# Prenatal Screening and Diagnosis of Fetal Anomalies

## Disclaimer

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Background – About Prenatal Screening and Diagnosis of Fetal Anomalies

- Every baby has a small chance of having a chromosomal or genetic condition.
- All patients planning or currently pregnant should be provided with information about the availability of:
  - genetic carrier screening for some X-linked or autosomal recessive conditions e.g. Fragile X, cystic fibrosis, spinal muscular atrophy.
  - prenatal screening tests for chromosomal conditions such as Down syndrome.
- Prenatal screening tests should not be considered routine. All such testing should be voluntary and only undertaken when the patient has been informed about the nature of the screening test, possible results, and the options available.

Assessment

Practice Point

Prenatal screening tests are not routine

It is a choice for patients to undertake testing after being informed about the nature of the screening test, possible results, and the options available.

1. Take a history in both partners to identify risk factors for genetic conditions or fetal structural abnormalities.

   **Risk factors (list not exhaustive)**
   - Maternal diabetes, epilepsy
   - Consanguinity
   - Previous pregnancy, child with:
     - chromosomal anomaly
     - other significant physical or learning disability
   - Family history of an inheritable genetic condition e.g. thalassaemia, cystic fibrosis, spinal muscular atrophy, fragile X syndrome
   - Increased risk group e.g. Ashkenazi Jewish

2. Offer all patients screening for thalassemia carrier status before or early in pregnancy, if not performed previously.

   **Screening for thalassemia**
   - Haemoglobinopathies are the most common genetic defect worldwide.
   - Perform FBE, ferritin, haemoglobin electrophoresis – with DNA analysis to follow, if indicated.
   - If performed previously, testing does not need to be repeated.
   - Consider testing partner at the same time, particularly if they are from Southern Europe, Middle East, Africa, South-East Asia, Indian subcontinent, or Pacific Islands. Write partner details on each request slip to link at the laboratory.
3. Counsel all patients planning or in early pregnancy about the availability of population-based reproductive carrier screening for genetic conditions such as cystic fibrosis, spinal muscular atrophy, fragile X-syndrome. This is not suitable for patients already identified with risk factors for these and other genetic conditions, who require an early genetic health referral.

Reproductive carrier screening
- Detects mutations responsible for autosomal recessive and X-linked genetic disorders.
- Currently does not attract Medicare rebate. Costs range between $350 and $1000.
- Unless time is limited (e.g., during pregnancy), test female partner first. If there is a positive result, perform partner screening, ensuring partner’s details are linked on the request form.
- Three gene panel detects carriers for cystic fibrosis (1 in 25), spinal muscular atrophy (1 in 35), and Fragile X syndrome (1 in 250)
- Expanded carrier screening can also detect carriers of many other genetic conditions. As up to 24% of adults will test positive for at least one recessive disorder, this should only be offered with appropriate genetic counselling.
- Screening is available via an increased number of genetic testing laboratories. Some services offer genetic counselling via phone or online.
- Patients can organise testing themselves (kit sent directly to home) or by having a sample (blood or saliva) collected at a pathology collection centre. Any known family history should be documented on the request form.

4. Counsel all patients as early as possible in the pregnancy on the availability of prenatal screening for fetal anomalies e.g. Down syndrome. If not confident with providing pre-test counselling, refer to a private genetic health service, genetic laboratory, specialist obstetrician, or specialty ultrasound service for counselling before performing test.

Prenatal screening
- Screening tests are not routine. It is a choice for patients and their partners to undertake screening or diagnostic testing.
- Advise patients that screening tests are not diagnostic, even if high risk. False positives and negatives can occur, and diagnosis can only be confirmed with chorionic villous sampling or amniocentesis.
- Clearly explain the possible results and the options available to the patient, including termination or continuation of a pregnancy with an abnormality.

