Prenatal Screening and Diagnosis in Ontario
Past, Present and Future

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DISCLOSURES

I have no conflict of interest and nothing to disclose

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Birth Defects

World Wide

- There are 139 million births/year
- 7.9 million babies are born with birth defects (6%)
- 3.3 Million die under age 5
- 3.2 Million are disabled for life

Ontario

- 140,000 births/year in Ontario
- Infant mortality rate 4.6/1000
- Number of babies born with Down syndrome/year ??
- BORN - **Ontario's** pregnancy, birth and childhood registry and network

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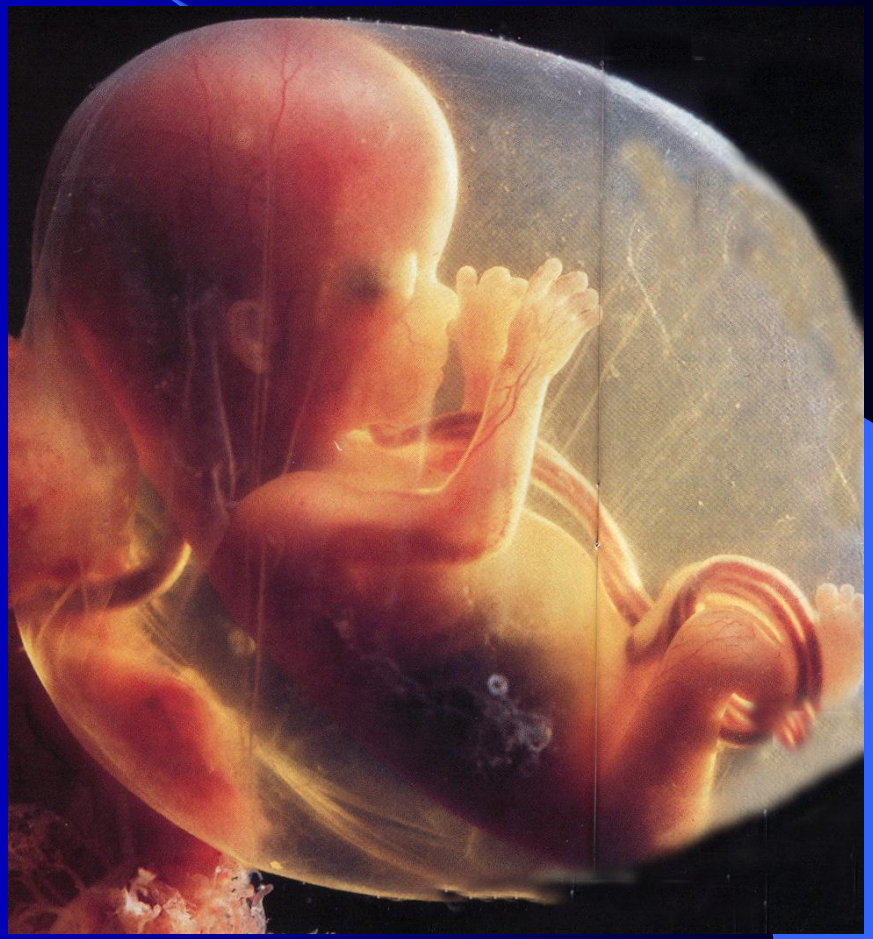
Prenatal Diagnosis

