Local impact of ‘Antenatal Screening for Down syndrome and other conditions’ on diagnosis and outcomes in a fetal medicine centre in New Zealand

Alicia C Mulligan, Jeannie Matthews, James Bingham, Rosemary A Reid

Abstract

Aim In 2010, the National Screening Unit of the Ministry of Health launched ‘Antenatal Screening for Down syndrome and other conditions’. Our aim was to assess the local impact of the new screening process on the number and outcomes of women attending a south island Fetal Medicine Centre.

Methods Retrospective audit; two time periods (T1 and T2) were reviewed. Data was prospectively collected in a viewpoint database and combined with data from other hospital databases and laboratories. Outcome measures included invasive procedures done and results and MSS1 results. Statistical analysis was done using Open Epi software.

Results 51% of women who were pregnant in T2 underwent MSS1 screening. There was a statistically significant decrease in the number of invasive procedures carried out 2.9% (175) vs. 4.1% (253), p=0.0003 in T2. The proportion of procedures undertaken by Chorionic Villus Sampling and amniocentesis did not change. In both time periods no babies with Down syndrome were born following pregnancies where screening was undertaken and was low risk.

Conclusions The implementation of the new antenatal screening process in Canterbury has so far proved to be successful in maintaining detection rates of genetic anomalies whilst decreasing the numbers of invasive diagnostic procedures being done.

In February 2010 the National Screening Unit of the Ministry of Health New Zealand launched 'Antenatal Screening for Down syndrome and other conditions'. The introduction of this quality improvement process has brought antenatal screening in New Zealand in line with international best practice and offers a risk assessment for all women including those at increased risk of chromosomal anomalies.

Similar screening programmes have been trialled and found cost-effective, as judged by high detection rates for low false positive rates in other countries including the United Kingdom and the United States of America, and provides a risk assessment of Down syndrome (trisomy 21) and other chromosomal anomalies including Patau syndrome (trisomy 13), Edwards syndrome (trisomy 18) and sex chromosome aneuploidy.

Prenatal diagnosis for Down syndrome and other chromosomal anomalies has been available in NZ since the early 1960s in the form of amniocentesis. Historically women were offered testing based on increasing maternal age >35 years, or due to a family history of chromosomal anomalies. In most developed countries, the maternal
Age of pregnant women is increasing, and now about 20% of all pregnancies are to women aged >35 years.\(^5\) Offering screening to only this sector of the maternity population is inequitable.\(^6\)

Recently, until the introduction of the new screening process in 2010, women in NZ were offered a nuchal translucency (NT) measurement alone done by ultrasound scan at the end of the first trimester (between 11 and 13+6 weeks gestation) on an ad hoc basis. This scan measures the fluid behind the neck of the fetus and increased levels can indicate increased risk of a fetal anomaly such as Down syndrome or structural anomalies.

Accurate NT measurement has strict parameters and therefore requires significant sonographic expertise to achieve. If women presented in the second trimester they were offered the quad screen of hormones, comprising free alpha human chorionic gonadotrophin (\(\alpha\)HCG), beta human gonadotrophin (\(\beta\)HCG), alpha fetoprotein (AFP) and unconjugated oestriol.\(^7\)

The new antenatal screening test is a combined test (first trimester screening) and comprises a nuchal translucency measurement in combination with a maternal serum biochemical test measuring two hormones; pregnancy associated plasma protein A (PAPP-A) and \(\beta\)HCG.

This first trimester combined test has been reported to have an 83–86% detection rate compared to the old second trimester serum screening which is reported to have a 70–77% detection rate, both for a 6–9% false positive rate.\(^1,3,8\) NT measurement alone in the first trimester only had a reported 60–70% detection rate at best for a 20–25% false positive rate.\(^1,3,8\) Second trimester screening is a quadruple screen of hormones, comprising \(\beta\)HCG, AFP, unconjugated oestriol and inhibin A and has a reported detection rate of 83% for a 6% false positive rate, and is now offered only to those women who missed MSS1 but wish for a form of screening.\(^1,3,8\)

If a woman has an increased risk of a chromosomal anomaly in either trimester she is then offered invasive testing: chorionic villus sampling (CVS) or amniocentesis. These tests are diagnostic but both carry an inherent risk of miscarriage of 0.5–1.0% in addition to the background risk of miscarriage which is higher at the gestation CVS is undertaken.\(^9,10\)

