LEARNING OBJECTIVES

- To be able to assess maternal risk factors for childbearing
- To be able to assess genetic risk factors in the family history
- To know when to refer a patient for genetic counselling
- To understand the difference between Prenatal Diagnosis versus Screening, and what options are currently available for patients
**Maternal Assessment / Risk Factors**

- **Medical history:** maternal or paternal genetic disorder or birth defect may warrant Genetics consultation regarding recurrence risk (e.g., patient had cleft lip and palate).

- **Pregnancy history:** recurrent miscarriages is an indication for parental karyotyping; previous child with congenital anomalies warrants discussion of recurrence risks.

- **Physical examination:** previously known or unknown symptoms of a possible genetic disorder should be assessed (e.g., cafe-au-lait spots, ear pits, neurological symptoms).
Family History

- Known genetic disorder in the family
- Birth defects in the family
- Ethnic background
- Other issues
Genetic disorder in the family

Patient has a previous child or family history of a known genetic disorder

- may increase the risk for the patient to have a child with the same condition, or for the patient to develop the condition herself

- level of risk depends on the pattern of inheritance and degree of relationship

Examples: cystic fibrosis, hemochromatosis, muscular dystrophy, Huntington disease, fragile X syndrome, Down syndrome
Birth defects in the family

Patient has a previous child or family history of congenital anomalies

- may increase the risk for a patient to have a similarly affected child (or a second affected child)
- level of risk depends on etiology and degree of relationship

Examples: child with spina bifida
           sib with heart defect
           cousin had “birth defects”

Remember that patients don’t always use the correct terminology and clarification of the history may be needed
**Ethnicity**

- Mediterranean, Asian, Middle Eastern, African: risk for hemoglobinopathy (thalassemia, sickle cell disease)
- Ashkenazi Jewish: risk for Tay Sachs disease; other “Jewish genetic diseases” not currently screened in Canada
Other issues in the history

- maternal or paternal psychiatric disorder
- developmental delay / mental retardation
- familial cancer

(level of risk depends on diagnosis, degree of relationship, and numbers of affected relatives)

- consanguinity (increases risk of multifactorial and / or autosomal recessive disorders)

Consider referral for genetic counselling
When to refer?

Prior to pregnancy whenever possible

Significant family history of many disorders (eg some cancers and many other adult disorders) can and should be assessed and counselled separately from pregnancy issues.

Don’t wait until the patient is pregnant to ask questions about something which has always been in the family history!
Overview of Prenatal Diagnosis

- Diagnostic Test versus Screening Test
- Indications for Prenatal Diagnosis
- Brief Overview of Amniocentesis and CVS
Diagnostic Test

- Identifies individuals who have a disease or condition
- Genetic amniocentesis or CVS
- Ultrasound can be diagnostic or can be used as a screening tool
Screening Test

- Designed to identify patients at increased risk for a certain disease
- When a screening test (e.g., MSS) is positive, then a diagnostic test (e.g., amniocentesis) is required to determine if there really is an abnormality
**Indications for Amniocentesis or CVS**

- Maternal age 35 or older (32 with twins)
- Previous chromosomal abnormality
- Carriers of a known chromosomal disorder
- Positive maternal serum screen (MSS)
- Carriers of X-linked disorders
- Carriers of a single gene disorder
- Abnormal ultrasound findings
**FAST FACTS: AMNIOCENTESIS**

- Procedure done at >15 weeks of gestation
- Research study evaluating weeks 13 - 14
- Fetal karyotyping routine; molecular or biochemical testing available for a wide variety of conditions if indicated by the history
- AFP testing for spina bifida
- Risk of miscarriage 0.5% (1/200)
FAST FACTS: CVS

- Transabdominal or transcervical
- Procedure done at 10 - 12 weeks of gestation
- Research study evaluating weeks 13 - 14
- Fetal karyotyping routine; molecular testing available for a growing number of conditions if indicated by the history
- MSAFP at 15 weeks for spina bifida
- Risk of miscarriage 1-2% (1/100 - 1/50)
Ultrasound In Prenatal Diagnosis

- **Dating ultrasound**: confirms viability, number of fetuses, and gestational age.
- **Prenatal diagnosis procedure ultrasound**: document gestational age and the position of the fetus for obtaining samples for testing.
- **Full obstetrical ultrasound**: “routine” mid-trimester ultrasound for fetal anatomy survey (18-20 weeks); SOGC guidelines recommends for all pregnancies.
- **Anatomical profile ultrasound**: targeted ultrasound for high risk pregnancies (such as an abnormality identified or suspected, or a family history of birth defects).
do not apply to

“investigation of suspected congenital anomalies”
Prior to 18 weeks of gestation, ultrasound should be offered for specific indication or as an aid for diagnostic procedure.

