SOUTH AUSTRALIAN MATERNAL SERUM ANTENATAL SCREENING (SAMSAS®) PROGRAM


“providing obstetric support”

Robert Cocciolone,
Head, Antenatal Screening,
Department of Genetic Medicine, WCH
“providing obstetric support”
SOUTH AUSTRALIAN MATERNAL SERUM ANTENATAL SCREENING PROGRAM (SAMSAS©)

Longest running program in Australia,
-1978 Neural Tube Defect (NTD) screening
-1990/91 Down syndrome & other pregnancy pathologies (15-20wks).
- June 2001 First Trimester Down syndrome screening (10-14wks).

Develop and manage own software and algorithms, with one of the largest databases in Australia.

Services SA, TAS & NT.

Offer Screening service support to PMH in WA

Integrated with Neonatal Screening database.

Electronic access to Cytogenetic and Ultrasound reports.

SAMSAS audits published in the SA Birth Defects Register Report.

www.wch.sa.gov.au

• Services
• A for Antenatal Screening or
• B for Birth Defects Register
South Australian Maternal Serum Antenatal Screening (SAMSAS) Programme
Women's and Children's Hospital, Adelaide (APA),
72 King William Road,
North Adelaide SA 5006

A/2352
Enquires tel 08 8161 7285
fax 08 8161 8085
samsas@wch.sa.gov.au

FAMILY NAME ________________________________
GIVEN NAMES ________________________________
DATE OF BIRTH _____ / _____ / _____ UR No ______
ADDRESS ______________________________________
_________________________________________________
POSTCODE _________________________________

First Trimester Screen □ or Second Trimester Screen □ or NTD only □
Cycle Length days ______  Maternal Weight kgs ______
EDD/LMP ______ / ______ / ______  Certain?  Yes □ No □
GA Clinical weeks + days ____________ on_____ / _____ / _____
GA Ultrasound weeks + days __________ on_____ / _____ / _____
Crown-rump length (CRL) mm ______ on_____ / _____ / _____
Nuchal Translucency mm ______ on_____ / _____ / _____
Is pregnancy  TWINS □ TRIPLETS □
For first trimester Screening an Ultrasound request form is required for Nuchal Translucency, 11-13w6d.
Name of Imaging Practice:

5–10 ml CLOTTED BLOOD SAMPLE REQUIRED

Signature ___________________ Request Date ______ / _____ / _____

COPIES OF REPORT TO (Name, Address)

Privacy Act Disclosure (Sections A5.3 & NPP2),
SAMSAS requires the use of personal information contained on this request form for the purpose of Risk Assessment and Programme Audits. SAMSAS may therefore request copies of ultrasound and cytogenetic reports in order to complete its testing and audits.

Specimen date ______ / _____ / _____
First Trimester Blood Sample 10–13w6d
Second Trimester Blood Sample 14–20w6d

Send to CHEMICAL PATHOLOGY,
WOMEN'S AND CHILDREN'S HOSPITAL,
ADELAIDE a NATA/RCPA accredited laboratory.
MSS is not just a test but is offered as a program with access to pre & post test information, counselling and diagnostic services – cvs, amnio & ultrasound.
Second trimester screening of pregnancies for fetal Down syndrome and neural tube defects remains in place and can still be requested as before. We recommend, however, that if a pregnancy is ascertained in the first trimester then any request in second trimester be confined to neural tube defect (NTD) screening only. First trimester screening does not include detection of fetal NTDs.

**Requesting first trimester screening**

Two request forms are required, one for the blood analysis and one for the ultrasound scan.

**BLOOD ANALYSIS**

1. 5-10 ml clotted blood sample, taken between 10 and 13 weeks gestation is required. A list of collection centres is provided on the reverse of the SAMSAS request form.
2. Use a SAMSAS request form, telephone (08) 8161 7285 if you require some of these,
   (a) the test request is “first trimester screen”;
   (b) complete the gestational age information, the gestation must be between 10+6 and 13+6 weeks;
   (c) specify the ultrasound practice performing the nuchal translucency scan;
   (d) refer patient to the Privacy Act Disclosure on the SAMSAS request form,
   (e) give the patient the SAMSAS pre-test information booklet;
   (f) send the blood specimen to Women’s and Children’s Hospital, for interstate or remote areas check with SAMSAS on what services are available.