Amniocentesis prior to 15 weeks is not recommended because of possibility of inadequate concentration of fetal cells in the sample, a higher incidence of talipes and a higher rate of miscarriage (<14 completed weeks) as found in the CEMAT study.\(^9,11,12\) In NZ, current cut off point for annotating a pregnancy as high risk is >1 in 300 risk of aneuploidies at term.\(^4\)

The Royal Australian and New Zealand College of Obstetricians and Gynaecologists guidelines suggest that all pregnant women should be offered an antenatal screening assessment as soon as possible in pregnancy.\(^13\) These guidelines are in line with the NICE guidelines produced in the UK.\(^14\)

In New Zealand, general practitioners and family planning centres are usually the first to come in contact with newly pregnant women prior to lead maternity carers (LMCs) and so these three groups are a pivotal link to the effectiveness and success of the antenatal screening process.
In this study, we aimed to assess the local impact of the introduction of ‘Antenatal Screening for Down syndrome and other conditions – quality improvement’ on the numbers of women attending the regional South Island referral Fetal Medicine Centre and how this translates to the type, gestation and percentage of abnormal results of invasive diagnostic procedures.

Method

The project was a retrospective audit on the impact of numbers and timing of diagnostic invasive testing after the introduction of a formalised antenatal screening process in the Canterbury region. Two time periods were reviewed; 1 February 2009 to 31 January 2010 (T1) and 1 May 2010 to 31 April 2011 (T2) to compare representative 1-year periods before and after introduction of the new screening. These time periods were set to enable the study to be carried out as a student research project, which is why T2 is set not long after the introduction of the new process.

Data had been prospectively collected in a viewpoint database of all women undergoing diagnostic procedures secondary to screening and this was utilised to collect data which was integrated with the information available from the Canterbury Health Laboratories on all MSS1 results. The denominator was all pregnant women in the Canterbury District Health Board catchment area during each of the time periods.

Cases were determined by putting the time periods into the viewpoint data base and extracting data and were cross checked with paper records of invasive procedures (amniocentesis and chorionic villus sampling) done at Christchurch Women’s Hospital.

Ethical approval was not required and confirmation of this was sought from the Upper South B Regional Ethics Committee. Permission was sought and given by the National Screening Unit for use of MSS1 denominator data.

All those women that underwent either amniocentesis or CVS in the above two time periods had their information collected from the Fetal Medicine Viewpoint Database, including:

- Maternal age
- Risk of Down Syndrome (T21) from maternal serum screening first or second trimester (MSS1 or MSS2)
- Reason for (either increased risk MSS1/2, maternal age, abnormal USS, known familial chromosomal anomalies or previous baby with a genetic condition) and gestation of invasive procedure
- Fluorescent in situ hybridisation (FISH) or not
- Time to result (number of days between amnio/CVS and outcome of chromosomal testing) and what the outcome was (e.g. normal karyotype, T21, T13, T18 or another chromosomal anomaly that is tested for)
- Outcome of the baby including mode of delivery, gestation at birth and birth weight
- Miscarriages and terminations and reasons for them

Results from postnatal chromosomal testing done by Canterbury Health Laboratories was obtained to determine those babies only diagnosed as having Down syndrome after birth. We extended our catchment out to 3 months past the end date of the time periods to account for late diagnosis.

A biostatistician was consulted and assisted with the statistics. Statistics were done using the Open epi software program which was accessed at http://www.openepi.com/v37/Menu/OE_Menu.htm Mid P exact P values (2-tailed) were used and confidence intervals used were in relation to the risk difference calculation. These were calculated by the Taylor series.
Results

In Canterbury in T1 (1 February 2009- 31 January 2010), there were 6210 babies born. In T2 (1 May 2010- 31 April 2011) there were 6072 babies born. All of these women who delivered in the second time period should have been offered the new antenatal screening program at the time of their booking and 3111 of them (51%) underwent MSS1 (number obtained from the National Screening Unit, Auckland).

