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:

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.

The Genetics Education Project

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 about 1 in 1000, 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 Canada is about 1 in 2,000, does not vary with maternal age.

Prenatal Screening Tests for the Detection of Down Syndrome

Test	Down syndrome Detection Rate (DR)	Down syndrome False Positive Rate (FPR)	Comments
IF PATIENT PRESENTS BEFORE 14 WEEKS			
Integrated Prenatal Screening (IPS) *First Trimester (11-13+6/7 wks)* • ↑NT – by certified sonographer • MS: ↓PAPP-A *Second Trimester (15–20+6/7 wks)* • MS: ↓AFP, ↑hCG, ↓uE3	85-90%	2-4%[1]	• Results available in 2nd trimester • Amniocentesis for diagnostic testing
Serum Integrated Prenatal Screening (SIPS) *First Trimester (11-13+6/7 wks)* • MS: ↓PAPP-A *Second Trimester (15–20+6/7 wks)* • MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA	80-90%	2-7%[1,2]	• Results available in 2nd trimester • Amniocentesis for diagnostic testing • Is available in most places where NT ultrasound is not available
First Trimester Combined Screening (FTS) *First Trimester (11-13+6/7 wks)* • ↑NT – by certified sonographer • MS: ↓PAPP-A, ↑*f*βhCG	78-85%	3-9%[1,2,3]	• Results available in 1st trimester, earliest results • CVS for diagnostic testing • **Does not screen for NTDs***
IF PATIENT PRESENTS AFTER 14 WEEKS			
Maternal Serum Screen (Quadruple Screening) *Second Trimester (15–20+6/7 wks)* • MS: ↓AFP, ↑hCG, ↓uE3, ↑DIA	75-85%	5-10%[1,2,3]	• Results available in 2nd trimester • Amniocentesis for diagnostic testing
Maternal Serum Screen (Triple Screening -MSS) *Second Trimester (15–20+6/7 wks)* • MS: ↓AFP, ↑hCG, ↓uE3	71%	7%[4]	• Results available in 2nd trimester • Amniocentesis for diagnostic testing

Abbreviation Key:

AFP:	Alpha-FetoProtein
DIA:	Dimeric Inhibin-A
*f*βhCG:	free-beta subunit of human Chorionic Gonadotropin
hCG:	human Chorionic Gonadotropin
MS:	Maternal Serum
NT:	Nuchal Translucency measured by ultrasound
NTD:	Neural Tube Defect
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.

Testing for Open Neural Tube Defects and Trisomy 18		
	Open Neural Tube Defects	**Trisomy 18**
MS	↑AFP	↑NT, ↓PAPP, ↓*f*βhCG, ↓AFP, ↓hCG, ↓uE3, ↓DIA
DR	80% for each test except FTS which does not screen for NTDs[5]	Slightly lower than the DR for Down syndrome for each test
FPR	Usually 5% or less for all tests except FTS[5]	Lower than the FPR for Down syndrome for each test. Usually 1% or less

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

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

Adapted from:

1. Wald NJ, *et al.* First and second trimester antenatal screening for Down's syndrome: the results of the Serum, Urine and Ultrasound Screening Study (SURUSS). *J Med Screen* 2003; 10:56-104.
2. Malone FD, *et al.* First- and Second-Trimester Evaluation of Risk (FASTER) Research Consortium. First-trimester or second-trimester screening, or both, for Down's syndrome. *N Engl J Med. 2005; 353:2001-11.*
3. Wapner R, *et al.* First trimester screening for trisomies 21 and 18. *N Engl J Med* 2003; 349:1405-1413.
4. Summers AS, *et al.* Maternal serum screening in Ontario using the triple marker test. *J Med Screen* 2003; 10:107-111.
5. American College of Obstetricians and Gynecologists. Clinical Management Guidelines for obstetricians-gynecologists. ACOG Practice Bulletin No. 44, *Obstet Gynecol* 2003; 102:203-211.