**ULTRASOUND**

3. Book a Nuchal Translucency scan with the imaging group of choice. The fetus must be between 11+6 and 13+6 weeks gestation at the time of the scan.
4. Complete an ultrasound request form, specifying “risk of fetal abnormality”; and “Copy to SAMSAS”. To comply with National Privacy Legislation, refer patient to the Privacy Act Disclosure on the SAMSAS request form.

SAMSAS will coordinate the results with the ultrasound practice and you will receive a single report giving the risks calculated for the pregnancy. Post-test information booklets are provided with all reports issued by SAMSAS on pregnancies found at increased risk of fetal abnormality.

**Availability of first trimester screening**

Combined ultrasound and biochemistry screening is not at present offered through all hospitals/clinics. Check with the hospital/clinic concerned.

**Costs**

For privately insured patients SAMSAS continues its policy of accepting ‘Medicare only’ for the serum biochemistry analyses. There may be a gap payment for the ultrasound measurement. Check with the practice providing this service.

Robert Coccolone, BAppSc, Med Lab Sc
on behalf of the South Australian Maternal Serum Antenatal Screening (SAMSAS) Programme

<table>
<thead>
<tr>
<th>Gestational Age Windows for Antenatal Screening for Birth Defects</th>
</tr>
</thead>
<tbody>
<tr>
<td>First Trimester</td>
</tr>
<tr>
<td>Second Trimester</td>
</tr>
</tbody>
</table>
Screening

“the systematic application of a test procedure to identify individuals at sufficient risk to warrant diagnostic investigations”

• CVS 12wks
• Amniocentesis 16wks
• Morphology Ultrasound 18wks

Aim is to maximise detection of affected pregnancies and minimise false +ves
## Biochemical Markers;

<table>
<thead>
<tr>
<th>2nd Trimester</th>
<th>1st Trimester</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFP</td>
<td>free β hCG</td>
</tr>
<tr>
<td>free β hCG</td>
<td>Papp-A</td>
</tr>
<tr>
<td>uE3</td>
<td></td>
</tr>
</tbody>
</table>

## Other Markers;

- Nuchal Translucency

- Maternal age
- Gestational age
• Risk Calculation ~ NT vs Biochemistry vs Combined vs Integrated
  • MoM values
  • Maternal Age
  • Gestational Age
  • Recurrence Risk
  • Singleton vs Twins
  • Maternal Weight
  • Ethnicity
  • Diabetes
  • Smoking
  • Analytical Imprecision

OUTCOME
 Screening for trisomy 21

Effectiveness of different methods of screening

100,000 pregnancies

Screen positive
5%
N=5,000

Trisomy 21
N=200

Method of screening

Detection rate

Number detected

Maternal age

30%
60

Serum biochemistry at 16 wks

65%
130

Nuchal translucency (NT) at 12 wks

75%
150

Fetal NT & ß-hCG & PAPP-A at 12 wks

90%
180

## Fetal loss per case of Down syndrome detected

<table>
<thead>
<tr>
<th></th>
<th>Maternal Age Screening alone</th>
<th>Second trimester biochemical screening</th>
<th>First trimester combined screening</th>
</tr>
</thead>
<tbody>
<tr>
<td>Amniocenteses performed per case detected</td>
<td>250</td>
<td>40</td>
<td>20</td>
</tr>
<tr>
<td>Fetal loss per case of Down syndrome detected</td>
<td>1:1</td>
<td>1:5</td>
<td>1:10</td>
</tr>
</tbody>
</table>

Marker Levels Change Significantly with Gestation

Measured levels are converted to Multiples Of the Population Median or MoM values.

Reference is therefore 1 MoM

beta hCG at 10 wks GA

Patient 120 IU/L = 2 multiples
Median 60 IU/L

MoM values are independent of gestational age and concentration Units

LogMoM values are used in calculations as they exhibit a Gaussian distribution (Mean +/- SD)
Unaffected 1st Trimester

Unaffected 2nd Trimester
Maternal Weight

Unaffected 1st Trimester

**Increasing Incidence of Twins**

(1990–2003) 1:70 to 1:55

* Assisted reproduction

* Rate of twinning increases with age.