- Prevention
- Diagnosis
- Treatment



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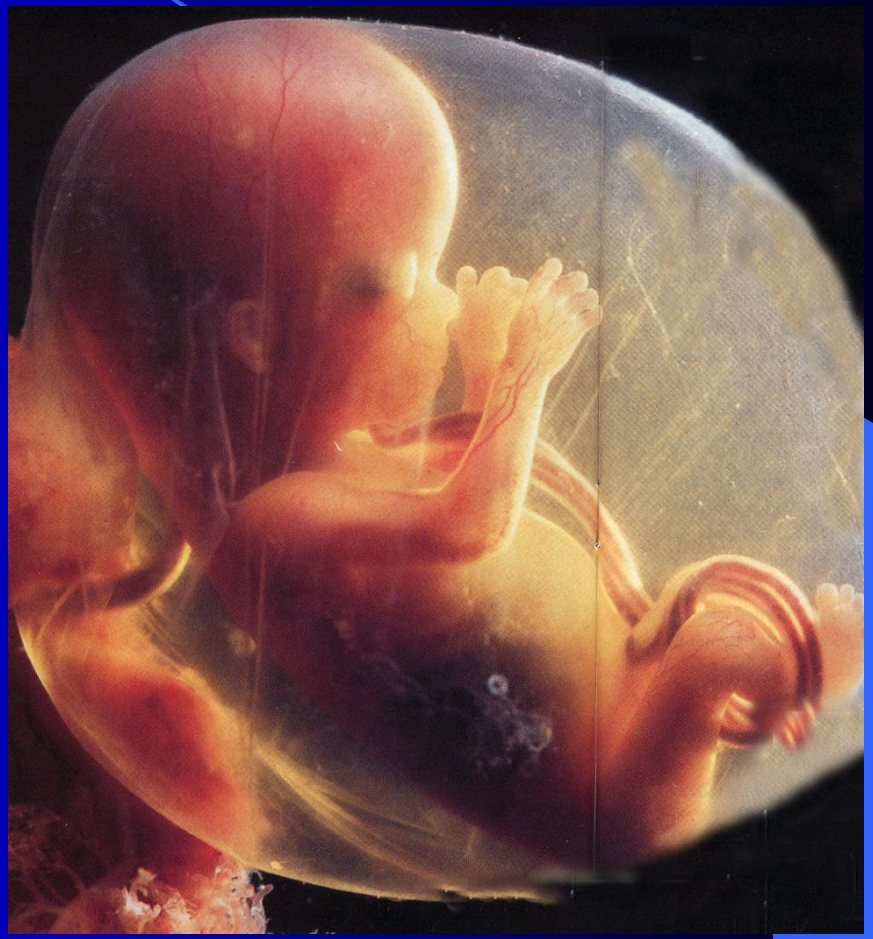
Prenatal Diagnosis

Prevention

Diagnosis

- **Treatment**



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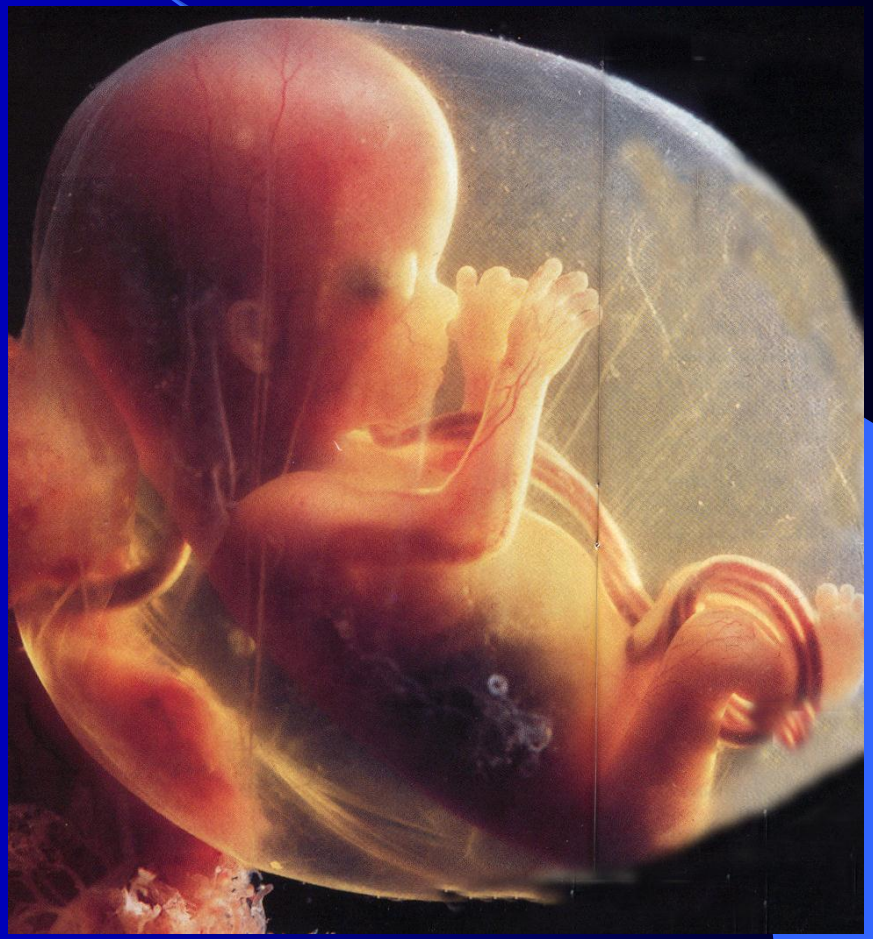
Prenatal Diagnosis

Prevention

- Primary prevention
- Secondary “prevention”



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Primary Prevention

"Only through the practice of preventive medicine will we keep the costs from becoming so excessive that the public will decide that Medicare is not in the best interests of the people of the country."

