Reference Guide for Health Care Providers

Prenatal Screening Tests for the Detection of:
Down Syndrome, Trisomy 18 and Open Neural Tube Defects

Advances in prenatal screening have resulted in new tests that offer an improved detection rate and fewer false positives in the detection of chromosome abnormalities. These include nuchal translucency (NT) ultrasound, and new biochemical markers (PAPP-A and DIA). Timing of these tests beginning at 11 weeks’ gestation necessitates discussion early in pregnancy.

In this monograph:
Page 1: - Disorders
Page 2: - Prenatal screening tests
Page 3: - Prenatal screening test algorithms
Page 4: - Risk of chromosome abnormalities with age
- Amniocentesis & chorionic villus sampling (CVS)
- Resources

Counselling Tip:
“A screening test can tell us if your baby has a higher than average chance of having a certain disorder. It does not tell us if your baby truly has the disorder or not. With screening, most babies with Down syndrome will be detected, but some will be missed.

Things to keep in mind:
- Informed choice - Before ordering the test, discuss benefits, risks and limitations.
- Autonomy - The patient should choose whether to have prenatal screening.
- What prenatal screening options are available in your area?
- What option is most suitable for your patient?
- Which test will provide the optimal care for your patient?
- A screening test is not diagnostic.

What disorders are being screened for?
Prenatal screening gives a woman her individual risk of having a child with Down syndrome, trisomy 18 and open neural tube defects. It does not screen for all chromosome abnormalities, so some may be missed. Following positive results, women will need to decide whether to go on to have diagnostic testing (i.e. CVS or amniocentesis). Prenatal screening should be offered as part of a program where diagnostic testing, counselling and follow up are available.

Down Syndrome (trisomy 21):
Intellectual disability of varying severity, characteristic facial appearance, hypotonia & other less common congenital anomalies. The general population incidence of Down syndrome is 1 in 800, but varies with maternal age.
Prenatal ultrasound findings: congenital heart defects (40%), intestinal obstruction (12%), approximately 1/3 of affected fetuses will have normal ultrasounds at 18-20 weeks.

Trisomy 18 (Edwards syndrome):
95% of pregnancies will result in a miscarriage or stillbirth, 95% of liveborn infants die by 1 year. Surviving infants will have severe intellectual disability and multiple congenital anomalies. The general population incidence of trisomy 18 is 1 in 6,000, but varies with maternal age.
Prenatal ultrasound findings: congenital heart defects (90%), choroid plexus cysts, distinct hand posture, club feet, micrognathia, intrauterine growth retardation and others. Though rare, affected fetuses may have a normal ultrasound at 18-20 weeks.

Open Neural Tube Defects (NTD)
- including anencephaly and spina bifida:
Anencephaly is lethal. Most babies with spina bifida survive and may have problems ranging from hydrocephalus, paralysis and learning/intellectual disabilities to no physical or mental disabilities. Non-gestational diabetes mellitus, anticonvulsant medications, family history of NTD and hyperthermia result in a higher chance of an affected child. The general population incidence in North America is about 1 in 2,000, does not vary with maternal age.

The Genetics Education Project

revised August, 2007
## Prenatal Screening Tests for the Detection of Down Syndrome

<table>
<thead>
<tr>
<th>Test</th>
<th>Down syndrome Detection Rate (DR)</th>
<th>False Positive Rate (FPR)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>IF PATIENT PRESENTS BEFORE 14 WEEKS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>→ Integrated Prenatal Screening (IPS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Trimester (11-13+6/7 wks)</td>
<td>• ↑NT – by certified sonographer</td>
<td>85-90%</td>
<td>• Results available in 2nd trimester.</td>
</tr>
<tr>
<td>• MS: ↓PAPP-A</td>
<td></td>
<td>2.4%¹</td>
<td>• Amniocentesis for diagnostic testing</td>
</tr>
<tr>
<td>Second Trimester (15–20+6/7 wks)</td>
<td>• MS: ↓AFP, ↑hCG, ↓uE3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>→ Serum Integrated Prenatal Screening (SIPS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Trimester (11-13+6/7 wks)</td>
<td>• MS: ↓PAPP-A</td>
<td>80-90%</td>
<td>• Results available in 2nd trimester.</td>
</tr>
<tr>
<td>• MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA</td>
<td></td>
<td>2.7%¹,²</td>
<td>• Amniocentesis for diagnostic testing</td>
</tr>
<tr>
<td>Second Trimester (15–20+6/7 wks)</td>
<td>• MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA</td>
<td></td>
<td>• Is available in most places where NT ultrasound is not available</td>
</tr>
<tr>
<td>→ First Trimester Combined Screening (FTS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First Trimester (11-13+6/7 wks)</td>
<td>• ↑NT – by certified sonographer</td>
<td>78-85%</td>
<td>• Results available in 1st trimester, earliest results</td>
</tr>
<tr>
<td>• MS: ↓PAPP-A</td>
<td></td>
<td>3.9%¹,²,³</td>
<td>• CVS for diagnostic testing</td>
</tr>
<tr>
<td>Second Trimester (15–20+6/7 wks)</td>
<td>• MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA</td>
<td></td>
<td>• Does not screen for NTDs*</td>
</tr>
<tr>
<td><strong>IF PATIENT PRESENTS AFTER 14 WEEKS</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>→ Maternal Serum Screen (Quadruple Screening)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second Trimester (15–20+6/7 wks)</td>
<td>• MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA</td>
<td>75-85%</td>
<td>• Results available in 2nd trimester.</td>
</tr>
<tr>
<td>• MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA</td>
<td></td>
<td>5-10%¹,²,³</td>
<td>• Amniocentesis for diagnostic testing</td>
</tr>
<tr>
<td>→ Maternal Serum Screen (Triple Screening -MSS)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Second Trimester (15–20+6/7 wks)</td>
<td>• MS: ↓AFP, ↑hCG, ↓uE3</td>
<td>71%</td>
<td>• Results available in 2nd trimester.</td>
</tr>
<tr>
<td>• MS: ↓AFP, ↑hCG, ↓uE3</td>
<td></td>
<td>7%⁴</td>
<td>• Amniocentesis for diagnostic testing</td>
</tr>
</tbody>
</table>