>17% of pregnancies are now to women 35yrs or over, up from <9% in 1990.
### RISKS

1. **Open Neural Tube Defects (NTD)**
2. **Down syndrome**
3. **Other**

<table>
<thead>
<tr>
<th>NTD</th>
<th>Down syndrome</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Trimester</td>
<td>1st &amp; 2nd Trimester</td>
</tr>
<tr>
<td>↑ AFP ≥ 2 MoM</td>
<td>↑ Risk ≥ 1 in 300</td>
</tr>
<tr>
<td>Independent of Maternal Age</td>
<td>Age Dependent</td>
</tr>
<tr>
<td>Morphology scan</td>
<td>CVS / Amnio</td>
</tr>
</tbody>
</table>

~ 1/30 will have a NTD                     ~ 1/20 or 1/40 will have DS

### Other

**Not NTD & Not DS:**

\[ AFP < 2 \text{ MoM} & \text{ DS risk is} < 1 \text{ in} 300 \]

But

**Biochemical results fall outside the Normal expected.**
NTD

A review of SAMSAS pregnancies screened N = 67,965.

1,976 or 2.9% had a raised AFP > 2 MoM.

Conditions found in the raised AFP group.

<table>
<thead>
<tr>
<th>NTD</th>
<th>61 (1 in 32)</th>
<th>32 anencephaly</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>27 meningomyelocele</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 encephalocele</td>
</tr>
<tr>
<td>Other Fetal Anomalies</td>
<td>19 (1 in 104)</td>
<td>5 exomphalocoele</td>
</tr>
<tr>
<td></td>
<td></td>
<td>9 gastroschisis</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 triploidy</td>
</tr>
<tr>
<td></td>
<td></td>
<td>2 trisomy 13</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Turner syndrome</td>
</tr>
<tr>
<td>FDIU</td>
<td>48 (1 in 41)</td>
<td>Fetal death at time of screen</td>
</tr>
<tr>
<td>Other Pregnancy Complications subsequent to maternal serum screen.</td>
<td>75 (1 in 26)</td>
<td>Missed Abortion, PROM, stillbirth, other fetal demise.</td>
</tr>
<tr>
<td>Unsuspected Twins</td>
<td>47 (1 in 42)</td>
<td></td>
</tr>
</tbody>
</table>

 TOTAL ANOMALIES IN RAISED AFP GROUP 250 (1 in 8)

NAD in 1726/1976 or 87.4% with raised maternal serum AFP.
Total pregnancies screened 65,328.

3,481 or 5.3 % were reported at increased risk for Down syndrome.

Conditions found in the increased risk group.

<table>
<thead>
<tr>
<th>Condition</th>
<th>Count</th>
<th>Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Down syndrome</td>
<td>84</td>
<td>1 in 41</td>
</tr>
<tr>
<td>T18, T13, Triploidy</td>
<td>9</td>
<td>1 in 386</td>
</tr>
<tr>
<td>Male &amp; Female Sex Chromosome Abnormalities</td>
<td>12</td>
<td>1 in 290</td>
</tr>
<tr>
<td>Unbalanced &amp; balanced de novo karyotypes</td>
<td>4</td>
<td>1 in 870</td>
</tr>
<tr>
<td>Balanced Translocations or inversions</td>
<td>17</td>
<td>1 in 204</td>
</tr>
<tr>
<td><strong>TOTAL ANOMALIES in increased risk group</strong></td>
<td>126</td>
<td>1 in 28</td>
</tr>
</tbody>
</table>

NAD in 3355/3481 or 96.4% with an increased risk report.
Triploidy 2nd Trimester

Diandric

Digynic

(1) Overestimate) T21 2nd Trimester

T18 2nd Trimester
Not NTD & Not Downs Profiles

SAMSAS screened pregnancies N=62,563

1st Trimester N= 26,914
Profile
Non Downs
N= 206 (0.77%)

2nd Trimester N= 35,649
Profile
Not NTD Not Downs
N= 123 (0.35%)

Total N = 329 (0.53%)

OUTCOMES

NOT KNOWN
N = 25 (7.6%)

NORMAL
N = 103 (31.3%)

FETAL DEATH
N = 171 (52%)

ABNORMAL
N = 30 (9.1%)

9 x Triploidy, 9 x T18
3 x T15, 3 x Anenceph.1st Tr
2 x Turners, 2 x Mult. Abn.
2 x Metabolic
1st Trimester Not Downs

• \textbf{N} = 57
• Not Known= 7
• Normal= 39
• Fetal Death= 3
• Abnormal= 8 (4xTriploidy,1xT18,1xOther,1xAnencephaly,1xRenal)

\textbf{Anomalies Found 11/50}
\textbf{Odds 1/4.5 (22%)}

Viable at time of screen.