Tommy Douglas (founding father of the Canadian Medicare)

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Primary Prevention Objective

To stop inherited and non-inherited congenital disorders from arising in the first place by identifying and avoiding causative factors

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Primary Prevention - Examples

- **Prevention of Rhesus hemolytic disease of the newborn by injecting Rhesus negative mothers with anti-D immunoglobulin during pregnancy and after delivery.**
- **Immunization of young girls against rubella infection**
- **Folic acid supplementation to prevent neural tube defects, and cardiac and renal abnormalities**

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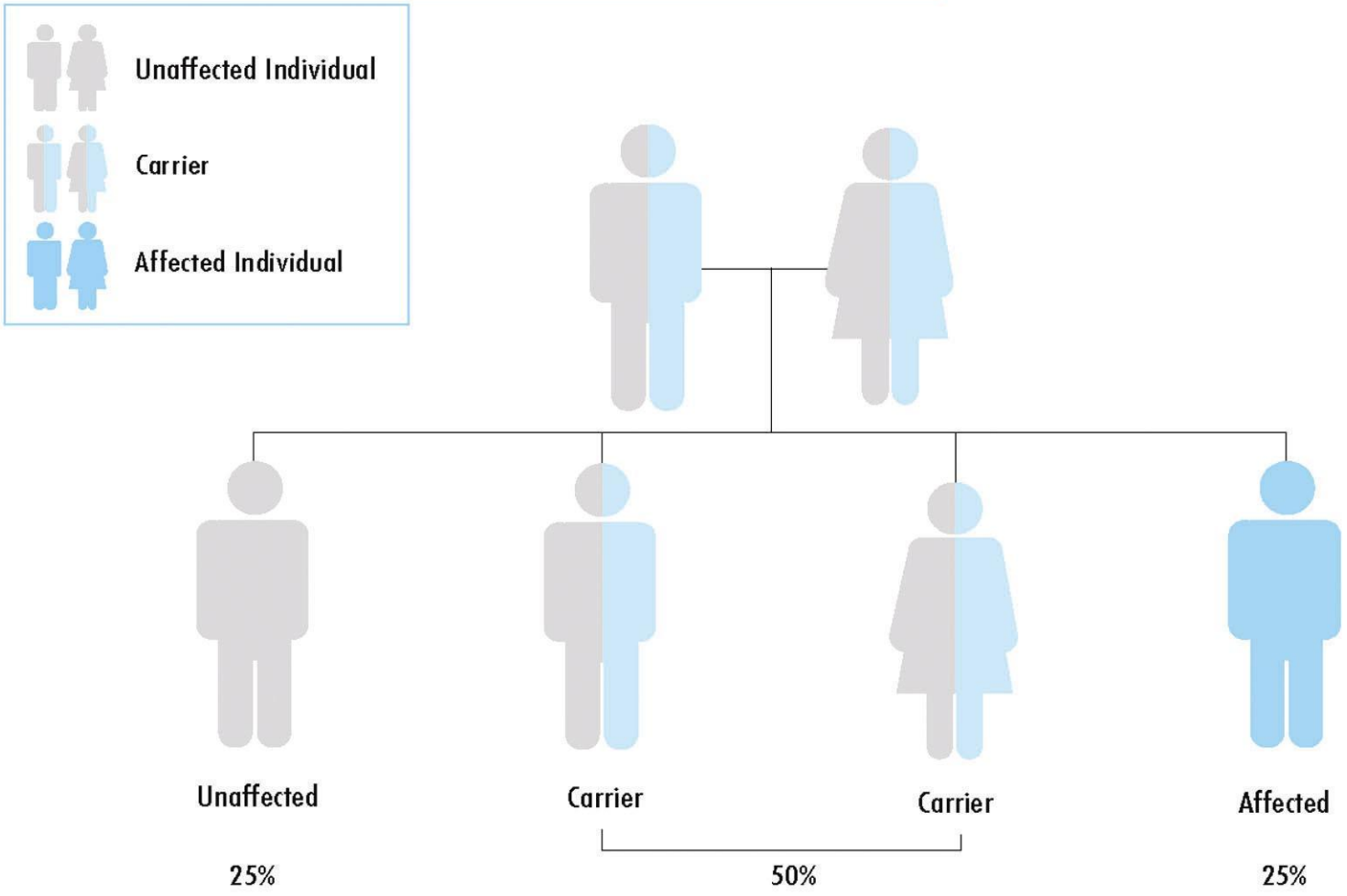
Autosomal Recessive Segregation, Both Parents Carriers