Algorithms

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 POSITIVE: chromosome problem

↓

Offer amniocentesis 15 - 22 weeks

↓

Abnormal result → Discuss options

Most results normal

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 if abnormal

SCREEN NEGATIVE

↓

Ultrasound at 18 - 20 weeks

First Trimester Combined Screening (FTS)

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

↓

SCREEN POSITIVE

↓

Discuss options
Offer referral to genetic services

↓

Offer CVS 11-13 weeks

Offer amniocentesis 15-22 weeks

↓

Abnormal result → Discuss options

Most results normal →

NTD screening:
MS-AFP 15-20 weeks
Ultrasound 18-20 weeks

SCREEN NEGATIVE

↓

NTD screening:
MS-AFP 15-20 weeks
Ultrasound 18-20 weeks

Abbreviation Key

AFP:	Alpha-FetoProtein
DIA:	Dimeric Inhibin-A
DR:	Detection Rate
*f*βhCG:	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 Defect
PAPP-A:	Pregnancy-Associated Plasma Protein A
uE3:	unconjugated Estriol

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 POSITIVE: Chromosome problem

↓

Offer amniocentesis 15 – 22 weeks

↓

Abnormal result → Discuss options

Most results normal

SCREEN POSITIVE: NTD

↓

Offer ultrasound 15 – 20 weeks and/or amniocentesis

↓

Abnormal result → Discuss options

Most results are normal
Risk of pregnancy complications with a high MS-AFP

SCREEN NEGATIVE

↓

Ultrasound at 18 - 20 weeks

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.

	Amniocentesis	CVS
Performed	15 -17 wks (ideal) - but available up to 22 wks[1]	11 - 13 wks[2]
Sample	Amniotic fluid	Placental villi
Results available	2 - 3 wks	2 - 3 wks
Miscarriage rate	0.01 - 0.5%[3]	1%
Advantage	- Accurate - Widely available - Tests for NTDs	- Accurate - 1st trimester test – earlier results
Disadvantage	2nd trimester test - later results	- Availability varies - Does not test for NTDs - ↑ rate of repeat procedures due to ambiguous results

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/
Genetics Education Project website, downloadable version of this Guide available and other genetics resources for your practice.

Canadian Association of Genetic Counsellors: http://www.cagc-accg.ca/
List of contact and referral information for Canadian genetics clinics.

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

The Genetics Home Reference Your Guide to Understanding Genetic Conditions
http://www.ghr.nlm.nih.gov/
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 Multiple Marker Screening (MMS) 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/
Practice guidelines.

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Risk Of Chromosome Abnormalities In Liveborn Infants at Term

Maternal Age (yrs)	Risk of Down Syndrome	Risk of any Chromosome Abnormalities
20	1/1,650	1/530
21	1/1,650	1/530
22	1/1,430	1/500
23	1/1,430	1/500
24	1/1,250	1/480
25	1/1,250	1/480
26	1/1,175	1/480
27	1/1,110	1/450
28	1/1,050	1/430
29	1/1,000	1/420
30	1/950	1/390
31	1/900	1/390
32	1/770	1/320
33	1/625	1/285
34	1/500	1/240
35	1/385	1/180
36	1/300	1/150
37	1/225	1/125
38	1/175	1/100
39	1/135	1/80
40	1/100	1/65
41	1/80	1/50
42	1/60	1/40
43	1/50	1/30
44	1/40	1/25
45	1/30	1/19
46	1/23	1/15
47	1/18	1/11
48	1/14	1/9
49	1/11	1/7

Adapted from:
Hook EB, Cross PK, Schreinemachers DM. Chromosomal abnormality rates at amniocentesis and in live-born infants. *JAMA* 1983;249:2034-38.
Hook EB. Rates of chromosomal abnormalities at different maternal ages. *Obstet Gynecol* 1981;53:282-85.

This monograph was prepared by members of The Genetics Education Project and the Education Subcommittee of the Ontario Multiple Marker Screening Committee in 2007. Health care providers must use their own clinical judgement in addition to the information presented herein. The authors assume no responsibility or liability resulting from the use of information in this monograph.

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