2nd Trimester Not NTD Not Downs

• \textbf{N} = 99
• Not Known= 12
• Normal= 62
• Fetal Death= 13
• Abnormal= 12 (4xTrip.,6xT18,1xMultiple Con. Abn.,1xMetabolic)

\textbf{Anomalies Found 25/87}
\textbf{Odds 1/3.5 (28.6%)}

Viable at time of screen.
## What does a risk report mean?

<table>
<thead>
<tr>
<th></th>
<th>% Recall</th>
<th>% Det.</th>
<th>ODDS Adverse Outcome</th>
<th>ODDS Affected</th>
<th>Miss Rate</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>2(^{nd}) Tr</strong></td>
<td>3%</td>
<td>&gt;90%</td>
<td>1 / 8</td>
<td>1 / 30</td>
<td>1 / 10,000</td>
</tr>
<tr>
<td>Raised NTD Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>2(^{nd}) Tr</strong></td>
<td>5%</td>
<td>65%</td>
<td>1 / 30</td>
<td>1 / 40</td>
<td>1 / 2,500</td>
</tr>
<tr>
<td>Raised DS Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>1(^{st}) Tr</strong></td>
<td>5%</td>
<td>90%</td>
<td>1 / 10</td>
<td>1 / 20</td>
<td>1 / 3,500</td>
</tr>
<tr>
<td>Raised DS Risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not NTD</td>
<td>0.5%</td>
<td>75%</td>
<td>1 / 4</td>
<td></td>
<td>1 / 500</td>
</tr>
<tr>
<td>Not Downs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>? Viability</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Reassurance of ≥ 99.8 % & Anomaly Risk of 2.5 – 25%**

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Summary data ~ SAMSAS yearly audits SA Birth defects Register Reports
Background Risk

Maternal age

Risk %

0.0001
0.001
0.01
0.1
1
10

Years

20 25 30 35 40 44

Trisomy 21

xxx/xy/xy

Trisomy 18

Trisomy 13

45x

Triploidy

Snijders et al 1995 Nicolaides et al., The 11-14-week scan, London 1999
Assessment of Risk

Previous Chromosomal Abnormality

Trisomy 21
Trisomy 18
Trisomy 13

\[ \text{Trisomy 21} \cup \text{Trisomy 13} \]

\[ \text{45XO} \]
\[ \text{47XYY/XXX} \]
\[ \text{Triploidy} \]

\[ 0.50 - 0.75\% \]
DS Risk = Mat. Age Risk \times LR
DS Risk = Mat. Age Risk \times LR

\[ Y = 0.425 \ln(\text{beta MoM}) - 0.631 \ln(\text{Papp-a MoM}) + 0.761 \ln(\text{NT MoM}) \]

\[ LR_{\text{aff}} = \frac{h2}{h1} \]
DS Risk = Mat. Age Risk $\times$ LR

- 20 yrs = 1 in 1600 $\times$ 2 = 1 in 800
- 30 yrs = 1 in 1100 $\times$ 2 = 1 in 550
- 35 yrs = 1 in 500 $\times$ 2 = 1 in 250
- 40 yrs = 1 in 156 $\times$ 2 = 1 in 78
- 45 yrs = 1 in 40 $\times$ 2 = 1 in 20
1st trimester Risk Odds show better separation between Unaffected and Affected pregnancies when compared to 2nd trimester Risk Odds.
Age Specific Performance
Comparison of 1st and 2nd Trimester Screening.
Maternal Age vs Recall and Detection

Maternal Age at Delivery

RR

DR

% %RR 2nd %DR 2nd %RR 1st %DR 1st
NUCHAL TRANSLUCENCY

- NT is an ultrasonographic feature visible in 1st Tr of pregnancy

- NT results from an accumulation of fluid at the base of fetal neck

- NT thickness increases with GA (0.8 to 1.6 mm)