Genetic Screening
Ethnic Background

- Screening of couples of Black, Asian and Mediterranean descent for hemoglobinopathies and thalassemia

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Genetic Screening for the most common mutations causing the following conditions in the Ashkenazi Jewish Population

- Bloom syndrome
- Canavan disease
- Familial dysautonomia
- Fanconi anemia, type C
- Mucolipidosis, type IV
- Niemann-Pick disease, type A and B
- Tay-Sachs disease

Table 1. Recessive Genetic Diseases Frequent Among Individuals of Eastern European Jewish Descent Amenable to Carrier Screening

Disorder	Disease Incidence	Carrier Frequency*	Detection Rate*
Tay–Sachs disease	1/3,000	1/30	98% by hexosaminidase A test, 94% by DNA-based test
Canavan disease	1/6,400	1/40	98%
Cystic fibrosis	1/2,500–3,000	1/29	97%
Familial dysautonomia	1/3,600	1/32	99%
Fanconi anemia group C	1/32,000	1/89	99%
Niemann-Pick disease type A	1/32,000	1/90	95%
Mucolipidosis IV	1/62,500	1/127	95%
Bloom syndrome	1/40,000	1/100	95–97%
Gaucher disease	1/900	1/15	95%

*Non-Jewish carrier frequency and detection rates are unknown except for Tay–Sachs disease and cystic fibrosis. Carrier frequency for Tay–Sachs disease is 1 in 30 if French Canadian or Cajun ancestry and 1 in 300 for others with a 99% carrier detection rate by hexosaminidase A test.

Modified from March of Dimes. Genetic screening pocket facts. White Plains (NY): MOD; 2001.

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My Recommendation to the Government Expanding the Prenatal/preconception Screen

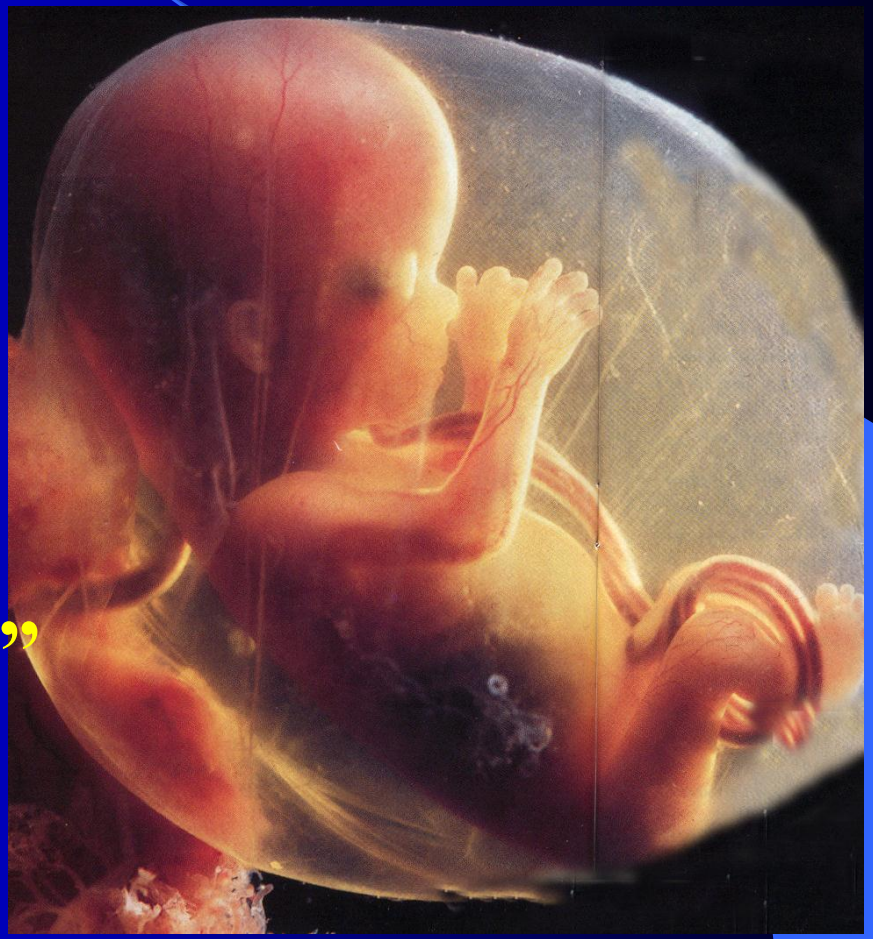
Condition	Carrier rate
CF	1/25
SMA	1/38
Fragile X	1:260 female