5. Discuss prenatal screening options (less accurate for multiple pregnancies – discuss with obstetric care provider):
   - First trimester
     - Non-invasive prenatal test (NIPT) – cell free DNA-based testing (cfDNA)
       - Fetal cell-free DNA (cfDNA) in maternal blood can be identified from 10 weeks gestation. Ensure dates are accurate prior to the test being taken. Some specialty ultrasound services offering NIPT routinely perform a pre-test ultrasound which can date the pregnancy simultaneously.
       - Screens for trisomy 21, 18, and 13, and sex chromosome aneuploidies e.g. Turner, Klinefelter.
       - Highly sensitive and specific for trisomy 21, detects about 99% of babies with Down syndrome. Less sensitive for other chromosomes screened. A positive result indicates further confirmation with invasive diagnostic testing is required.
Diagnostic testing
- Available via Specialist Obstetric Imaging Groups or via Public Hospital Genetics Services.
- Chorionic villus sampling (CVS)
  - Performed from 11 weeks of pregnancy.
  - A sterile needle is inserted into the placenta under ultrasound guidance, and a sample is collected for testing.
  - If test unsatisfactory, further testing may be necessary i.e. amniocentesis.
- Amniocentesis
  - Performed from 15 weeks of pregnancy.
  - A sample of amniotic fluid is collected via a sterile needle inserted under ultrasound guidance through the abdomen.
  - Overall rates of fetal loss are usually quoted from around 1 in 200 for amniocentesis, and 1 in 100 for CVS. These rates take into account background risk of miscarriage as well as procedural risk, which decreases with operator experience.
- Failure to obtain a result occurs in 4 to 5% of pregnancies, usually due to a low cfDNA if the sample is collected too early in the pregnancy or because of maternal obesity.
- Does not attract a Medicare rebate and is available through genetic testing laboratories and some specialty obstetric ultrasound providers. Costs range upwards from $400.
- Some tests offer different options e.g. screening for microdeletions or assessing all chromosomes. The potential for unanticipated findings of relevance to maternal health (including maternal genomic imbalances) should be included in pre-test counselling if ordering these tests. These abnormalities also have a higher false positive rate.
- A nuchal translucency ultrasound is recommended for all patients having cfDNA testing.

- Nuchal translucency ultrasound
  - Performed between 11 weeks and 13 weeks plus six days' gestation.
  - Not recommended alone as a screening test for aneuploidies.
  - Measures fetal nuchal translucency thickness, which is generally increased in fetuses with Down syndrome.
  - Performed as part of combined first trimester screening.
  - Offer to all women having cfDNA testing, as a nuchal fold > 3.5 mm can be a marker of other abnormalities not detected on cfDNA e.g. cardiac conditions.
  - Referral form to include patient's age, weight, estimated delivery date, diabetic status, and ethnicity.
  - This can be combined with a 12 to 13 week morphology ultrasound which can detect other major structural abnormalities at this early stage (e.g. anencephaly, some major cardiac defects).

- Combined first trimester screening (cFTS)
  - Involves the combination of maternal age, blood biomarkers, and ultrasound findings (nuchal translucency +/- nasal bone).
  - Screens for trisomy 21, 18, and 13.
Detects about 85% of babies with Down syndrome.
A positive test result (risk of > 1 in 300) indicates high risk and further testing with cfDNA or invasive diagnostic testing is indicated. Only about 1 in 20 women who screen positive will have a baby with down syndrome.

- **Investigations:**
  - Nuchal translucency ultrasound

- **Blood test:**
  - Performed between 9 weeks and 13 weeks plus 6 days' gestation.
  - Measures free beta-hCG and pregnancy-associated plasma protein A (PAPP-A). A low result PAPP-A result (< 0.45 MoM) may be associated with an increased frequency of adverse obstetric outcomes including fetal growth restriction.
  - Referral form to include patient’s age, weight, estimated delivery date (EDD), diabetic status, and ethnicity.
  - Request that a copy of results be sent directly to the ultrasound provider.
  - Does not attract a Medicare rebate and is available through private pathology providers.

Some specialist obstetric imaging groups and genetic laboratories offer screening for early onset pre-eclampsia, which can be performed at the same time as cFTS. It is estimated to detect up to 8 out of 10 pregnancies at risk. Women with a positive result require increased monitoring during pregnancy and treatment with low dose aspirin. Blood tests should be performed between 11 weeks and 13 weeks plus 6 days.

