By the end of the session, participants will be familiar with:

- the concept and tests available for prenatal screening for Down syndrome, trisomy 18 and open neural tube defect

- the practical issues related to screening for Down syndrome

- the screening tests available for some of the more common autosomal recessive disorders.
What are we screening for?

- Down syndrome – trisomy 21
- Trisomy 18
- Open neural tube defects: anencephaly and spina bifida.

Estimating risk of Down syndrome.

- Patient a priori risk – age related risk.
- Modify the “a priori risk” by factoring in the results of the “markers” measured.
- Patient’s Down syndrome risk in this pregnancy.

How are we screening?

- We measure a combination of markers for which the levels seen in a normal population differ from those seen in a population of Down syndrome pregnancy.
MSAFP (MoM)

% of population

MSAFP levels in maternal serum at a specific gestational age

- Down Syndrome
- unaffected

% of population

MSAFP (MoM)

LR = height of affected curve
height of normal curve

LR = 1.0

LR = 2.6

LR = 2.6

0.8MoM

0.5MoM
### MSAFP levels in maternal serum at a specific gestational age

- **Down Syndrome**
- **unaffected**

![Graph showing MSAFP levels](image)

- **LR**: height of affected curve / height of normal curve
- **LR=0.2**

### Patterns of markers

<table>
<thead>
<tr>
<th>Condition</th>
<th>PAPP-A</th>
<th>AFP</th>
<th>uE3</th>
<th>hCG</th>
<th>InhibinA</th>
</tr>
</thead>
<tbody>
<tr>
<td>ONTD</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Down syndrome</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
</tbody>
</table>

### Nuchal Translucency

- **Gestation 11-14 wks**
- **CRL 45-84 mm**
- **Mid-sagittal view**
- **Image size: calipers 0.1mm**
- **Neutral position**
- **Away from amnion**
- **Maximum lucency**
- **Callipers on-to-on**
**Example of T21 risk calculation**

Maternal age at delivery is 30 years old
A priori risk =1/900
SIPS screen with MoM for 5 markers
Likelihood ratios are:
- PAPP-A LR 1.1
- AFP LR 2.5
- uE3 LR 1.5
- hCG LR 0.80
- Inhibin A LR 1.0

Quad screen Down’s risk is:
\[
\frac{1}{900} \times 1.1 \times 2.5 \times 1.5 \times 0.80 \times 1.0 = \frac{1}{272}
\]

“Positive Screen”

**Based on all available markers for Down syndrome – a number of tests available.**

- Quad screening in 2nd trimester - QUAD
- Serum integrated screening - SIPS
  - 1st and 2nd trimester biochemical markers
- Integrated prenatal screening – IPS
  - NT and 1st and 2nd trimester biochemical markers

**BC Prenatal Genetic Screening Options**

<table>
<thead>
<tr>
<th>Screening Options</th>
<th>Risk cut-off</th>
<th>DR</th>
<th>FPR</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIPS</td>
<td>1:300</td>
<td>87%</td>
<td>5%</td>
<td>99.9%</td>
</tr>
<tr>
<td>IPS</td>
<td>1:200</td>
<td>89%</td>
<td>2.5%</td>
<td>99.9%</td>
</tr>
<tr>
<td>QUAD</td>
<td>1:385</td>
<td>87%</td>
<td>8%</td>
<td>99.9%</td>
</tr>
</tbody>
</table>
**BC Prenatal Genetic Screening Options**

- **Tests available:**

<table>
<thead>
<tr>
<th>Screening Options</th>
<th>Risk cut-off</th>
<th>DR</th>
<th>FPR</th>
<th>Negative Predictive Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIPS</td>
<td>1:300</td>
<td>&lt;35 - 78%</td>
<td>&lt;35 - 3.3%</td>
<td>99.9%</td>
</tr>
<tr>
<td>IPS</td>
<td>1:200</td>
<td>≥35 - 92%</td>
<td>≥35 - 10%</td>
<td>99.9%</td>
</tr>
<tr>
<td>QUAD</td>
<td>1:385</td>
<td>&lt;35 - 75%</td>
<td>&lt;35 – 5.6%</td>
<td>99.9%</td>
</tr>
</tbody>
</table>

These figures apply for Down syndrome and assume dating by US in women ≥35 years.

**BC Prenatal Genetic Screening Options**

- **Tests available:**

<table>
<thead>
<tr>
<th>Screening Options</th>
<th>How</th>
<th>11 – 13 w</th>
<th>10-13 w</th>
<th>15 – 20 w</th>
</tr>
</thead>
<tbody>
<tr>
<td>SIPS</td>
<td>1st and 2nd</td>
<td>PAPPA</td>
<td>AFP, HCG, UE3 and Inhibin A</td>
<td></td>
</tr>
<tr>
<td>IPS</td>
<td>1st and 2nd</td>
<td>NT U/S</td>
<td>PAPPA</td>
<td>AFP, HCG, UE3 and Inhibin A</td>
</tr>
<tr>
<td>QUAD</td>
<td>2nd</td>
<td></td>
<td></td>
<td>AFP, HCG, UE3 and Inhibin A</td>
</tr>
</tbody>
</table>

**Some factors to consider**

- ~ 25,000 women have prenatal screening
- 7000 are women 35 years or older - "higher risk"
- NT requires training, certification and maintenance of competence.
- Limited ultrasound capacity in BC – limited capacity for NT for next few years.
BC Prenatal Genetic Screening Options

- Test to be offered will depend:
  - Age of the patient at time of delivery
  - Gestational age at first prenatal visit
  - Singleton vs multiple gestations
  - Presence of absence of other risk factors: e.g. previous history of trisomy 21, 18, or 13.

