Learning objectives:

• Which antenatal screening tests should be done
• The rationale for particular antenatal screening tests
• What to do with positive antenatal screening test results
Criteria for screening tests

- The condition should be an important health problem in pregnancy or for the future life of the fetus.
- The natural history of the condition in pregnancy should be understood.
- There should be a test that is easy to perform and interpret, acceptable, accurate, reliable, sensitive and specific.
- Detection should prompt a change in management which will change the outcome of the pregnancy.
- Diagnosis and treatment should be cost effective.
The standard antenatal screen:

- **FBE**
  - For haemoglobin and platelet counts, note MCV
- **Blood group and antibody**
  - For Rhesus status and red cell antibodies
- **Infection screen**
  - HIV, hepatitis B & C, syphilis and rubella
  - Consider varicella serology
- **MSU**
  - To detect asymptomatic bacteruria
Women and their families should understand the purpose of all tests before they are taken.

**Pre-conception**
- Commence folic acid
- Give pre-screening information as soon as possible

**Antenatal**
- Blood for haemoglobin, group, rhesus & antibodies as early as possible, or as soon as a woman arrives for care, including labour
- Blood for Sickle Cell & Thalassaemia
- Blood for early Down's syndrome test
- Blood for later Down's syndrome test
- Repeat haemoglobin & antibodies

**Newborn**
- Physical Examination by 72 hours
- Physical Examination by 8 weeks

**Screening Timeline - optimum times for testing**

Key to screening programmes:
- Down's syndrome & Fetal Anomaly Ultrasound
- Sickle Cell & Thalassaemia
- Screening for infectious diseases in pregnancy
- Newborn Blood Spot
- Newborn Physical Examinations
- Newborn Hearing

www.screening.nhs.uk/an
Screening Timeline Version 2, March 2008
Beyond the standard screen:

- Hypothyroidism
- Vitamin D deficiency
- Gestational diabetes mellitus (or T2DM)
- STIs such as Chlamydia and gonorrhoea
- Screening for aneuploidy
- Screening for pre-eclampsia
Case One

A 24 year old woman presents after her initial antenatal blood tests. She is now 14 weeks pregnant in her second pregnancy. One of your colleagues ordered TFTs and thyroid autoantibodies. The results were:

- TSH: 2.8
- T4: 12.4
- Thyroid peroxidase antibodies: negative

Will you:

a. Do nothing and reassure the woman
b. Recheck TFTs in 4-6 weeks
c. Commence thyroxine
d. Refer to an endocrinologist
Hypothyroidism

• Why?
  • Overt hypothyroidism is associated with adverse pregnancy outcomes:
    • Miscarriage
    • Preterm delivery
    • Reduced cognitive function in pregnancy
  • The adverse effects of subclinical hypothyroidism are less clear

• Who?
  • Everyone
  • Women with risk factors: age, history of thyroid or autoimmune disease, adverse pregnancy outcome
Hypothyroidism

• How?
  • TSH
  • Thyroid peroxidase antibodies

• What to do with a positive result
  • Normal range of TSH in first trimester is <2.5mIU/L
  • Treat overt hypothyroidism
  • Insufficient evidence either way for supplementation in women with subclinical hypothyroidism
  • Treat women with subclinical hypothyroidism with positive TPOAb
Case Two

A 37 year old woman in her first pregnancy presents for her first antenatal visit. Would you check her vitamin D levels?

a. Yes, there is good evidence that screening and treatment improves pregnancy outcome
b. Yes, but you are unsure whether this produces a real benefit
c. Only if she has risk factors for vitamin D deficiency
d. No
Vitamin D

- Why:
  - Prevalence rates of 18-84% depending upon country
  - Severe vitamin D deficiency is associated with adverse pregnancy outcomes:
    - Pre-eclampsia / hypertension
    - Gestational diabetes
    - Preterm delivery
    - Caesarean section
    - Bone disease in offspring
      - Rickets
      - Deficits in total body bone mineral density
  - Also linked to other disorders such as neonatal craniotabes, prematurity, T1DM, schizophrenia and childhood respiratory infections
Vitamin D

- Who?
  - Everyone
  - Especially women with dark skin, limited sun exposure, obesity or malabsorptive syndromes

- How?
  - Vitamin D assay

- What to do with a positive result?
  - Commence a cholecalciferol at 1000 IU-2000 IU daily
  - Recheck at 28 weeks gestation to check adequacy of supplementation
Case Three

An eighteen year old woman presents at about 9 weeks gestation. It is an unplanned pregnancy and she has only been with her current partner for three months. You decide to screen her for chlamydia. What test will you do?

