Antenatal Screening for Down Syndrome and Other Conditions
• Screening in NZ – practice in 2007 and why change
• New guidelines
• How screening works
• Scenarios
DS

![Graph showing the risk of Down syndrome in live births (%) vs maternal age (years).]
History

• 1966 fetal karyotype from cultured amnocytes.
• 1972 association between raised AFP in amniotic fluid and NTD’s recognised.
• 1974 association between NTD in fetus and raised maternal serum AFP.
• 1984 association between MSAFP and Down Syndrome identified
More History – aneuploidy risk….

• 1987 incorporation of other serum “markers” (estriol and HCG) with MSAFP
• 1990’s saw the recognition of the role of “soft” USS markers.
• Late 1990’s evaluation of combined MSS and USS (1st trimester NT)
The NZ Experience

- Diagnostic amniocentesis initiated in early 1970’s
- First described locally in May 1971 NZMJ as a presentation at the Annual Meeting.
- In October 1972 Dr Helen McCreanor (Wellington) wrote a letter to the NZMJ describing the first attempts at “amniotic cell culture for the antenatal diagnosis of chromosome anomalies such as Down Syndrome” routinely available from 1974
NZ History 2

• Amnio/karyotyping for LMA (>37y) remained the standard for all of the 1970’s and early 1980’s.
• Uptake was uneven (urban >>>>> rural) but gradually increased over that time
• International changes to practice were already underway in the early 1980’s
• 1985 publication for the Department of Health
  – “Medical Genetic Services in NZ”
  – Recommended the introduction of MSAFP for NTD screening.
• 1990, only amniocentesis for LMA was available.
2005

- NO coordinated national prenatal screening program
- no standards, audit, evaluation etc
- “screening “ strategy (LMA) is long discredited
- ad-hoc “screening” (NT) is unsafe (not all practitioners trained or used algorithm)
- MSS (user pays) reaches only a selected few
Women being offered screening

Stone 2005
2006+

Quality Improvements 1

- 2008 MOH NSU introduced step 1 - paid T2 triple tests
Preferentially screening older women

![Bar chart showing the percentage of births and the percentage of women screened in 2008 and 2009 across different age groups.](chart.png)
Less Maori and Pacific, more European and ‘other’ ethnicities screened
There are substantial regional inequalities (ADHB v CMDHB & WHL)
Specialists screen a higher proportion of their patients than midwives.
Quality Improvements 2

- Paid choice of either
- T1 combined test (PAPP-A, $\beta$-hCG and NT)
- OR
- T2 biochemistry ($\beta$-hCG, $uE_3$, AFP, inhibin-A)
AND

• Lab will report risk incorporating NT (1st T blood result alone not reported – if no NT, recommend 2nd T blood) – all women should have access to a test of equal performance.

• Agreed to report abnormal analyte-U/S patterns (other conditions)

• Nationally consistent resources
## Screening Performance - SURUSS

<table>
<thead>
<tr>
<th>Test Type</th>
<th>DR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>T1 combined</td>
<td>83%</td>
<td>5%</td>
</tr>
<tr>
<td>T2 quad test</td>
<td>83%</td>
<td>5%</td>
</tr>
<tr>
<td>T1 combined test</td>
<td>85%</td>
<td>6.1%</td>
</tr>
<tr>
<td>T2 quad test</td>
<td>85%</td>
<td>6.2%</td>
</tr>
</tbody>
</table>

*Compare -*

<table>
<thead>
<tr>
<th>Test Type</th>
<th>DR</th>
<th>FPR</th>
</tr>
</thead>
<tbody>
<tr>
<td>NT</td>
<td>60-70%</td>
<td>5%</td>
</tr>
<tr>
<td>T2 triple test</td>
<td>77%</td>
<td>5%</td>
</tr>
<tr>
<td>NT</td>
<td>85%</td>
<td>20-25%</td>
</tr>
<tr>
<td>T2 triple test</td>
<td>85%</td>
<td>9.3</td>
</tr>
</tbody>
</table>
SURUSS Data 85% DR

FPR %

Number of markers

* Includes NT
First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS).

Wald NJ, Rodeck C, Hackshaw AK, Walters J, Chitty L, Mackinson AM.

Or from http://www.hta.ac.uk (UK Health Technology Assessment website)
National Practitioner Guidelines
Laminated summary sheet
Wheel
Consumer information sheets (3)
3.2 Timing of screening tests

