCDA) pregnancy	▪ There are 2 chorionic and 2 amniotic layers ▪ There is a thick inter-twin membrane (> 2 mm) ▪ Lambda sign
Monochorionic diamniotic (MDCA) pregnancy	▪ There are 2 amniotic layers only ▪ There is a thin inter-twin membrane (< 2 mm) ▪ T-sign
Monochorionic monoamniotic (MCMA) pregnancy	There is no intertwin membrane

If chorionicity cannot be determined, a second opinion by a senior sonographer or a referral should be considered. If chorionicity remains undetermined, pregnancy should be managed as monochorionic pregnancy

Transvaginal ultrasound may be used as an alternative to transabdominal ultrasound in women with high body mass index and uterine retroversion. 3D ultrasound should not be used

Antenatal care

- **Care providers:**

Antenatal care is provided to women with multiple pregnancy by a multidisciplinary team

Core team

The team consists of specialist obstetricians, specialist midwives and sonographer who have experience with multiple pregnancy

Role

They provide emotional support, information and advice on nutrition, risk of preterm labour, time and mode of birth, breastfeeding, and parenting

Enhanced team

The team consists of a perinatal mental health professional, women's health physiotherapist, and an infant feeding specialist

Role

Enhanced team is available for referral only if indicated (not a routine)

Dietitian

Nutritional recommendations are similar to routine antenatal care of singleton pregnancy

- **Antenatal care appointments:**

Type	Number of appointments	Combined appointments	Appointments without scans
Dichorionic diamniotic twin pregnancy	• At least 8 appointments with providers from the core team • At least 2 appointments with a specialist	• Combined appointment (appointment + ultrasound scan) should be offered between 11^{+2} and 14^{+1} weeks [crown rump length between 45 and 84 mm]) • Combined appointment should be offered every 4 weeks between 20 weeks and 36 weeks	Additional appointments (without scan) are offered at 16 and 34 weeks
Monochorionic diamniotic twin pregnancy	• At least 11 appointments with providers from the core team • At least 2 appointments with a specialist	• Combined appointment (appointment + ultrasound scan) should be offered between 11^{+2} and 14^{+1} weeks [crown rump length between 45 and 84 mm]) • Combined appointment should be offered every 2 weeks between 16 weeks and 34 weeks	None
trichorionic triamniotic triple pregnancy	• At least 9 appointments with providers from the core team • At least 2 appointments with a specialist	• Combined appointment (appointment + ultrasound scan) should be offered between 11^{+2} and 14^{+1} weeks [crown rump length between 45 and 84 mm]) • Combined appointment should be offered at 20 and 24 weeks and then every 2 weeks between 24 weeks and 34 weeks	Additional appointments (without scan) are offered at 16 weeks

Dichorionic triamniotic or monochorionic triamniotic triplet pregnancy	• At least 11 appointments with providers from the core team • At least 5 appointments with a specialist	• Combined appointment (appointment + ultrasound scan) should be offered between 11^{+2} and 14^{+1} weeks [crown rump length between 45 and 84 mm]) • Combined appointment should be offered every 2 weeks between 16 weeks and 34 weeks	None
Twin and triplet pregnancies with a shared amnion	Individualised care should be offered by a consultant in a tertiary level foetal medicine centre (monochorionic monoamniotic twins, dichorionic diamniotic triplets, monochorionic diamniotic triplets, and monochorionic monoamniotic triplets)		

- **Foetal screening:**
  - **Screening for chromosomal abnormalities:**

Twin pregnancy	▪ Women are offered screening for Down's syndrome, Edwards' syndrome and Patau's syndrome ▪ As routine, screening follows the NHS foetal anomaly screening programme (FASP)
Triple pregnancy	▪ Women are offered screening for Down's syndrome, Edwards' syndrome and Patau's syndrome ▪ Triplet pregnancy is associated with higher risk of aneuploidy, different screening strategies, higher false positive results and probability of invasive testing, higher risk of complications with invasive testing • Nuchal translucency (between 11^{+2} and 14^{+1} weeks [crown rump length between 45 and 84 mm]) is used for screening