BC Prenatal Genetic Screening Options

- Singleton pregnancies that present before 13 weeks 6 days offer:
  - Serum Integrated Prenatal Screen
  - If ≥ 35 years or increased risk by family history or obstetrical history AND NT available, add NT to SIPS = IPS

BC Prenatal Genetic Screening Options

- Singleton pregnancies that present after 13 weeks 6 days and before 20 wks 6 days offer:
  - QUAD
Screening in Multiple Gestations

- Most reliable marker in twins is NT as allows assessment of each twin individually
- Regardless of maternal age, twin gestations qualify for IPS if diagnosed in first trimester

Screening Stats 2009 / 2010

<table>
<thead>
<tr>
<th>Prenatal Genetic Screening Testing</th>
<th>March 2009 to October 2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>IPS</td>
<td>SIPS</td>
</tr>
<tr>
<td>Quad</td>
<td>AFP only</td>
</tr>
<tr>
<td>NT only</td>
<td>NT only</td>
</tr>
</tbody>
</table>

Uptake of screening

<table>
<thead>
<tr>
<th>Age</th>
<th>2009</th>
<th>2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;35</td>
<td>46%</td>
<td>51%</td>
</tr>
<tr>
<td>35-39</td>
<td>58%</td>
<td>66%</td>
</tr>
<tr>
<td>40+</td>
<td>62%</td>
<td>69%</td>
</tr>
<tr>
<td>Total</td>
<td>50%</td>
<td>55%</td>
</tr>
</tbody>
</table>

Baseline: 43% uptake for <35 yrs; 37% for ≥35yrs
2 yr target: 48% uptake for <35 yrs; 61% for ≥35yrs
5 yr target: 50% uptake for <35 yrs; 64% for ≥35yrs
By the end of the session, participants will be familiar with:

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- the practical issues related to screening for Down syndrome
- the screening tests available for some of the more common autosomal recessive disorders.

Maternal Serum Median Values

Medians for all analytes vary with gestational age.

Because of this accurate dating is crucial

Dating

- Screening performance is improved with U/S dating compared to LMP dating.
- If dating ultrasound done, CRL should be provided and will be used above LMP for risk calculation.
- If no dating scan done and 2nd trimester U/S shows dating discrepancy of 8 days or more, contact the laboratory for reinterpretation.
Timeline ..... 

- Results within 10 days of second blood draw
- Negative result - reassuring.
- Positive screen results requires additional testing.
  - Amniocentesis
  - Option of termination available until 23\textsuperscript{rd} wks

Prompt "dispatching" of samples is crucial.

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Genetic screening

- For single gene disorders
  - review of the family history
  - specific testing based on ethnic background

Identify carriers who are at risk of having an affected child so that specific prenatal diagnosis can be offered.
Tay-Sachs disease

- more common amongst Ashkenazi Jewish individuals
- carrier frequency of 1/30 (compared to 1/250 -1/300 in non-Jews.)
- severe disease: neurodegenerative which starts between 3-6 months, death by 4 years.

Carrier screening for Tay Sachs

- DNA testing for the common mutations in the HEX A gene seen in Ashkenazi Jewish individuals – picks up 98% of carriers.
- prenatal testing is possible by DNA analysis of CVS or amniotic fluid.

Canavan disease

- seen in all ethnic groups but more common amongst Ashkenazi Jewish individuals
- carrier frequency of 1/37 - 1/57 (disease freq. of 1/5476 - 1/12996)
- severe disease: neurodegenerative which starts around 3-6 months, hypotonia, spasticity, death in childhood.
Canavan disease

- carrier testing: in the Ashkenazi Jewish population - 3 mutations account for 98% of alleles.
- prenatal testing is possible by DNA analysis of CVS or amniotic fluid.

Familial Dysautonomia

- Autosomal recessive condition seen almost exclusively in Ashkenazi Jewish population
- Carrier freq. of 1/32
- Severe neurological disorder affecting the the sensory and autonomic system. Affects swallowing, digestion, pain sensation. Death is usually before age 30.
- carrier testing: in the Ashkenazi Jewish population - 2 mutations account for 99% of alleles.
- prenatal testing is possible by DNA analysis

Ethnic specific carrier testing
Ashkenazi Jewish Individuals

- If both members of the couple are AJ:
  - DNA testing for Tay Sachs, Canavan, Familial Dysautonomia, Fanconi Anemia - Ashplex panel

- If only one member is AJ: offer TaySachs screening only – can be done by enzymatic assay Hexoaminidase A
Sickle cell disease

- more common amongst African Americans
- carrier frequency of 1 in 12
- Also increased in Middle East, Mediterraneans
- definite burden of disease: bone pain, chest pain from occlusive disease in lung, stroke, hepatosplenomegaly, anemia, aplastic crisis
- carrier testing:
  - Hemoglobin electrophoresis
- Prenatal diagnosis by DNA testing

Thalassemia: β and α

- more common Mediterraneans, Arabian peninsula, Turkey, Iran, Africa, India, South-East Asia, Southern China.
- carrier frequency: β thal in Cyprus and Sardinia - 14% in Chinese - 2-4%
  α thal in Chinese - 5%
- Beta thalassemia: severe anemia – transfusion dependant
- Alpha thalassemia: fetal hydrops.

- Carriers of β and α thalassemia present with a low MCV on their CBC. MCV<80
- Carriers of β thalassemia have increased HbA2 on Hemoglobin electrophoresis.
- Prenatal diagnosis by DNA testing if both partners are carriers.
Ethnic specific carrier testing

- African Americans, Mediterraneans, Middle Eastern, South East Asians, Western Pacific
  Should have CBC and Hb Electrophoresis.

(Everyone except Northern Europeans, Native Americans, Japanese, Koreans)

For more information

- www.bcprenatalscreening.ca
- www.elabhandbook.info