Table 1. Comparison of results between T1 (1 February 2009 – 31 January 2010) and T2 (1 May 2010 -- 31 April 2011)

<table>
<thead>
<tr>
<th>Variables</th>
<th>TP1</th>
<th>TP2</th>
<th>Risk difference</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Numbers and percentage of Women Undergoing invasive Testing (% of total birthing women)</td>
<td>253 (4.1%)</td>
<td>175 (2.9%)</td>
<td>1.2%</td>
<td>0.55, 1.84</td>
<td>0.0003*</td>
</tr>
<tr>
<td>Proportion of invasive testing: amniocentesis</td>
<td>58.7%</td>
<td>59.5%</td>
<td>0.8%</td>
<td>-9.54, 7.83</td>
<td>0.85</td>
</tr>
<tr>
<td>CVS</td>
<td>41.3%</td>
<td>40.5%</td>
<td>0.8%</td>
<td>-7.83, 9.54</td>
<td>0.85</td>
</tr>
<tr>
<td>Detection rate (of abnormalities)</td>
<td>11.8%</td>
<td>15.4%</td>
<td>-3.08%</td>
<td>-9.12, 2.96</td>
<td>0.32</td>
</tr>
<tr>
<td>Numbers and percentage of T21 in those undergoing invasive testing</td>
<td>13/288 (4.5%)</td>
<td>14/215 (6.5%)</td>
<td>-1.99%</td>
<td>-6.07, 2.08</td>
<td>0.33</td>
</tr>
</tbody>
</table>

TP = time period.

^ Confidence Intervals calculated in relation to risk difference.

*P<0.05 level of significance.

There were no differences between the two time periods in the ages of women undertaking procedures; (mean 34.3yrs for CVS and 32.7yrs for amniocentesis) or the gestation at which the invasive procedures were undertaken at (13+0 and 17+5 days respectively) as would be expected.

The presence or absence of a nasal bone was only documented in 13.2% and then 25.6% of scans in the first and second time period (a significant increase in reporting p 0.0004). Twenty four percent of scans in both time periods reported an absent nasal bone and in 11% and then 15.4% (T1 and T2) of these babies a chromosomal anomaly was found.

Table 2. Comparison of miscarriage rates between T1 and T2

<table>
<thead>
<tr>
<th>Comparison</th>
<th>TP1</th>
<th>TP2</th>
<th>Risk Difference</th>
<th>95% Confidence Interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Miscarriage rates – amniocentesis</td>
<td>0.6%</td>
<td>0.8%</td>
<td>-0.19%</td>
<td>-2.10, 1.72</td>
<td>0.86</td>
</tr>
<tr>
<td>Miscarriage rates – CVS</td>
<td>1.7%</td>
<td>1.1%</td>
<td>0.53%</td>
<td>-2.68, 3.75</td>
<td>0.81</td>
</tr>
<tr>
<td>Miscarriage rates – amniocentesis euploid</td>
<td>0.6%</td>
<td>0.8%</td>
<td>-0.19%</td>
<td>-2.10, 1.72</td>
<td>0.86</td>
</tr>
<tr>
<td>Miscarriage rates – CVS euploid</td>
<td>0%</td>
<td>1.1%</td>
<td>-1.15%</td>
<td>-3.39, 1.09</td>
<td>0.42</td>
</tr>
</tbody>
</table>
Overall miscarriage rates for amniocentesis were 0.3% and for CVS 1.5%. Miscarriage rates in euploid pregnancies were 0.3% post amniocentesis and 0.5% post CVS.

**Down syndrome (T21) diagnosis in the neonatal period**

**First time period**—There were six babies diagnosed with Down syndrome after birth. All of these babies were born to women that did not have any NT measurements or early pregnancy scans. Two women had no scans at all throughout their pregnancy.

**Second time period**—In the second time period, of those six that were diagnosed with Down syndrome after birth, only two had MSS1 antenatal screening and they were both categorised high risk (>1:100). They both declined invasive diagnostic testing. Of the four that didn't have MSS1, two had increased NT results (2.5 and 2.8) and also declined invasive diagnostic testing.

**Discussion**

This study was aimed at analysing the impact and implementation of the new ‘Antenatal screening for Down syndrome and other conditions- quality improvement’ in the regional South Island referral Fetal Medicine Centre in Christchurch.