- Non specific marker,

  thickness > 2.5 mm associated with an increased risk of aneuploidy, cardiovascular & pulmonary defects, skeletal dysplasia, renal, metabolic defects & congenital infections & fetal demise.
• Fetus must occupy 3/4 of the image
• Fetus must be in a Neutral position
• Hyperextension of fetal neck can increase the NT by 0.6 mm
• Flexion of the neck can decrease the NT by 0.4 mm
• Umbilical cord round the fetal neck (5-10% of cases) can increase the NT by 0.8 mm
• Amniotic membrane and Nuchal membrane must be separate
• Measure the max thickness of the subcutaneous translucency
Increased nuchal translucency and exomphalos in a trisomy 18 fetus at 12 weeks of gestation
Turners syndrome - cystic hygroma
Severe asymmetrical growth restriction in a 13-week fetus with triploidy.
BENEFITS OF AN EARLY SCAN

• confirms the fetus is alive
• permits accurate dating of pregnancy
• allows early diagnosis of multiple pregnancy & chorionicity
• detects major structural abnormalities and missed abortion
Why did we introduce 1\textsuperscript{st} trimester combined screening into SA?
<table>
<thead>
<tr>
<th></th>
<th>Detect</th>
<th>Recall</th>
<th>%≥35</th>
<th>%PG≥30</th>
<th>Age</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Tr</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>91-95</td>
<td>63%</td>
<td>4.9%</td>
<td>9%</td>
<td>20%</td>
<td>28</td>
</tr>
<tr>
<td>96-00</td>
<td>76.7%</td>
<td>6.6%</td>
<td>15%</td>
<td>30%</td>
<td>29</td>
</tr>
<tr>
<td>01-03</td>
<td>76.7%</td>
<td>7.4%</td>
<td>17%</td>
<td>35%</td>
<td>30</td>
</tr>
<tr>
<td>1st Tr</td>
<td>90%</td>
<td>5.6%</td>
<td>&gt;30%</td>
<td></td>
<td>32</td>
</tr>
</tbody>
</table>

PG = Primigravida
Advantages of 1st trimester screening

• benefits of an early scan
• less false +ves & -ves
• less normal fetuses lost
• higher detection
• personal benefits to patients from earlier diagnosis

Disadvantages

• cost of the nuchal translucency scan
• logistically more difficult to manage
Logistical considerations?

1TR & 2TR screening will coexist.

Management of reports & requests.

How many risks, by whom and when?

Audits and ongoing programme evaluation.
How can these be addressed?

Centralised service & database for,
- all patient demographics
- biochemical results
- NT measurements & providers
- reporting
- recalculation of risks
- retrievable data for analysis

Logical software - risks linked to gestation (1TR & 2TR algorithms)
South Australian Maternal Serum Antenatal Screening Program – SAMSAS

Patient Name: SAMSAS
Test
Birth Date: 29/04/1968
Patient ID: 123456
SAMSAS Lab. No. 100
Requesting Doctor: CNC Antenatal Clinic WCH
Ref. Lab. No.

FIRST TRIMESTER SCREEN

Maternal weight: 100 kg used for MoM adjustment
Gestational Age: 11w0d
Estimated by: Crown Rump Length
Sample Date: 10/10/2002

Risk of open NTD: assessment not valid in first trimester

Risk of Down syndrome: increased risk of Down syndrome (risk 1:132)

The fetus is at increased risk of having Down syndrome based on biochemical and nuchal translucency measurements (cut-off risk 1:300). Amniocentesis or CVS for karyotyping should be considered.

Nuchal Translucency measurement at Benson Radiology 8239 0550

Copies sent to:
Dr Brian Peat
CNC Antenatal Clinic WCH
1st Floor QV Building
Women's & Children's Hospital
NORTH ADELAIDE SA 5006

CORRECT INTERPRETATION DEPENDS ON THE ACCURACY OF GESTATIONAL AGE, MATERNAL AGE AND SAMPLE DATE. Should this be different from that shown, please contact SAMSAS for immediate re-calculation of risk and amended report.