- Provide free of charge PGD to couples who are carriers of an AR or X-linked conditions

Prenatal Diagnosis

Prevention

- Primary prevention
- Secondary "prevention"



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Secondary Screening "Prevention"

- **Screening for** Down syndrome and other fetal chromosome abnormalities
- **Screening for** Open Neural Tube Defects and Abdominal wall defect
- **Screening for** structural fetal abnormalities

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Secondary "Prevention"

- **Screening for** Down syndrome and other fetal chromosome abnormalities
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- **Screening for** structural fetal abnormalities

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History of Prenatal Screening and Biomarkers

1960's - Maternal age associated with risk for having a baby with Down syndrome

1972 - **HIGH** AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - **LOW** AFP = T18 + Down syndrome (Merkatz et al., AJOG)

1990's - Multiple biomarkers (AFP, uE3, hCG, DIA…)

- Ultrasound
- NT
- (NB, DV, TR, fronto-maxillary angle…)

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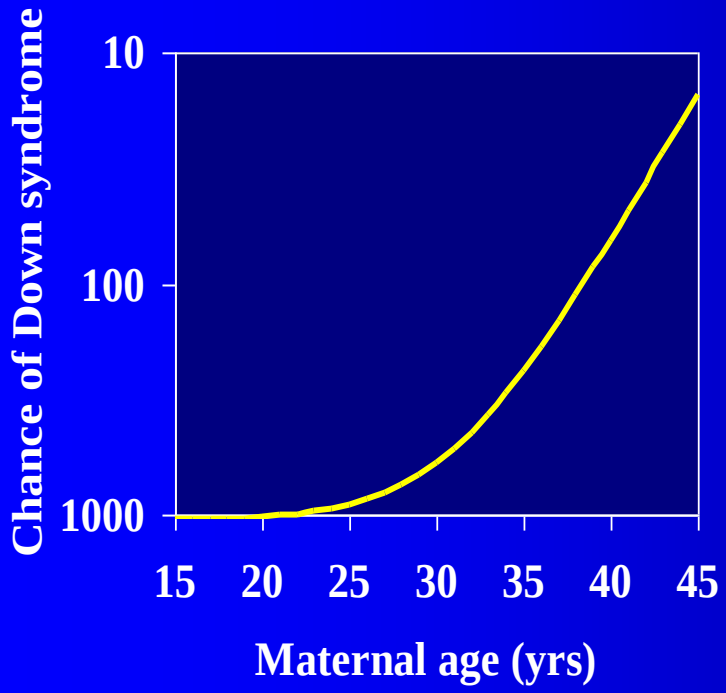
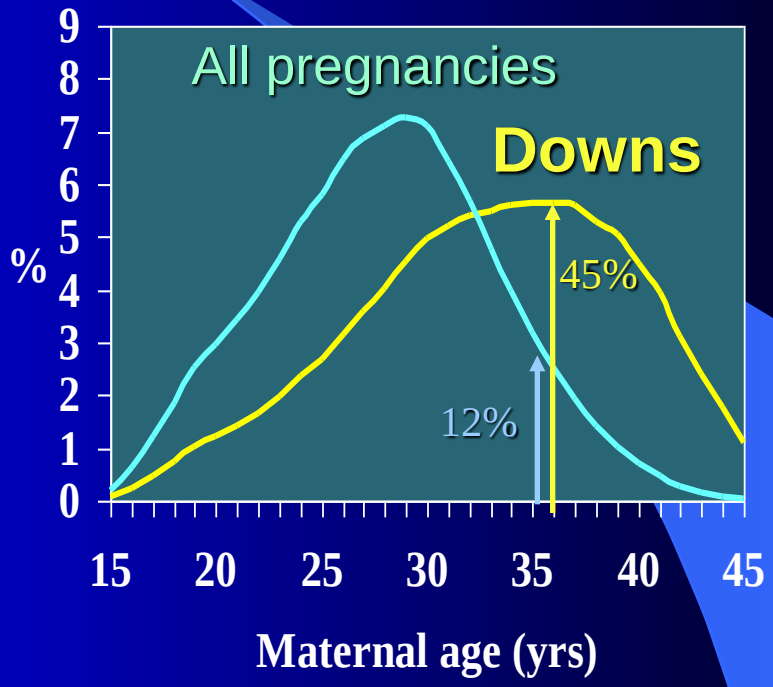
Maternal age & Trisomy 21