Prior to 18 weeks of gestation, discuss and offer the option of a complete obstetrical ultrasound examination.

Patient accepts ultrasound? Yes  No

If no, ultrasound should only be offered for specific medical indications.
SOGC Guidelines - algorithm B

Ultrasound at 18-19 weeks

Normal fetus?

**YES**
No further ultrasound unless for specific medical indications.
*(was the ultrasound complete?)*

**NO**
Counsel patient and consider prompt referral to a tertiary care centre for consultation. Counsel patient about possible false positive findings.
INDICATIONS FOR
DETAILED ULTRASOUND

Risk factors based on history:

- Previous pregnancy or child with a birth defect *detectable by ultrasound*
- Family history of a birth defect *detectable by ultrasound*
INDICATIONS FOR DETAILED ULTRASOUND

Risk factors in the current pregnancy:

- MSS positive for open spina bifida
- Exposure in pregnancy (anticonvulsant drugs, chicken pox)
- Ultrasound abnormalities
- Ultrasound “soft signs”
Ultrasound markers ("soft signs") to adjust the risk of Down syndrome

- distinguish between ultrasound "markers" and ultrasound "abnormalities"

- markers: short femur, nuchal fold, borderline hydronephrosis, borderline ventriculomegaly etc

- abnormalities: heart defect, cleft lip, true ventriculomegaly or hydronephrosis

The use of ultrasound markers to screen for Down syndrome is controversial; 50 to 70% of fetuses with DS have no ultrasound findings.
Ultrasound markers to adjust the risk of Down syndrome

- Risk of chromosome abnormality may be inversely related to the severity of the (apparently isolated) anomaly

  eg. mild ventriculomegaly is more likely chromosomal than is severe ventriculomegaly
Examples of Ultrasound “Soft signs”

- choroid plexus cysts
- ventriculomegaly
- cleft lip / palate
- thickened nuchal fold
- nuchal translucency
- echogenic bowel
- dilated renal pelves

- echogenic chordae
- short femur
- clinodactyly
- ascites / hydrops
- 2 vessel cord
“Availability of non-invasive screening (maternal serum screening, ultrasound aneuploidy markers) is increasing but cannot be considered a standard of care in Canada at present”
MATERNAL SERUM SCREENING

- Screens for: trisomy 21
  - trisomy 18
  - open spina bifida

- Triple screen: AFP
  - uE3
  - HCG
  - maternal age
  - gestational age
MATERNAL SERUM SCREENING

- should be offered to all women
- designed for women under 35, can be used for any age
- best done 16-18 weeks of gestation, can be interpreted from 15w0d to 20w6d
date of birth (*a priori* age related risk for trisomy21)

gestation (by LMP or by ultrasound)

maternal weight (marker levels decrease with increasing maternal weight)

diabetic status (maternal diabetes increases risk for neural tube defects; MSAFP is lower in diabetic women)

race (Blacks have higher MSAFP and lower risk of spina bifida)

multiple gestation (AFP increases with numbers of babies; screening for Down syndrome not available for multiple pregnancy)
MSS positive for Down syndrome

- Risk of DS is $\geq$ risk of 35 yr old at EDC (cut-off in Ontario is risk of 1/385 or 0.3% risk)
- Screen positive results have a numerical risk assigned per patient (i.e., risk of Down syndrome is 1/300; 1/85; 1/20); patient should be counselled accordingly
- Greater than 98% of “positive results” are false positive
What to do when the MSS is positive for Down syndrome?