**USE OF SAMSAS REQUEST FORMS IMPROVES TESTING EFFICACY**

This report printed: November 14, 2002 @ 11:49
Trends in state-based Down syndrome screening and invasive prenatal testing with the introduction of first trimester combined Down syndrome, South Australia 1995-2005
Utilization of maternal serum Down syndrome screening % of all confinements

69-79%
Utilization of second trimester maternal serum (Δ) and first trimester combined Down syndrome screening (□), % of all confinements

* P < 0.001
% confinements ≥ 35 years (●) of age vs % of confinements undergoing invasive prenatal tests (△)

* P < 0.001

9.3%

7.6%
Confinements $\geq 35$ years of age undergoing invasive prenatal tests

% of confinements $\geq 35$ years of age with invasive prenatal test

* $P < 0.001$
Number of invasive prenatal tests to detect one DS fetus

<table>
<thead>
<tr>
<th>Year</th>
<th>Down syndrome cases</th>
<th>Rate of DS per invasive procedure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>32</td>
<td>1/86</td>
</tr>
<tr>
<td>1996</td>
<td>32</td>
<td>1/94</td>
</tr>
<tr>
<td>1997</td>
<td>41</td>
<td>1/83</td>
</tr>
<tr>
<td>1998</td>
<td>46</td>
<td>1/61</td>
</tr>
<tr>
<td>1999</td>
<td>42</td>
<td>1/71</td>
</tr>
<tr>
<td>2000</td>
<td>37</td>
<td>1/79</td>
</tr>
<tr>
<td>2001</td>
<td>36</td>
<td>1/90</td>
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<tr>
<td>2002</td>
<td>44</td>
<td>1/66</td>
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<td>2003</td>
<td>42</td>
<td>1/46</td>
</tr>
<tr>
<td>2004</td>
<td>34</td>
<td>1/49</td>
</tr>
<tr>
<td>2005</td>
<td>47</td>
<td>1/40 *</td>
</tr>
</tbody>
</table>

*p < 0.001
Number of invasive prenatal tests to detect one aneuploid fetus

<table>
<thead>
<tr>
<th>Year</th>
<th>Aneuploidy cases</th>
<th>Rate of aneuploidy per invasive procedure*</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>51</td>
<td>1/35</td>
</tr>
<tr>
<td>1996</td>
<td>46</td>
<td>1/47</td>
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<tr>
<td>1997</td>
<td>50</td>
<td>1/38</td>
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<td>1998</td>
<td>65</td>
<td>1/31</td>
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<tr>
<td>1999</td>
<td>60</td>
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<td>2000</td>
<td>56</td>
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<td>2001</td>
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<tr>
<td>2003</td>
<td>64</td>
<td>1/24</td>
</tr>
<tr>
<td>2004</td>
<td>65</td>
<td>1/21</td>
</tr>
<tr>
<td>2005</td>
<td>91</td>
<td>1/15</td>
</tr>
</tbody>
</table>

*p < 0.001
### Overall Prenatal Detected Down Syndrome cases (%)

<table>
<thead>
<tr>
<th>Year</th>
<th>Down syndrome cases</th>
<th>Prenatal detected DS cases (%)**</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995</td>
<td>32</td>
<td>71.9</td>
</tr>
<tr>
<td>1996</td>
<td>32</td>
<td>81.3</td>
</tr>
<tr>
<td>1997</td>
<td>41</td>
<td>70.7</td>
</tr>
<tr>
<td>1998</td>
<td>46</td>
<td>73.9</td>
</tr>
<tr>
<td>1999</td>
<td>42</td>
<td>71.4</td>
</tr>
<tr>
<td>2000</td>
<td>37</td>
<td>70.3</td>
</tr>
<tr>
<td>2001</td>
<td>36</td>
<td>58.3</td>
</tr>
<tr>
<td>2002</td>
<td>44</td>
<td>65.9</td>
</tr>
<tr>
<td>2003</td>
<td>42</td>
<td>81.0</td>
</tr>
<tr>
<td>2004</td>
<td>34</td>
<td>88.2</td>
</tr>
<tr>
<td>2005</td>
<td>47</td>
<td>83.0</td>
</tr>
</tbody>
</table>

**p = 0.21
• Demonstrated an improved efficiency in the utilization of invasive prenatal tests

• Despite the increase in gravid women ≥ 35 years of age the number of invasive prenatal tests in this age group has significantly declined

• Despite the significant decrease in invasive prenatal tests the overall antenatal detection of Down syndrome did not decrease, and appears to increase once the utilization of first trimester combined Down syndrome screening reaches > 30% of confinements
To review changes in the utilization and effectiveness of state/population-based antenatal screening for NTDs in South Australia from 1986 to 2004
Utilization of MSAFP and First Trimester Screening