### Testing for Open Neural Tube Defects and Trisomy 18

<table>
<thead>
<tr>
<th>Test</th>
<th>Open Neural Tube Defects</th>
<th>Trisomy 18</th>
</tr>
</thead>
<tbody>
<tr>
<td>MS</td>
<td>↑AFP</td>
<td>↑NT, ↓PAPP, ↓βhCG, ↓AFP, ↓hCG, ↓uE3, ↓DIA</td>
</tr>
<tr>
<td>DR</td>
<td>80% for each test except FTS which does not screen for NTDs⁵</td>
<td>Slightly lower than the DR for Down syndrome for each test</td>
</tr>
<tr>
<td>FPR</td>
<td>Usually 5% or less for all tests except FTS⁴</td>
<td>Lower than the FPR for Down syndrome for each test. Usually 1% or less</td>
</tr>
</tbody>
</table>

* NTDs can be screened for by MS-AFP and/or by ultrasound at 18-20 weeks

**Abbreviation Key:**

- AFP: Alpha-FetoProtein
- DIA: Dimeric Inhibin-A
- βhCG: free-beta subunit of human Chorionic Gonadotropin
- hCG: human Chorionic Gonadotropin
- MS: Maternal Serum
- NT: Nuchal Translucency measured by ultrasound
- NTD: Neural Tube Defects
- PAPP-A: Pregnancy-Associated Plasma Protein A
- uE3: unconjugated Estriol

**Detection Rate (DR):**

Also known as sensitivity, is the probability that a fetus affected with Down syndrome will be detected by the prenatal screening test.

**False Positive Rate (FPR):**

The proportion of women with unaffected pregnancies who have positive results.

---

**Pregnancy Dating**

Ultrasound (U/S) dating is more accurate than LMP; a dating U/S will lower the FPR.

---

**Integrated Prenatal Screening (IPS) and Serum Integrated Prenatal Screening (SIPS)**

Step 1: First trimester: 11 – 13+6/7 weeks
- **IPS:** NT measurement then MS:PAPP-A
- **SIPS:** MS:PAPP-A

Step 2: Second trimester: 15 – 20+6/7 weeks
- **IPS:** MS:AFP, uE3, hCG
- **SIPS:** MS:AFP, uE3, hCG, DIA

### SCREEN POSITIVE
- Discuss options
- Offer referral to genetic services

### SCREEN NEGATIVE
- Ultrasound at 18 - 20 weeks
- Abnormal result
  - Offer amniocentesis 15 - 22 weeks
  - Most results normal
  - Discuss options if abnormal

### SCREEN POSITIVE: Chromosome problem
- Offer amniocentesis 15 – 22 weeks

### SCREEN POSITIVE: NTD
- Offer ultrasound 15 – 20 weeks and/or amniocentesis
- Most results are normal
- Risk of future pregnancy complications with a high MS-AFP
- Discuss options

**First Trimester Combined Screening (FTS)**

**First trimester:** 11 – 13+ 6/7 weeks
- NT measurement then MS:PAPP-A, fβhCG

### SCREEN POSITIVE
- Discuss options
- Offer referral to genetic services

### SCREEN NEGATIVE
- Offer CVS 11-13 weeks
- Offer amniocentesis 15-22 weeks

### Abnormal result
- Most results normal
- Discuss options

### SCREEN POSITIVE: Chromosome problem
- Offer amniocentesis 15 – 22 weeks
- Most results normal
- Discuss options

**Maternal Serum Triple and Quadruple Screening**

**Second trimester:** 15 – 20+ 6/7 weeks
- **Triple screening:** MS:AFP, uE3, hCG
- **Quadruple screening:** MS:AFP, uE3, hCG, DIA