- Validate the result: dating ultrasound to confirm gestational age (dating discrepancy of >10 days will require recalculation by the laboratory)
- Discuss and offer amniocentesis
- Discuss and offer level II ultrasound (efficacy of ultrasound to screen for signs of Down syndrome is controversial)
Example 1: Initial positive for Down syndrome

Maternal Age at EDD: 30.8 years
Gestational Age: 17w6d by LMP

AFP = 0.99 MoM
uE3 = 0.50 MoM
hCG = 2.11 MoM

Risk Assessment:
Open Spina Bifida = 1:13800
Down syndrome = 1:165

INTERPRETATION: SCREEN POSITIVE
Follow up for risk of Down syndrome is suggested
Example 1: Initial positive converts to negative with ultrasound dating

Maternal Age at EDD: 30.8 years
Gestational Age: 16w0d by BPD

AFP = 1.25 MoM
uE3 = 0.75 MoM
hCG = 1.49 MoM

Risk Assessment:
Open Spina Bifida = 1:5860
Down syndrome = 1:1160

INTERPRETATION: SCREEN NEGATIVE
Example 2: Down syndrome

Maternal Age at EDD: 34.5 years
Gestational Age: 16w5d by ultrasound

- AFP = 0.69 MoM
- uE3 = 0.83 MoM
- hCG = 1.31 MoM

Risk Assessment:

Open Spina Bifida = 1:27300
Down syndrome = 1:344

INTERPRETATION: SCREEN POSITIVE

Follow up for risk of Down syndrome is suggested
Example 2: time sequence

- Blood drawn [May15th]  (16w5d by ultrasound)
- Risk of Down syndrome by MSS = 1:344
- Verbal report to physician [May18th]  (17w1d)
- Request for consultation [May23rd]  (17w6d)
- PND clinic consultation [May26th]  (18w2d)
- Amniocentesis [May26th]  (18w2d)

- Karyotype: 47, XX, +21  [06/08] (20w1d)

Note the time sequence to identify a “true positive”
MSS positive: Open Spina Bifida

- Maternal serum alpha-fetoprotein (AFP)
- “MSS Positive for OSB”: \( \text{AFP} \geq 2.20 \text{ MoM} \)
- An open neural tube defect will increase AFP in the amniotic fluid and maternal serum
Factors affecting AFP levels:

- number of babies (higher AFP in multiple pregnancy)
- gestational age (AFP increases with week of gestation)
- race (Blacks have higher AFP)
- IDDM (lower AFP in diabetic women)
- maternal weight (higher AFP with increasing weight)
What to do when the MSS is positive for Spina Bifida?

- Validate the result: dating ultrasound to confirm viability, gestational age and number of babies (dating discrepancy of >10 days will require recalculation by the laboratory)

- Discuss and offer: detailed ultrasound (the majority of fetal neural tube defects are identifiable by good quality ultrasound)
Example 1: MSS Positive for spina bifida due to fetal demise

Maternal Age at EDD: 27.3 years
Gestational Age: 18w2d by LMP

AFP = 11.58 MoM
uE3 = <0.07 MoM
hCG = 2.45 MoM

Risk Assessment:
Open Spina Bifida = 1:5
Down syndrome = 1:553

INTERPRETATION: SCREEN POSITIVE
Follow up for risk of open spina bifida is suggested

Ultrasound:
Fetal demise
Example 2: *spina bifida*

Maternal Age at EDD: 20.6 years  
Gestational Age:  18w0d by ultrasound  
AFP = 3.93 MoM  
uE3 = 0.82 MoM  
hCG = 0.59 MoM

**Risk Assessment:**

*Open Spina Bifida = 1:18*  
*Down syndrome = 1:50000*

**INTERPRETATION:** SCREEN POSITIVE  
Follow up for risk of *open spina bifida* is suggested
Example 2: spina bifida cont’d

- Blood drawn at 18w0d by ultrasound
- Risk of spina bifida 1:18
- 18 week community ultrasound: lemon sign, lumbar and sacral spine not well visualized
- Anatomical ultrasound at HHS: distal spinal defect, arnold chiari, lemon sign
- Requested and booked pregnancy termination

Admitted for induction of labour; reversed decision; continued pregnancy
**Example 3: Spina bifida**

Maternal Age at EDD: 20.7 years
Gestational Age: 16w4d by ultrasound

- AFP = 3.47 MoM
- uE3 = 0.88 MoM
- hCG = 0.95 MoM

**Risk Assessment:**
- Open Spina Bifida = 1:39
- Down syndrome = 1:31800

**Ultrasound:** normal

**INTERPRETATION:** SCREEN POSITIVE

Follow up for risk of open spina bifida is suggested
Unexplained Elevations of MSAFP

- Increased risk for placental complications in the third trimester:
  - Fetal growth failure
  - Preterm delivery
  - Maternal hypertension
MSS positive for trisomy 18

- Low AFP, low uE3, low HCG
- Likelihood of incorrect dates or non-viable pregnancy
What to do next?