	▪ Second trimester serum screening is not recommended ▪ Dichorionic and monochorionic triplet pregnancy should be referred to a tertiary level foetal medicine centre if they are interested in screening

Women are referred to a tertiary-level foetal medicine centre if the risk od any aneuploidy is higher than 1 in 150 at term

- **Screening for structural abnormalities:**

Ultrasound screening is similar to routine antenatal care of a singleton pregnancy. However, it should be offered at a later gestational age. Scheduled scanning time should be 45 minutes for the anomaly scan and 30 minutes for growth scans

- **Screening for preterm labour:**
  - Women with multiple pregnancy are at higher risk of preterm labour
  - Foetal fibronectin alone is not recommended to screen for preterm labour. Home uterine activity monitoring should not be used
  - Routine use of intramuscular progesterone, cerclage, arabin pessary, tocolytics, or bedrest is NOT recommended
  - Antenatal steroids are not used routinely unless otherwise indicated

- **Screening for foetal growth restriction (dichorionic or trichorionic foetuses):**

First trimester	Screening methods should not be offered
Second and third trimester	• Symphyseal fundal height is not used for screening. Ultrasound should be performed routinely • Starting from 24 weeks, dichorionic or trichorionic foetuses should be screened by 2 biometry measurements and deepest vertical pocket (DVP) at each side (screening interval is 4 weeks in dichorionic twins and 2 weeks in trichorionic triplets) • At each screening, discordance should be calculated

	• If estimated foetal weight (EFW) of any foetus is < 10th percentile or if discordance is > 20%, scans should be scheduled weekly with umbilical artery Doppler • If EFW of any foetus is below the 10th percentile or if discordance is > 25%, consider referral to tertiary level foetal medicine centre (selective foetal growth restriction)

Discordance in twins	Discordance in triplets
This is calculated by: (estimated foetal weight in the larger twin – estimated foetal weight in the smaller twin)/estimated foetal weight in the larger twin	This is calculated by: (estimated foetal weight in the largest foetus – estimated foetal weight in the smallest foetus)/estimated foetal weight in the largest foetus AND (the largest – the middle foetus)/the largest foetus

- **Screening for foetal complications of multiple pregnancy:**

Feto-fetal transfusion syndrome	• A monochorionic twin or triplet pregnancy should be scanned every 2 weeks starting at 16 weeks. Assessment of DVP should be performed • Scanning is performed every 1 week along with Doppler assessment if difference in DVP between sacs is > 4 cm • If one DVP is < 2 cm and the other DVP is > 8 cm (before 20 weeks) or > 10 cm (after 20 weeks), women should be referred to a tertiary level fetal medicine centre • If one DVP is normal and the other is < 2 cm or ≥ 8 cm, women should be referred to their specialist obstetrician

Foetal growth restriction in monochorionic twins	• Monochorionic twin or triplet pregnancy is screened every 2 weeks starting at 16 weeks using 2 biometric parameters and DVP at each side. Discordance is calculated at each scan • If discordance is ≥ 20% or EFW of one foetus is < 10th percentile, they should be screened every 1 week including umbilical artery Doppler • Women are referred to a tertiary level foetal medicine centre if discordance is ≥ 25% or EFW is < 10th centile (selective foetal growth restriction)
Twin anaemia polycythaemia sequence (TAPS)	• Screening for TAPS is indicated if: ① Feto-fetal transfusion syndrome after laser photocoagulation ② Selective foetal growth restriction • Screening is performed by weekly middle cerebral artery peak systolic velocity (MCA-PSV) assessment starting at 16 weeks • If monochorionic twins show cardiovascular compromise (hydrops or cardiomegaly), unexplained isolated polyhydramnios or abnormal umbilical artery Doppler, women should be assessed by MCA-PSV and referred to a tertiary level foetal medicine

