The prenatal diagnosis of chromosomal abnormalities in a resource-poor setting

Lut Geerts
Tygerberg O&G US Unit
Congenital anomalies - PNM

5th cause of PNM (UK 3rd)

- 1983: 7.9%
- 1996: 9.2%
- 2007: 11.4%

2nd cause of NNM: 17.2%
Chromosomal abnormalities

- Most common abnormality
- PND creates options:
  - Legal TOP
  - Prepare for birth
Screening - Public sector

- Mainly maternal age
  Variable, arbitrary cut-off

“We cannot afford more.....”

Laboratory cost is HIGH!
50 karyotypes = annual sonographer salary
Screening – Public sector

- Expanding ultrasound service
- Value for aneuploidy detection? Not yet evaluated
Screening - TBH

Maternal age (37)/Historical risk 11-23w

Opportunistic risk assessment

Routine ultrasound: 11-14w and 18-23w

Selective ultrasound: When clinically indicated

- Typical major anomalies
- High risk >1/200 after US
- Calculation with software package (FMF)
### Chromosomal markers

<table>
<thead>
<tr>
<th>Condition</th>
<th>Normal</th>
<th>Tr 21</th>
<th>LR+</th>
<th>LR-</th>
<th>LR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild hydronephrosis</td>
<td>2.6%</td>
<td>17.1%</td>
<td>6.8</td>
<td>0.85</td>
<td>1.0</td>
</tr>
<tr>
<td>Echogenic foci</td>
<td>4.4%</td>
<td>30.3%</td>
<td>6.4</td>
<td>0.75</td>
<td>1.0</td>
</tr>
<tr>
<td>Short femur</td>
<td>5.2%</td>
<td>42.0%</td>
<td>7.9</td>
<td>0.62</td>
<td>1.5</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>0.6%</td>
<td>17.3%</td>
<td>21.2</td>
<td>0.87</td>
<td>3.0</td>
</tr>
<tr>
<td>Nuchal fold &gt;6 mm</td>
<td>0.6%</td>
<td>41.1%</td>
<td>53.1</td>
<td>0.67</td>
<td>10.0</td>
</tr>
<tr>
<td>Major defect</td>
<td>0.7%</td>
<td>21.4%</td>
<td>33.0</td>
<td>0.79</td>
<td>5.0</td>
</tr>
<tr>
<td>Short NB</td>
<td>2.4%</td>
<td>48.2%</td>
<td>42.8</td>
<td>0.40</td>
<td></td>
</tr>
</tbody>
</table>

**Risk (%)**

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>100</th>
<th>30</th>
<th>35</th>
<th>40</th>
<th>45</th>
<th>20</th>
<th>25</th>
<th>30</th>
<th>40</th>
</tr>
</thead>
<tbody>
<tr>
<td>28</td>
<td>1/600</td>
<td>1/60</td>
<td>1/200</td>
<td>1/60</td>
<td>1/60</td>
<td>1/60</td>
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</tr>
</tbody>
</table>

All markers absent = Risk reduction (not 14–18 weeks)
Audit @ TBH

Effectiveness of integrated US risk assessment, compared to MA alone

- Retrospective
- 3 years (2003 - 2005)
- All aneuploidies @ TBH genetic lab
- Matched with all prenatal US reports
- Results of risk assessment
Intermediate background risk (T21 1/333 - all 1/151)

9662 women formal scan (13.3% AMA 85% for routine karyo)

921 invasive procedures (72% for AMA)

46 Abnormal results (1:20)

136 abnormal perinatal karyotypes

124 classic aneuploidies (91.2%)

114 autosomal trisomy (83.4%)

71 T21 (52.2%)
Aneuploidy ~ Maternal age

Mean 33.4±8.4y - Mode 40

MA known in 103/135 (86/114 trisomies)

Missed >=37y: 56.7%
Aneuploidy ~ Maternal age

Uptake of karyotyping: 52.3% (685/1310)
PPV: 2.2% (29/1310)

Autosomal trisomies (screened population):
• PPV: 1.9% (25/1310)
• FPR: 13.4% (1285/9613)
### US - All abnormal karyotypes

<table>
<thead>
<tr>
<th>Description</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>9 nl US</td>
<td>6</td>
</tr>
<tr>
<td>12 markers only</td>
<td>11</td>
</tr>
<tr>
<td>43 structural abnl</td>
<td>42</td>
</tr>
</tbody>
</table>

(8 young) (23 young)

#### Result

- **92% High Risk result** (59/64) (31 young)
- **73% PND** (43/59)
US - All abnormal karyotypes

Normal US (9)
- Only 4 severe - 2 <24w
  2 T21 (16w, 37w), 1 T13 (late), 1 del (4p) (early)
- 5 not severe

Abnormal US (55) (31 young)
ALL severe
27 T21, 13 T18, 6 T13, 2 Triploidy, 2 Turner’s
Unbalanced rearrangements

P < 0.0001
US - Autosomal Trisomies (49/114)

4 nl US
10 markers only
35 structural abnl

HR 2
HR 9 (6 young)
HR 35 (16 young)
12 “minor” (5 young)

3/49 not suspected

• T21, 39y, small NT, echogenic focus, risk<1/300
• T21, young, 28 weeks, bleeding placenta praevia
• T13, young, 27 weeks, bleeding placenta praevia
Efficiency

Prenatal samples with abnormal result

AMA - US risk assessment

Advanced maternal age

Ultrasound (young women)

All abnormalities

Trisomies

p<0.0001
AMA 156 (6 months)

Too late: 20
14-17w only: 15
0/15 abnormal

Risk assessed: 118

High Risk: 37
3/23 abnormal

Low Risk: 81
0/48 abnormal

If karyotyping restricted to US-risk > 1/200
Potentially 2/3 reduction in AMA amnios
AMA - US risk assessment

Efficacy
Detection Rate (%)

Advanced maternal age
US-based risk (all ages)

All abnormalities

<table>
<thead>
<tr>
<th></th>
<th>41.7</th>
<th>92.2</th>
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</table>

Trisomies

|        | 44.1 | 93.9 |

P < 0.0001
Overall “prenatal detection”

43%  (59/136)

Overall prenatal confirmation

33%  (Private 27%)

Postnatally diagnosed autosomal trisomy

- 3/81 “missed” on US
- 13/81 suspected on US
  (TOP, too late or refused PND)
- 65/81 no US screening!
Conclusions

US based risk assessment superior to AMA
Efficacy and Efficiency

US screening more than doubled PND
(add 26 cases in young women; 8 markers only + 5 “minor”)

Further improvement in aneuploidy detection requires wider access to US screening
Improved exposure to screening

- Educate community + Staff
- Sonographer-based routine US in primary care
  Improved skills strong markers (NT, AVSD, NB, Vemeg, Fists)

Funding?

- AMA referral for RISK assessment (not routine amnio)
Equitable access to the most efficient and effective PND service + many other advantages.....

Thank you