The following diagram shows when the different antenatal screening tests for Down syndrome and other conditions may be undertaken. The timing of screening relative to the woman’s gestation may be important in relation to the choices available to her.
<table>
<thead>
<tr>
<th>First trimester combined screening to be offered to all women who present early in pregnancy</th>
<th>Second trimester maternal serum screening to be offered to all women who present later in pregnancy</th>
<th>Recommendations for practice</th>
</tr>
</thead>
<tbody>
<tr>
<td>• Blood test that measures two maternal serum markers (PAPP-A and ( \beta )hCG) combined with NT scan results</td>
<td>• Blood test that measures four maternal serum markers (( \beta )hCG, AFP, ( \mu )E3 and inhibin A)</td>
<td>• The discontinuation of the use of maternal age and nuchal translucency as screening tools in isolation</td>
</tr>
<tr>
<td>• Available to all women who present in the first trimester</td>
<td>• Available to women who present after the first trimester or who do not access first trimester combined screening</td>
<td></td>
</tr>
<tr>
<td>• The blood test is fully funded</td>
<td>• The blood test is fully funded</td>
<td></td>
</tr>
<tr>
<td>• Women are usually required to make a co-payment for the NT scan</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Provision of accurate and non-directive information (both medical and non-medical)

Unconditional support for decisions made by women throughout pregnancy, including the decision as to whether or not to participate in screening

Support if women want family/whānau to be actively involved
3 THE PRACTICALITIES

3.1 The screening pathways

FIRST TRIMESTER COMBINED SCREENING

- Provision of information about screening
  Section 3.6
- Initial discussion
  Section 3.7
- Offer of screening
  Section 3.8
- Screening accepted
- Screening declined
- Results to maternity provider
  Section 3.10
- First trimester combined screening
  + Blood test
  (maternal serum markers)
  + NT scan
  Section 3.6.1
- Low risk
  Section 3.10
- Increased risk
  Section 3.10.1
- Offer of specialist referral
  Section 3.10.1
- End of screening process

OR

SECOND TRIMESTER MATERNAL SERUM SCREENING

- Provision of information about screening
  Section 3.6
- Initial discussion
  Section 3.7
- Offer of screening
  Section 3.8
- Screening accepted
- Screening declined
- Results to maternity provider
  Section 3.10
- Second trimester maternal serum screening
  + Blood test
  (maternal serum markers)
  Section 3.8.2
- Low risk
  Section 3.10
- Increased risk
  Section 3.10.1
- Offer of specialist referral
  Section 3.10.1
- End of screening process
• P Stone – Guideline for the interpretation of unusual analyte patterns
• From Peter or NSU
• Nicola_Deveraux@moh.govt.nz
Choice

• Screening gives information about the pregnancy
• Choice not to know
• Options once knowledge is available
  – Continue pregnancy, increased vigilance for associated health problems so eg plan appropriate delivery, tell family
  – TOP
  – Decision may depend on particular aneuploidy
• Can change mind along screening pathway
Markers

- T1 PAPP-A – placenta protease in IGF system
- T1 NT (and nasal bone if available)
- T1 and T2 β-hCG – placenta
- T2 AFP – fetal oncotic protein (liver)
- T2 uE₃ – placenta (precursors from fetus)
- T2 Inhibin-A – placenta
Human Chorionic Gonadotrophin & Inhibin-A

PAPP-A (from maternal ovarian granulosa cell)

Nuchal translucency

Unconjugated oestriol

Alpha-fetoprotein
MoMs

- AFP increases with gestational age
- Normal values worked out for the population at each gestational age

**Example**
- Median AFP at 15 weeks = 28 kU/L
- Median AFP at 20 weeks = 57 kU/L
- Measured AFP = 70 kU/L

<table>
<thead>
<tr>
<th>Gestation</th>
<th>Measured Value</th>
<th>MoM</th>
</tr>
</thead>
<tbody>
<tr>
<td>15</td>
<td>70/28</td>
<td>2.5</td>
</tr>
<tr>
<td>20</td>
<td>70/57</td>
<td>1.2</td>
</tr>
</tbody>
</table>
Algorithm – PerkinElmer Lifecycle

• Calculates MoM by GA
• Corrects MoM for
  – Ethnicity
  – Weight (dilution of analytes)
  – No of fetuses (increases analytes)
  – IVF (incr $\beta hCG$)
  – IDDM (decr AFP $\beta hCG$ uE$_3$)
  – Smoking (decr $\beta hCG$)
• Uses MoMs to estimate risk
Likelihood Ratio

\[ LR = \frac{\text{Height of Distribution in Unaffected}}{\text{Height of Distribution in Down’s}} \]

Risk = prior risk × LR
Risks estimated

- T-21
- T-18
- T-13
- Smith Lemli Opitz (T2)
- Cornelia de Lange
- NTD (15+ weeks)
- Turner syndrome (non-hydrops)
- Triploidy (non molar)
- Plus abnormal analytes reported
Estimate?