% confinements with first trimester combined DS screening
% confinements with MSAFP
<table>
<thead>
<tr>
<th>Year</th>
<th>Average births/Yr (#)</th>
<th>Average NTDs/Yr (#)</th>
<th>Overall antenatal detection of NTD(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1986-91</td>
<td>19,714</td>
<td>41</td>
<td>86</td>
</tr>
<tr>
<td>1992-98</td>
<td>19,437</td>
<td>32*</td>
<td>88.8</td>
</tr>
<tr>
<td>1999-2004</td>
<td>17,867</td>
<td>24</td>
<td>94.5 **</td>
</tr>
</tbody>
</table>

*State-wide educational drive on the benefits of Folic Acid supplementation for the reduction of NTDs 1994

** p<0.001
Despite a significant decrease in the utilization of MSAFP screening, the population-based detection of NTDs has increased significantly in South Australia.

The decreased utilization of second trimester MSAFP represents improve clinician confidence in second trimester ultrasound for the detection of NTDs.
What detection rates need to be achieved in First Trimester?

key variables:

• Fetal loss Rate of T21
• Second Trimester Detection rates
## Rates of fetal death in Down syndrome pregnancies.

<table>
<thead>
<tr>
<th>Fetal loss rate study</th>
<th>Age Range Years</th>
<th>First Trimester Fetal Loss rate (cases)</th>
<th>Second Trimester Fetal Loss rate (cases)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook <em>et al</em> (1995)</td>
<td>16-49</td>
<td>75% (8)</td>
<td>50% (168)</td>
</tr>
<tr>
<td>Halliday <em>et al</em>. (1995)</td>
<td>36-43</td>
<td>31% (39)</td>
<td>18% (73)</td>
</tr>
<tr>
<td>Bray and Wright (1998)</td>
<td>35-50</td>
<td>31% (341)</td>
<td>12% (1159)</td>
</tr>
<tr>
<td>Morris <em>et al</em>. (1999)</td>
<td>16-49</td>
<td>31% (441)</td>
<td>24% (2035)</td>
</tr>
<tr>
<td>Snijders <em>et al</em>. (1999)</td>
<td>35-45</td>
<td>31% (221)</td>
<td>21% (317)</td>
</tr>
</tbody>
</table>
Minimum First Trimester Detection Rates

<table>
<thead>
<tr>
<th>Fetal loss rate study</th>
<th>60% Second Trimester Detection</th>
<th>65% Second Trimester Detection</th>
<th>70% Second Trimester Detection</th>
<th>75% Second Trimester Detection</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hook et al. (1995)</td>
<td>75</td>
<td>78.8</td>
<td>82.4</td>
<td>85.7</td>
</tr>
<tr>
<td>Halliday et al. (1995)</td>
<td>64.9</td>
<td>69.6</td>
<td>74.2</td>
<td>78.7</td>
</tr>
<tr>
<td>Macintosh et al. (1995, 1996)</td>
<td>70</td>
<td>74.3</td>
<td>78.4</td>
<td>82.4</td>
</tr>
<tr>
<td>Bray and Wright (1998)</td>
<td>68.6</td>
<td>73</td>
<td>77.3</td>
<td>81.4</td>
</tr>
<tr>
<td>Morris et al. (1999)</td>
<td>63.8</td>
<td>68.6</td>
<td>73.3</td>
<td>77.9</td>
</tr>
<tr>
<td>Snijders et al. (1999)</td>
<td>64</td>
<td>68.8</td>
<td>73.5</td>
<td>78.1</td>
</tr>
<tr>
<td><strong>AVERAGE</strong></td>
<td><strong>67.7</strong></td>
<td><strong>72.2</strong></td>
<td><strong>76.5</strong></td>
<td><strong>80.7</strong></td>
</tr>
</tbody>
</table>
Assume 10% will abort before 2nd TR (90% progress to 2TR).

OBS prevalence of T21 in 1st TR = 1:347

17,500 pregnancies x 1:350 = 50 cases

45 cases progress to 2nd TR

61.9% Detected in 2nd TR = 27 cases

82.6% Detected in 1st TR = 37 cases

_________________________ or 10 more viable cases.
Frequency of death and/or major anomaly in fetuses with an increased nuchal translucency and a normal karyotype

Death or major anomaly

<table>
<thead>
<tr>
<th>NT</th>
<th>2.5-3.4</th>
<th>3.5-4.4</th>
<th>4.5-5.4</th>
<th>5.5-6.4</th>
<th>&gt;6.5 mm</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>3%</td>
<td>14%</td>
<td>23%</td>
<td>33%</td>
<td>69%</td>
</tr>
</tbody>
</table>