- **Screening for maternal complications:**
  - **Hypertension:**
    - Blood pressure and proteinuria are screened at each antenatal visit
    - Low dose aspirin should be offered to women who have 2 or more risk factors of preeclampsia

  - **Anaemia:**

    Women with multiple pregnancy are at higher risk of anaemia compared to singleton pregnancy. These women should be offered a complete blood count at 20 to 24 weeks

Intrapartum management

Intrapartum plan of care should be discussed at 24 weeks (28 weeks is the latest) including place and time of birth, intrapartum foetal monitoring and analgesia, and management of third stage of labour. Intrapartum care should be provided by a multidisciplinary team of obstetricians and midwives

- **Timing of birth:**

Type	Recommended gestational age of planned delivery*
Uncomplicated dichorionic diamniotic twins	37 weeks
Uncomplicated monochorionic diamniotic twins	36 weeks (after completion of steroid course)
uncomplicated monochorionic monoamniotic twin	32-33^{+6} weeks (after completion of steroid course)
Uncomplicated trichorionic triamniotic or dichorionic triamniotic triplets	35 weeks (after completion of steroid course)

Spontaneous labour occurs in 60% of twins before 37 weeks and 75% of triplets before 35 weeks

* Beyond these gestational ages, women should be informed that there is increased risk of fetoal loss

  - Timing of birth is individualized in women with complicated twin or triplet pregnancy, monochorionic triamniotic triplet pregnancy, or triplet pregnancy with a shared amnion
  - If delivery is declined at the planned date, weekly appointments should be scheduled with the specialist obstetrician with assessment of amniotic fluid level and umbilical artery Doppler at each visit and foetal growth assessment every 2 weeks

- **Mode of birth:**

  One third of Women who are eligible for vaginal delivery eventually undergo caesarean delivery. Of those, a small percentage may undergo caesarean section to deliver the second twin after vaginal delivery of the first twin

Indications of vaginal delivery	Indications of caesarean section
Both vaginal deliveries and caesarean section can be offered if dichorionic diamniotic or monochorionic Diamniotic twins with: ① Uncomplicated pregnancy beyond 32 weeks ② The first twin is a cephalic presentation ③ No significant discordance between the twins ④ No obstetric contraindications to vaginal delivery Vaginal birth may be considered in monochorionic monoamniotic twins only if the first twin is close to birth (decision is made by a senior obstetrician)	Women are offered caesarean section if: ① The first twin is non-cephalic at the time f planned birth ② The first twin is non-cephalic, if preterm labour is established between 26-32 weeks ③ Monochorionic monoamniotic twin pregnancy (at time of planned delivery or if there is preterm labour and there is reasonable chance of survival of twins) ④ Triplet pregnancy (at time of planned delivery or if there is preterm labour and there is reasonable chance of survival of twins)

Decision is individualized if preterm labour occurs before 26 weeks

- **Foetal monitoring:**
  - Bedside ultrasound is performed at the onset of labour to assess twin presentation, location, and location of foetal beats
  - Continuous cardiotocography (CTG) should be considered in twin pregnancy at or beyond 26 weeks of gestation who are in labour. Intermittent consultation should not be offered
  - Simultaneous record of twin heart rates and maternal pulse should be made, and they should all be recorded on the same trace. Separating twin heart rates by 20 beats/minute may be considered if differentiation between the 2 heart rates is not feasible
  - Twin pregnancy is a risk factor that should be considered when interpreting traces (abnormal versus non-reassuring)
  - Foetal scalp stimulation should not be used

- If pregnancy is earlier than 26 weeks, a discussion should be made between the patient, her family or carers and the obstetric specialist to decide on foetal monitoring