a. First pass urine PCR
b. Endocervical swab for PCR
c. Serology
d. Self-taken low vaginal swab
Chlamydia

• Why?
  • Prevalence rates in Australia
  • Associated with:
    • Preterm prelabour rupture of membranes
    • Preterm birth
    • Low birth weight
    • Neonatal conjunctivitis and pneumonia

• Who?
  • Women under the age of 25 (or with partners under the age of 25)
  • Recent change of sexual partner or two or more sexual partners in the last 12 months

• Routine screening in pregnancy currently recommended in US but not in the UK
Chlamydia

• How?
  • Self taken vulvovaginal swabs are significantly better than endocervical swabs at detecting chlamydia (97% vs. 88%)

• What to do with a positive result:
  • Stat dose of 1gm azithromycin orally OR erythromycin 500mg QID for seven days
  • Treat the partner
  • Test of cure
Case Four

A 35 year old woman at 32 weeks gestation presents to you for a shared care antenatal visit. She has been diagnosed with gestational diabetes and has modified her diet. On home BSL monitoring she has had six fasting levels above 5.0 and three post-prandial levels above 6.7, all associated with a recognised dietary indiscretion. Do you:

a. Organise an earlier appointment at antenatal clinic
b. Reassure her and tell not to worry about an occasional high reading
c. Reiterate dietary guidelines
d. Commence metformin
Gestational diabetes

- Background:
  - Uncontrolled maternal gestational diabetes exposes the fetus to an abnormal glucose load leading to compensatory increases in fetal insulin secretion
  - This leads to excessive growth and diabetic fetopathy (babies born LGA with increased adiposity and hyperinsulinaemia)
  - There is a continuous relationship of glycaemia with adverse outcomes
  - Therefore no set of glucose values can provide perfect separation between normal and abnormal
Gestational diabetes

- RANZCOG have recently released a communique:
  - Screening of GDM should be done with a 75gm OGTT at 26-28 weeks gestation
  - This should replace the current two-step process of OGCT followed by OGTT
  - Reasoning includes:
    - Up to 25% of GDM is missed with the current process
    - 30% of women will need an OGTT anyway
    - Diagnosis can be delayed
  - Diagnostic criteria:
    - Fasting glucose $> 5.0$ mmol/l
    - 1-hour glucose $> 10.0$ mmol/l
    - 2-hour glucose $> 8.5$ mmol/l
    - If the fasting glucose level is $> 7.0$ mmol/l or 2-hour glucose $> 11.1$ mmol/l a diagnosis of diabetes in pregnancy should be considered
Gestational diabetes

• Why?
  • Women with GDM have a 40-60% increased risk of developing T2DM within 10-15 years
  • A small proportion of women with GDM will actually have pre-existing diabetes
  • Women with GDM have a higher incidence of macrosomia and adverse pregnancy outcomes

• Who?
  • Current evidence suggests that there is benefit in reduced perinatal morbidity in screening for and treating GDM
  • Everyone
  • Consider early screening (at diagnosis of pregnancy) in those at risk of overt diabetes:
    • Strong family history, PCOS, obesity
Gestational diabetes

- **How?**
  - OGTT at 26-28 weeks gestation

- **What to do with a positive result?**
  - Diet is the mainstay with reduced fat, increased fibre and regulation of carbohydrate intake (low GI)
  - Exercise
  - Home BSL monitoring with targets of:
    - Fasting < 5.0mmol/l
    - 2-hour < 6.7mmol/l
  - If persistent fasting or post-prandial levels commence hypoglycaemic agents
  - Referral to a diabetes educator
Case Five

A forty-one year old woman presents for her first antenatal visit. She wants to organise testing to ensure that her baby does not have Down syndrome. Which test do you recommend?

a. Combined first trimester screen (USS + PAPP-A + bHCG)
b. Noninvasive prenatal testing (NIPT)
c. Referral to a tertiary ultrasound service for invasive testing
d. Both cFTS and NIPT
Combined first trimester screen

- Consists of an ultrasound plus two biochemical markers
- Performed by an accredited sonographer
- Utility beyond predicting aneuploidy
  - Dating
  - Detection of multiple pregnancy and chorionicity
  - Detecting structural abnormalities
  - Abnormal biochemistry can predict other adverse obstetric outcomes
- Medicare rebate
Non-invasive prenatal testing

- **What is NIPT?**
  - Non-invasive testing of fetal genome through a maternal blood sample
  - Works by detecting fragments of cell-free DNA in maternal blood, primarily from the placenta

- Does not screen for all abnormalities

- Test from 10/40

- Small failure rate related to insufficient fetal fraction

- Binary result:
  - Screen negative ‘low risk’ = -ve LR 0.005%
  - Screen positive ‘high risk’ = PPV 50%
## Screening for aneuploidy: NIPT