### SCREEN POSITIVE
- Discuss options
- Offer referral to genetic services

### SCREEN NEGATIVE
- Ultrasound at 18 - 20 weeks
- Abnormal result
  - Offer ultrasound 15 – 20 weeks
  - Most results normal
- Discuss options

### SCREEN POSITIVE: NTD
- Offer amniocentesis 15 – 20 weeks and/or amniocentesis
- Most results normal
- Discuss options

### Abnormal result
- Most results are normal
- Risk of pregnancy complications with a high MS-AFP
- Discuss options

**Abbreviation Key**

- **AFP:** Alpha-FetoProtein
- **DIA:** Dimeric Inhibin-A
- **DR:** Detection Rate
- fβhCG: free-beta subunit of human Chorionic Gonadotropin
- **FPR:** False Positive Rate
- **hCG:** human Chorionic Gonadotropin
- **MS:** Maternal Serum
- **NT:** Nuchal Translucency measured by ultrasound
- **NTD:** Neural Tube Defects
- **PAPP-A:** Pregnancy-Associated Plasma Protein A
- **UE3:** unconjugated Estriol

*All pregnancies have a 2-3% risk for any birth defect; which may or may not be detected by prenatal screening.*
Prenatal Diagnostic Testing:
Currently, pregnant women are eligible for amniocentesis or CVS if they are ≥ 35 years, have a positive prenatal screening test, family history of genetic disease or certain ultrasound findings.

<table>
<thead>
<tr>
<th>Amniocentesis</th>
<th>CVS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Perfomed</td>
<td>15 -17 wks (ideal)</td>
</tr>
<tr>
<td></td>
<td>- but available up to 22 wks¹</td>
</tr>
<tr>
<td>Sample</td>
<td>Amniotic fluid</td>
</tr>
<tr>
<td>Results available</td>
<td>2 - 3 wks</td>
</tr>
<tr>
<td>Miscarriage rate</td>
<td>0.01 - 0.5%³</td>
</tr>
<tr>
<td>Advantage</td>
<td>- Accurate</td>
</tr>
<tr>
<td></td>
<td>- Widely available</td>
</tr>
<tr>
<td></td>
<td>- Tests for NTDs</td>
</tr>
<tr>
<td>Disadvantage</td>
<td>2nd trimester test</td>
</tr>
<tr>
<td></td>
<td>- later results</td>
</tr>
<tr>
<td></td>
<td></td>
</tr>
</tbody>
</table>

¹ Amniocentesis may be available later than 22 weeks in certain circumstances. ² The timing of CVS may vary between centres. ³ Recent studies suggest that miscarriage rate is lower than 1 in 200 (0.5%).

Resources & Links
Mount Sinai Hospital Family Medicine Genetics: http://www.mtsinai.on.ca/FamMedGen/Default.htm
Genetics Education Project website, downloadable version of this Guide available and other genetics resources for your practice.

Canadian Association of Genetic Counsellors: http://www.cage-accg.ca
Canadian Genetics Clinics list of contact and referral information.

Centre for Effective Practice: http://www.effectivepractice.org/
Primary care resources for your practice.

An excellent genetics educational site.

March of Dimes: http://marchofdimes.com/
Excellent source of patient information for questions during pregnancy.

Motherisk: http://www.motherisk.org/ or 416-813-6780
A teratogen information service.

Ontario Provincial Maternal Serum Screening Program: http://www.lhsc.on.ca/programs/rmgc/mss/
Patient information on IPS, FTS and second trimester MSS.

The Society of Obstetricians and Gynaecologists of Canada: http://www.sogc.org/guidelines/index_casp
Practice guidelines.

<table>
<thead>
<tr>
<th>Authors:</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dr. June Carroll, family physician</td>
</tr>
<tr>
<td>Dr. Judith Allanson, geneticist</td>
</tr>
<tr>
<td>Dr. Mary Jane Esplen, nurse</td>
</tr>
<tr>
<td>Dr. Gail Graham, geneticist</td>
</tr>
<tr>
<td>Dr. Wendy Meschino, geneticist</td>
</tr>
<tr>
<td>Ms. Joanne Miyazaki, laboratory services</td>
</tr>
<tr>
<td>Ms. Linda Spooner, nurse</td>
</tr>
<tr>
<td>Dr. Sherry Taylor, molecular geneticist</td>
</tr>
<tr>
<td>Ms. Andrea Rideout, genetic counsellor</td>
</tr>
<tr>
<td>Dr. Sean Blaine, family physician</td>
</tr>
<tr>
<td>Dr. Sandra Farrell, geneticist</td>
</tr>
<tr>
<td>Dr. Jennifer MacKenzie, geneticist</td>
</tr>
<tr>
<td>Dr. Fiona Miller, epidemiologist</td>
</tr>
<tr>
<td>Ms. Cheryl Shuman, genetic counsellor</td>
</tr>
<tr>
<td>Dr. Anne Summers, geneticist</td>
</tr>
<tr>
<td>Dr. Brenda Wilson, epidemiologist</td>
</tr>
</tbody>
</table>

© 2007