Odds of affected pregnancy in women age ≥35 years:

One live birth per 155 pregnancies

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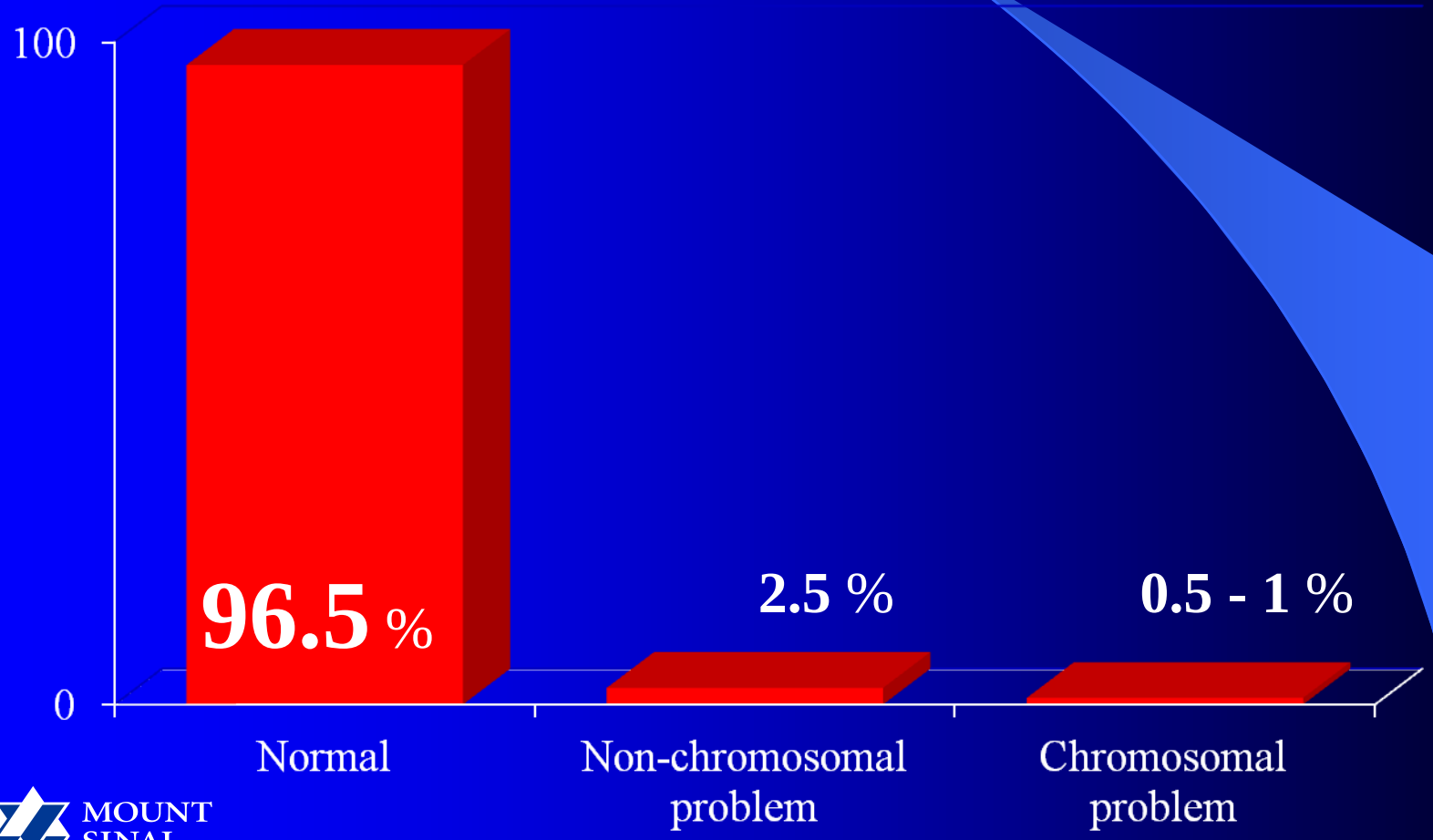
Birth outcomes
Maternal ages 35-40 years