<table>
<thead>
<tr>
<th>Test (company)</th>
<th>Provider in Brisbane</th>
<th>Chromosomes tested</th>
<th>GA (wks)</th>
<th>Sn</th>
<th>Sp</th>
<th>Cost ($)*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Verifi¹ (Verinata)</td>
<td>SNP</td>
<td>21,18,13 (X&amp;Y optional)</td>
<td>10+</td>
<td>&gt;99.9</td>
<td>99.8</td>
<td>900</td>
</tr>
<tr>
<td>iGeneScreen¹ (BGi)</td>
<td>QML</td>
<td>21,18,13</td>
<td>12+</td>
<td>99</td>
<td>99</td>
<td>850</td>
</tr>
<tr>
<td>MaterniT21plus (Sequenom)</td>
<td>Healthscope</td>
<td>21,18,13, 16, 22, X, Y, microdeletions</td>
<td>10+</td>
<td>99.1</td>
<td>99.9</td>
<td>1’250</td>
</tr>
<tr>
<td>Harmony (Ariosa)</td>
<td>so+gi</td>
<td>21,18,13,X,Y</td>
<td>10+</td>
<td>&gt;99</td>
<td>&gt;99.9</td>
<td>750 1’090 with US</td>
</tr>
<tr>
<td>Panorama (Natera)</td>
<td>Virtus Health (QFG)</td>
<td>21,18,13,X,Y</td>
<td>9+</td>
<td>&gt;99</td>
<td>100</td>
<td>895</td>
</tr>
</tbody>
</table>

No medicare rebate available
Screening for aneuploidy

Normal process of risk assessment
e.g. Combined first trimester screening (cFTS)

Low risk women
cFTS Risk <1 in 300

High risk women
cFTS Risk ≥1 in 300

choice of

NIPT

‘negative’

No further testing

Invasive test

‘positive’
Screening for aneuploidy

All women offered cFTS as primary test
Risks interpreted in three rather than two groups

Low risk women
- cFTS Risk <1 in 1000
  (estimate 86.5% of women)
  
  NIPT
  ‘negative’
  (estimate 98%)

  No further testing
  (a total of 99.2% of women)

Intermediate risk women
- cFTS Risk <1 in 10 to >1 in 1000
  (estimate 13% of women)
  
  NIPT
  ‘positive’
  (estimate 2%)

High risk women
- cFTS Risk >1 in 10
  (estimate 0.5% of women)
  
  Invasive test
  (a total of 0.8% of women)
Screening for aneuploidy

- Test accuracy:
  - NIPT
    - Sensitivity >99%
    - FPR < 1%
  - cFTS
    - Sensitivity = 90%
    - FPR = 5%

- Conclusion:
  - Consider NIPT but don’t forget the additional benefits of the cFTS
Case Six

A twenty-nine year old women presents for her first visit at 7 weeks gestation in her second pregnancy. Her first pregnancy was complicated by severe pre-eclampsia necessitating delivery at 28 weeks gestation. She wants to know if you can predict whether she will have pre-eclampsia again. Do you:

a. Give her the standard recurrence rates
b. Treat her with aspirin and calcium as she will be high risk for recurrence regardless of any testing
c. Tell her that no good screening tests for pre-eclampsia exist
d. Refer her to a specialist centre for screening with MAP, PAPP-A, uterine artery dopplers and placental growth factors
Screening for pre-eclampsia?

- No single biomarker has been identified with sufficient predictive value to be of clinical utility.

- Assessing multiple parameters in combination is achieving good results

- Combining factors such as:
  - Maternal factors
  - Mean arterial pressure
  - Uterine doppler pulsatility indices
  - Placental growth factor
  - PAPP-A

- Detected 93% of early onset pre-eclampsia for a FPR of 5%
Screening for pre-eclampsia?

- But what to do with a positive result?
  - Aspirin has been shown to reduce the risk of pre-eclampsia, especially if started in early pregnancy
  - The use of aspirin in reducing those that screen positive in these tests is currently the subject of an RCT

- Other possible targets coming soon:
  - Preterm labour:
    - Cervical length + maternal factors
    - Progesterone for treatment
  - Fetal growth restriction:
    - Maternal factors, biophysical and biochemical markers
    - Increased surveillance
Questions?
Summary

• Which tests should be done:
  • Always screening for aneuploidy and GDM
  • Strongly consider screening for vitamin D and hypothyroidism
  • Consider chlamydia screening in young patients

• The rationale for antenatal screening

• What to do with positive screening results