The new antenatal screening quality improvement process should be offered to all women who become pregnant and it is an individual decision as to whether they undertake the screening tests (there is a charge in most ultrasound providers for NT scanning) and, if indicated, the more invasive diagnostic procedures.

We anticipated that there would be a high uptake of screening by women in Canterbury however only 51.2% of women undertook the MSS1 testing in their first trimester in the period analysed which was early on in the new process. This study does not assess the reason for the low level of uptake; for example whether women are informed and chose not to undertake the screen or whether they are not aware of this offer.

One strength of our study was the follow up rates. Out of all the women that underwent invasive procedures, only five (1%) were lost to follow up presumed as having left the area/New Zealand.

The rates of invasive procedures (combined) have significantly (p<0.0003) decreased by 29% (from 4.1% of the total number of pregnant women during T1 to 2.9% in T2) after the introduction of the new antenatal screening quality improvement process.

Meanwhile the detection rates of abnormalities including Trisomy 21 have increased, although not significant. This is a statistically significant decrease in testing and is encouraging in the fact that the new antenatal screening program was designed to improve specificity without diminishing the true positive or detection rates.

The trend is suggesting that women are being given a more accurate assessment of their risk of certain chromosomal anomalies, with fewer women submitted to invasive diagnostic testing, without a diminution of detection rates. When national data are available, further analysis of this trend will be possible.
These results highlight that no babies were missed through the screening and diagnostic process as having Down syndrome. Those six babies that were diagnosed with the condition only after birth, had either not had any screening, or had, and had declined further diagnostic invasive testing (both declined after a specialist fetal medicine consultation).

The numbers in this study are too small to be able to calculate false positive and false negative rates of the new screening program.

The proportion of tests undertaken by CVS vs. Amniocentesis remained stable between T1 and T2. We expected that there may be an increase in the numbers of CVS being done as the new screening is done early so it was anticipated that invasive procedures would also be done earlier (CVS can be undertaken from 11 weeks gestation).

The static rates of CVS could reflect delays in referral (initial consult always within a week of receipt) or time taken by couples to reflect following risk assessment or patient preference to defer to amniocentesis. Unfortunately this data was not collected.

The number of tests that had FISH carried out was high in both time periods (61% and 66%). Criteria for offering FISH was risk 1:100.

The number of abnormal results which had FISH analysis ranged from 80-100% (amnio and CVS) over the two time periods. This is encouraging that those results that were abnormal were having FISH done and therefore a quicker result generated, but obviously has resource implications. Practise has more recently changed to risk 1:50. Miscarriage rates were low in these series as would be expected in a Fetal Medicine Centre where all procedures were undertaken by one of three trained specialists.

Interestingly the percentage of fetuses that had their nasal bones analysed was low, but in those scans where the nasal bone was reported as absent (24% of fetusus) there were low rates of chromosomal anomalies, however the numbers are too small to make further comment. The NSU doesn’t require the nasal bone to be reported, hence likely the reason few were measured.

Our results are not in line with larger series studies which have concluded that an absent nasal bone can be seen in only 2.6% of euploid fetuses. At 11-13 weeks the nasal bone is considered to be absent in 60% of those with T21, 50% of those with T18 and 40% of those with T13. This perhaps raises the question of accuracy in obtaining views to visualise the nasal bone effectively.

Other studies conclude that visualisation of the nasal bone is a useful parameter and can improve the performance of first trimester screening for Down syndrome.

The implementation of the new antenatal screening process in Canterbury has so far proved to be successful in maintaining detection rates of genetic anomalies whilst decreasing the numbers of invasive diagnostic procedures being done.

As the programme is still relatively new, uptake rates are modest (2011 data suggests rates are static, 2013 data is pending) but we anticipate these will rise with increasing awareness of the program in years to come and its potential benefits which
also include early anatomical appraisal and early detection of multiple pregnancy with determination of chorionicity.

We hope that with increased awareness of the new program and informed LMCs and other primary health care workers, all pregnant women will be offered screening. Improved antenatal screening programs like this have increased screening uptake in parts of the UK\(^1\) and we would hope to see this in NZ. A larger multi-centre study is needed to further evaluate the benefits of the quality improvement process.

**Competing interests:** Nil.

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**References:**