- **Second trimester**
  - **Non-invasive prenatal test (NIPT) – cell free DNA-based testing (cfDNA)**
    - **Second trimester maternal serum screening (STMSS) or quadruple test**
      - Indicated if the patient is unable to have the cFTS or cfDNA due to financial limitation or advanced gestation. It is less accurate at detecting Down syndrome than either of these options.
      - Involves a blood test collected between 14 and 20 weeks’ gestation.
      - Measures alpha-fetoprotein (AFP), free BhCG, unconjugated estriol (E3), and inhibin.
      - Provides a risk assessment for:
        - trisomy 21 and sometimes trisomy 18 (trisomy 13 is not detected).
        - neural tube defect i.e., spina bifida.
      - Request form to include age, weight, LMP, EDD, and history of any previous pregnancy with chromosomal anomalies or neural tube defect.

6. Ensure patients who prefer to directly access diagnostic testing, rather than undergo screening, are fully informed of the risks, benefits, costs, and limitations of prenatal diagnosis. Even in women of advanced maternal age, it is no longer recommended to undergo diagnostic testing without having previously had a high risk screening test result.

7. Offer all patients a morphology ultrasound scan at 20 to 22 weeks of pregnancy.
Management

1. If personal or family history of a specific inherited disorder, or at high risk of a chromosomal or genetic condition, offer an early genetic health referral.

2. If reproductive carrier screening ordered:
   - Schedule a follow-up appointment with the patient and partner in 1 to 2 weeks to discuss results.
   - If a positive result, organise partner testing if not already performed.
   - If a positive result of the same condition in both partners, refer for genetic counselling to discuss options for pregnancy e.g. pre-implantation genetic diagnosis (only relevant pre-conception), amniocentesis, chorionic villus sampling (CVS).

3. If a pre-natal test is ordered:
   - Schedule a follow-up appointment in 1 to 2 weeks to discuss results.
   - If a high-risk pre-natal result is reported on cFTS or STMSS, discuss options:
     - Further screening with NIPT, or
     - Provide or arrange urgent genetic counselling to confirm the diagnosis with invasive diagnostic testing.

4. If a high-risk NIPT result, provide or arrange urgent genetic counselling to confirm the diagnosis with further diagnostic testing.

5. If a fetal anomaly is confirmed on diagnostic testing, provide or refer for urgent genetic counselling and obstetric review to discuss available options. Offer ongoing support to the patient and partner.

   Available options for diagnosed fetal anomaly
   - Continuation of the pregnancy in the light of fetal anomaly.
   - Termination of pregnancy

6. If a fetal anomaly is detected on ultrasound, refer for genetic counselling and urgent obstetric review.

Referral

- Refer for genetic counselling if:
  - patient or partner has personal or family history of a genetic or chromosomal condition (ideally before pregnancy).
  - genetic carrier screening in both partners gives a positive result of same condition.
  - a high-risk pre-natal screening result, to discuss diagnostic testing.
  - fetal anomaly detected on ultrasound.
  - fetal anomaly confirmed on diagnostic testing.

- If fetal anomaly is detected on diagnostic testing or ultrasound, refer for genetic counselling or urgent obstetric review.

Note that statewide referral criteria apply for referral of some congenital anomalies to a level 6 public hospital maternity service.
For health professionals

Further information

- Australian Family Physician – Noninvasive Prenatal Testing
- Australian Journal of General Practice – Preconception and Antenatal Carrier Screening for Genetic Conditions
- RACGP – Genomics in General Practice
- RANZCOG:
  - Prenatal Screening and Diagnostic Testing for Fetal Chromosomal and Genetic Conditions
  - Prenatal Screening for Fetal Genetic or Structural Conditions
- Victorian Clinical Genetics Services – Pre and Early Pregnancy Screening Clinic

For patients

- Centre for Genetics Education – Fact Sheet 65: Reproductive Carrier Screening
- Murdoch Children's Research Institute:
  - Prenatal Screening Tests in Pregnancy
  - Screening Choices
- Pregnancy, Birth and Baby – Prenatal Screening
- The Royal Women's Hospital – Genetic Testing in Pregnancy

Disclaimer

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