- Inherent inaccuracies in measurement
  - Ultrasound crl bpd nt nb
  - Biochemical markers analysis and sample handling
- Algorithm distributions of affected v unaffected
- Other factors (weight, ivf etc)
<table>
<thead>
<tr>
<th>T1</th>
<th>PAPP-A</th>
<th>free βHCG</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Triploidy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Small placenta</td>
<td>↓↓</td>
<td>↓↓</td>
</tr>
<tr>
<td>Molar placenta</td>
<td>←→</td>
<td>↑↑</td>
</tr>
</tbody>
</table>
T2

<table>
<thead>
<tr>
<th></th>
<th>free βHCG</th>
<th>uE₃</th>
<th>AFP</th>
<th>inhibin-A</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trisomy 21</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td>Trisomy 18</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Trisomy 13</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Triploidy</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
<td>↑</td>
</tr>
<tr>
<td>TS</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td>Small placenta</td>
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</tbody>
</table>
Abnormal analytes
\[ \leq 0.2 \text{ MoM} \geq 5 \text{ MoM} \]

- My be incorrect if lab has not used correct gestational and other information laboratory to assess risk.
NT - anomalies

• NT scan shows obvious anomalies, woman removed from screening pathway and offered appropriate diagnostic testing eg karyotyping, tertiary scanning, ongoing specialist care
Raised NT

• Raised NT and normal chromosomes
  – Cardiac
  – Diaphragmatic hernia
  – Omphalocoele
  – Body stalk anomaly
  – Skeletal defects
  – Noonan syndrome
  – Smith-Lemli-Opitz syndrome
  – Spinal muscular atrophy
Risks

• Miscarriage or fetal death
  – 1.3% if nt between 95th and 99th centile
  – 20% if nt ≥ 6.5 mm

• Cardiac anomaly
  – 1.7% if nt between 2.5 and 3.4 mm
  – 7.5% if nt ≥ 3.5 mm

• NT as screen for cardiac problems
  – 99%ile (2.5 MoM) sensitivity 9.6% ppv 5.0%

• Action – tertiary ultrasound (fetal-pediatric cardiology if concern remains)
NT with cystic hygroma

- 5x risk of aneuploidy
- 12x risk of cardiac anomalies
- 6x risk of perinatal death

- Offer karyotype, if normal MFM or clinical genetics advice sought if hygroma does not resolve.
High AFP

• If not NTD
  – Bleeding – threatened miscarriage
  – Anterior abdominal wall defects
  – Rare tumours
Low $uE_3$

• If not aneuploidy
  – Smith Lemli Opitz (disorder of cholesterol biosynthesis 1:50,000)
  – Steroid sulphatase deficiency (1:1500-6000)
  – Especially with other low analytes miscarriage
High and low $\beta$hCG

- Associated with pregnancy problems (miscarriage, low birthweight, preeclampsia, premature delivery, etc.)
- No specific management recommendation
Low PAPP-A

• Low PAPP-A (and/or high or low βHCG) associated with pregnancy problems – e.g. fetal growth restriction, preeclampsia - develop plan for assessment of fetal growth and welfare
GA difference

• Report is flagged if there is a greater than 2 week difference between GA determined from scan and from LMP so LMC can assess accuracy of data used for calculation and if accurate fetal growth.
What alters risk?

- Incorrect gestational age
- Weight (dilutes analytes)
- More than one fetus (incr all analytes)
- Ethnic Origin
- IVF (incr hCG)
- IDDM (decr AFP hCG uE\textsubscript{3})
- Smoking (decr hCG)
- Bleeding or threatened miscarriage (incr hCG)
Ms GA

- 37 yo at edd
- Prior risk 1:350
- GA at time of sample 15,1
- MoMs
  - AFP 0.73
  - uE₃ 0.66
  - βhCG 1.29
  - Inhibin-A 1.81
- T-21 risk 1:220
- Has scan – GA now 14,1 – risk?
• MoMs now
  – AFP 0.83
  – uE$_3$ 0.92
  – βhCG 0.99
  – Inhibin-A 1.59

• T-21 risk now 1:910

• Or scan GA now 16,1
- MoMs now
  - AFP 0.63
  - uE₃ 0.49
  - βhCG 1.63
  - Inhibin-A 2.21

- T-21 risk now 1:30
GA

- GA for screen determined by scan metric (crl,bpd)
- Clinical GA from LMP and not changed unless scan metric different (by 5-10 days depending on local practice)
- Clinical GA can differ significantly from actual GA hence estimated risk can have wide variation without scan.
Ms WT

- 37yo
- Weight not given on form
- Calculated risk T-21 at average weight 1:260
- What if she was 45kg? Or 110 kg?
Ms WT

- 45 kg risk T-21 1:340
- 110 kg risk T-21 1:180

Inhibin v weight

![Graph](attachment:graph.png)
Ms TW

• 37yo
• MoMs
  – AFP 1.77
  – uE₃ 1.33
  – βhCG 2.80
  – Inhibin-A 1.78

• T-21 risk 1:250
• Has scan ...
Twins!

- MoMs unchanged
  - AFP 1.77
  - $uE_3$ 1.33
  - $\beta$hCG 2.80
  - Inhibin-A 1.78

- T-21 risk now 1:380
New markers

• Adam12 A Disintegrin and Metalloprotein 12 Good T1 Trisomy 21 marker
• PIGF Placental growth factor probably not useful for aneuploidies but ok for preeclampsia
• PP13 Placental protein 13 – not very useful for Trisomy 21 but good for 13 and 18. Good for preeclampsia.