- Validate the result: dating ultrasound
- Discuss and offer amniocentesis
- Discuss and offer level II ultrasound
  (>80% of fetuses with trisomy 18 will have structural abnormalities identifiable by ultrasound)
Example 1: trisomy 18 (false positive)

Maternal Age at EDD: 31.1 years
Gestational Age: 15w6d by ultrasound

AFP = 0.75 MoM
uE3 = 0.54 MoM
hCG = 0.39 MoM

Risk Assessment:
Open Spina Bifida = 1:13300
Down syndrome = 1:5700
Trisomy 18 = positive (no number given)

INTERPRETATION: SCREEN POSITIVE
Follow up for risk of TRISOMY 18 is suggested

amniocentesis: 46, XX
Example 2: trisomy 18

Maternal Age at EDD: 33.6 years
Gestational Age: 16w1d by LMP

AFP = 0.41 MoM
uE3 = 0.20 MoM
hCG = 0.18 MoM

Risk Assessment:

Open Spina Bifida = 1:27300
Down syndrome = 1:2820
Trisomy 18 = GREATER THAN 1:8

INTERPRETATION: SCREEN POSITIVE

Follow up for risk of TRISOMY 18 is suggested
Example 2: trisomy 18 cont’d

- Blood drawn at 16w1d by LMP
- Risk of trisomy 18 greater than 1:8
- 16 week community ultrasound normal and consistent with dates
- Anatomical ultrasound at HHS: bilateral CPC, borderline ventriculomegaly, possible sacral agenesis
- Amniocentesis at 19w2d

**Karyotype: 47, XY, +18 (21w4d)**

*note time sequence for true positive*
Benefits of MSS

- Better screening test than maternal age alone
- Provides reassurance if negative
- Provides options for further testing if indicated
- May avoid invasive testing for women over 35
Problems with MSS

- Significant number of false positives
- Anxiety of a “positive” result (especially when pre-testing information not provided or not understood and how the patient perceives the MSS result)
- Stress of decision making about diagnostic testing and associated risks
- Negative result doesn’t eliminate the risk (validate negative results using ultrasound)
MSS: practical points

- Should be offered to all women
- Gestational time constraints:
  - options to stop pregnancy to 22 wks
  - routine chromosome analysis 2-3 week
- In Ontario MSS program, all positives are reported by phone
- Important to check gestational dating even if negative
What’s new in Prenatal Screening?

- Nuchal translucency screening
- First trimester serum screening
- Integrated prenatal screening
Nuchal Translucency Screening

- Ultrasound at 10 – 14 weeks post LMP
- Measured by skilled ultrasonographers
- Interpreted by clinicians in conjunction with *a priori* risk (usually age related risk of Down syndrome; can incorporate history of previous baby with trisomy)
- Down syndrome detection rate 80%
Nuchal Translucency

Normal

Abnormal
First Trimester Screening

- Done between 11 - 14 weeks of gestation
- Nuchal translucency ultrasound
- 2 serum markers: PAPP-A, free beta hCG
- Age-related *a priori* risk
- Revised risk for trisomy 21 and trisomy 18
- Down syndrome detection rate 90%

*Not currently standard of care in Ontario and not widely available at the present time (dec 2001)*
IPS
Integrated Prenatal Screening

Part One: 10-14 weeks
- NT ultrasound
- Serum PAPP-A

Part Two: 15-18 weeks
- MSS

- Results reported only after Part Two
- Decreased false positives compared to MSS alone

Pilot project currently underway at two centres in Ontario (2001)
**Patient Autonomy**

**and**

**Informed Decision-Making**

- Provide non biased information
- Back up with written information
- Provide non directive counselling