Finding	Management
If CTG cannot be achieved or if simultaneous assessment of both heart beats is doubtful	• A senior obstetrician/senior midwife should be called • A bedside ultrasound is performed to check both heart rates • A foetal scalp electrode is applied to the first twin (if gestational age > 34 weeks). Abdominal monitoring of the second twin is performed • Caesarean section should be considered if all measurements fail
If CTG of the first twin is suspicious	• The senior obstetrician and senior midwife are called • Possible causes are corrected • A foetal scalp electrode is applied to the first twin (if gestational age ≥ 34 weeks). Abdominal monitoring of the second twin is performed
If CTG of the first twin is pathological in the first stage	• The senior obstetrician and senior midwife are called • Foetal blood sampling of the first baby (if gestational age ≥ 34 weeks) should be offered after counselling • If foetal blood sampling cannot be obtained, is contraindicated, or is not available within 20 minutes, immediate caesarean section should be considered
If CTG of the first twin is pathological in the second stage	• The senior obstetrician and senior midwife are called • If feasible, assisted vaginal birth should be offered. However, if delivery cannot be achieved in 20 minutes, an immediate caesarean section should be performed
If CTG of the second twin is suspicious or pathological after delivery of the first twin	If delivery does not occur within 20 minutes, immediate caesarean section should be considered

- **Labour analgesia:**
  - Epidural analgesia is offered to women with multiple pregnancy who undergo vaginal delivery
  - Regional anaesthesia is offered to women who will be delivered by caesarean section

- **Management of third stage of labour:**
  - **Umbilical cord clamping:**

    After delivery, cords should be double clamped to sample umbilical cord blood. Samples should be labelled by twin

  - **Prevention of postpartum haemorrhage:**
    - **IV access:**

      IV access should be established in all women with multiple pregnancy when labour is established. Blood products should be available if needed
    - **Active management of the third stage:**

      Women with multiple pregnancy are at higher risk of postpartum haemorrhage. Therefore, active management of the third stage should be offered (rather than conservative management). An additional uterotonic should be added if there are two or more risk factors of postpartum haemorrhage including multiple pregnancy

Foetal medicine

Abstract

Diagnosis and management of a silent, non-complaining patient who may be threatened by a serious condition, is the essence of foetal medicine. Unlike other medical specialties, health, and wellbeing of 2 persons, the mother and the foetus, affects clinical outcomes of the patient. The patient cannot be directly examined or seen, making foetal medicine a unique subspeciality.

Keywords

FGR, IUFD, prenatal testing, alloimmunization

Further readings

1. Royal college of obstetricians and gynaecologists. Amniocentesis and Chorionic Villus Sampling. Green-top Guideline no. 8: 2010.
2. Mackie FL, Allen S, Morris RK, Kilby MD. Cell-free fetal DNA-based noninvasive prenatal testing of aneuploidy. Obstet Gynecol. 2017 Jul 1;19(3):211-8.
3. Royal college of obstetricians and gynaecologists. Red Cell Antibodies during Pregnancy, management. Green-top Guideline no. 65: 2014.
4. Royal college of obstetricians and gynaecologists. Small-for-Gestational-Age Fetus, Investigation and Management. Green-top Guideline no. 31: 2013.
5. Royal college of obstetricians and gynaecologists. Reduced Fetal Movements. Green-top Guideline no. 57: 2011.
6. Karkhanis P, Patni S. Polyhydramnios in singleton pregnancies: perinatal outcomes and management. The Obstetrician & Gynaecologist. 2014 Jul;16(3):207-13.
7. Royal college of obstetricians and gynaecologists. Late Intrauterine Fetal Death and Stillbirth. Green-top Guideline no. 55: 2010.
8. Royal college of obstetricians and gynaecologists. Monochorionic Twin Pregnancy, Management. Green-top Guideline no. 51: 2016.
9. National Institute for Health and Care Excellence. Multiple pregnancy: antenatal care for twin and triplet pregnancies. Clinical guideline CG129. Published date: 26 September 2011.