Early (10 - 13 weeks gestation) Presentation

Presents to GP/Clinic/Obstetrician

given pre-test information

decides screening
accepts screening

arranges blood specimen
arranges nuchal translucency
Early (10 - 13 weeks gestation) Presentation

blood specimen (SAMSAS)

measure pappA, free beta hCG
wait / enquire for NT

no NT possible
issue biochemical risk

NT
issue combined risk

single risk report to
GP/Clinic/Obstetrician
Mean Calculated Risk for Down syndrome vs Prevalence at term

$R^2 = 0.9991$

~ 50% of affected pregnancies will return risk odds of $\geq 1 : 20$

~ 75% of affected pregnancies will return risk odds of $\geq 1 : 100$

~ 85 - 90% of affected pregnancies will return risk odds of $\geq 1 : 300$
<table>
<thead>
<tr>
<th>Screening Modality</th>
<th>Number Screened</th>
<th>% Recalled</th>
<th>Number Of Pregnancies Affected With Down syndrome</th>
<th>% of affected pregnancies Detected</th>
</tr>
</thead>
<tbody>
<tr>
<td>2nd Trimester</td>
<td>11,782</td>
<td>5</td>
<td>21</td>
<td>61.9</td>
</tr>
<tr>
<td><strong>1st Trimester Combined Biochemistry &amp; Nuchal Translucency</strong></td>
<td><strong>26,000</strong></td>
<td><strong>5</strong></td>
<td><strong>46</strong></td>
<td><strong>82.6</strong></td>
</tr>
<tr>
<td>1st Trimester Biochemistry Only</td>
<td>26,000</td>
<td>5</td>
<td>46</td>
<td>69.6</td>
</tr>
<tr>
<td>1st Trimester Nuchal Translucency only</td>
<td>26,000</td>
<td>5</td>
<td>46</td>
<td>56.5</td>
</tr>
</tbody>
</table>
future directions

• new biochemical markers
  • fetal cells in maternal circulation
  • fetal DNA in maternal circulation
• complex protein profiles - mass spectrometry
ADAM12, a disintegrin and metalloprotease

The superfamily of zinc peptidases – Metzincins

- Reprolysins/Adamalysins
- SVMPs (snake venom proteases)
- ADAMs (a disintegrin and metalloprotease)
- ADAMTS (with thrombospondin motifs)
- Matrix metalloproteases (MMPs)
- Astacins
- Serralysins

Note that ADAM12 cannot be measured from EDTA plasma!
ADAMs are of high research focus

Several studies have shown that ADAMS are mainly located inside cells.

Translocation from intracellular storage to the cell surface might be regulated.

ADAM12 metalloprotease is activated inside the cell unlike matrix metalloproteases which are secreted as proforms and become activated outside the cell.

ADAM12-S cleaves IGFBP-3 and IGFBP-5 via its cysteine-rich domain, which may regulate bioavailability of IGF (PAPP-A is a protease for IGFBP-4).

ADAM12 releases soluble HB-EGF activating epidermal growth factor and thus promotes cardiac hypertrophy.

ADAM12 interacts with integrin and syndecan adhesion receptors.

ADAM12 has one of the longest cytoplasmic domains compared to other ADAMs; the tail is at least involved in the regulation of ADAM12 localization (inside the cell or at the cell surface).

19 genes in the human ADAMs are of high research focus.
ADAMs are focus in asthma, alzheimer and cancer research

- In humans ADAM mRNA is present at low levels in most adult tissues
  - human placenta expresses very high levels of ADAM12

- A large proportion of human carcinomas express ADAM12
  - breast carcinoma tissue and urine of breast cancer patients, liver metastases of colon carcinoma

- Overall, it appears that ADAMs are mainly expressed during growth and development
Frozen vs Fresh

$y = 0.00311x^3 - 0.61794x^2 + 48.68645x - 1169.09506$

$R^2 = 0.99984$

$y = 0.0023x^3 - 0.4218x^2 + 33.979x - 765.04$

$R^2 = 0.9999$
Nuchal Translucency vs NT provider

NT Expressed in MoM

Reference line 1 MoM +/- 20%

Diagram 1

Nuchal Translucency Distribution all Providers

NT expressed in MoM

Reference line 1MoM +/- 20%