Maternal age, fertility and Spontaneous abortions

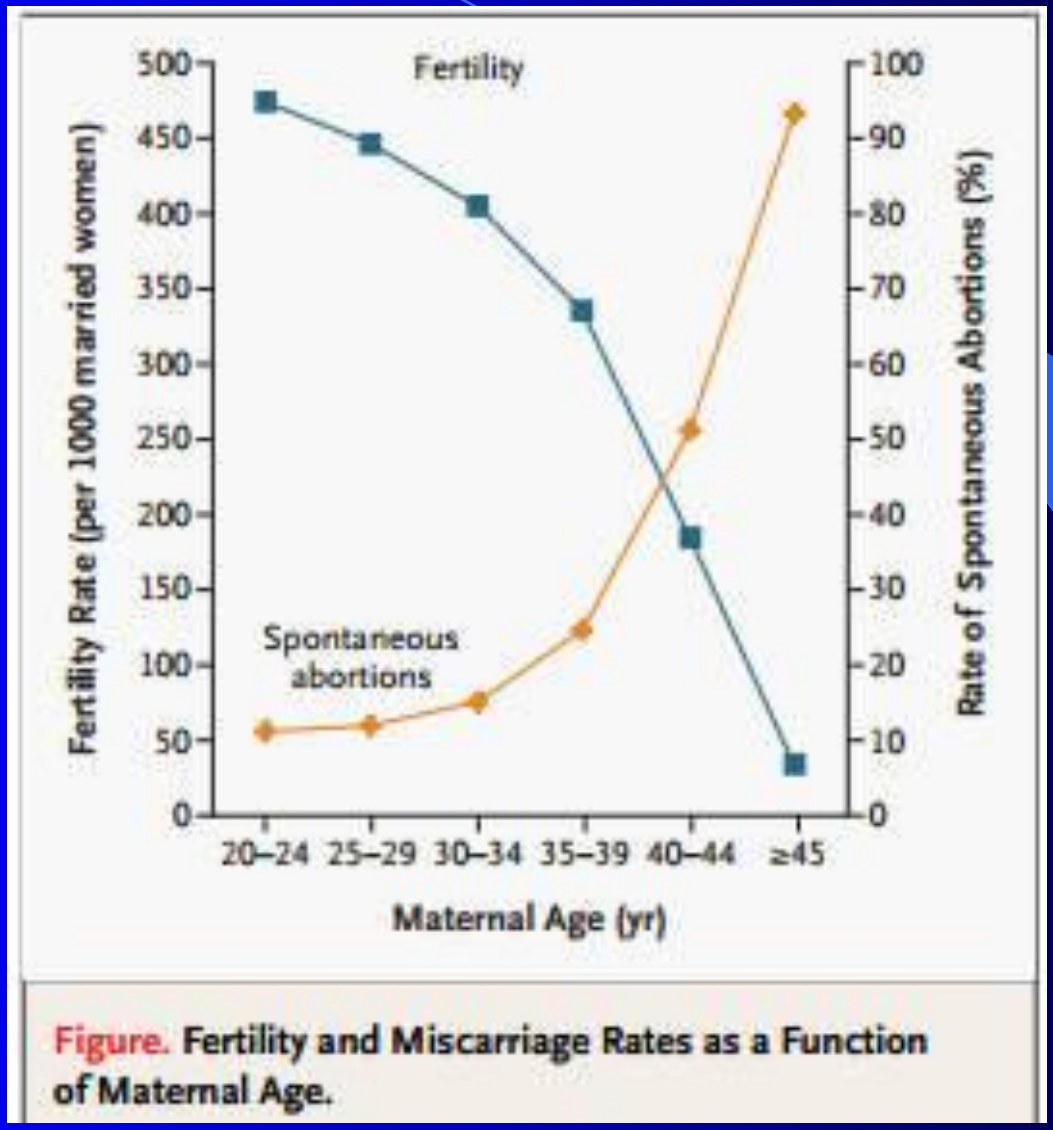


Figure. Fertility and Miscarriage Rates as a Function of Maternal Age.

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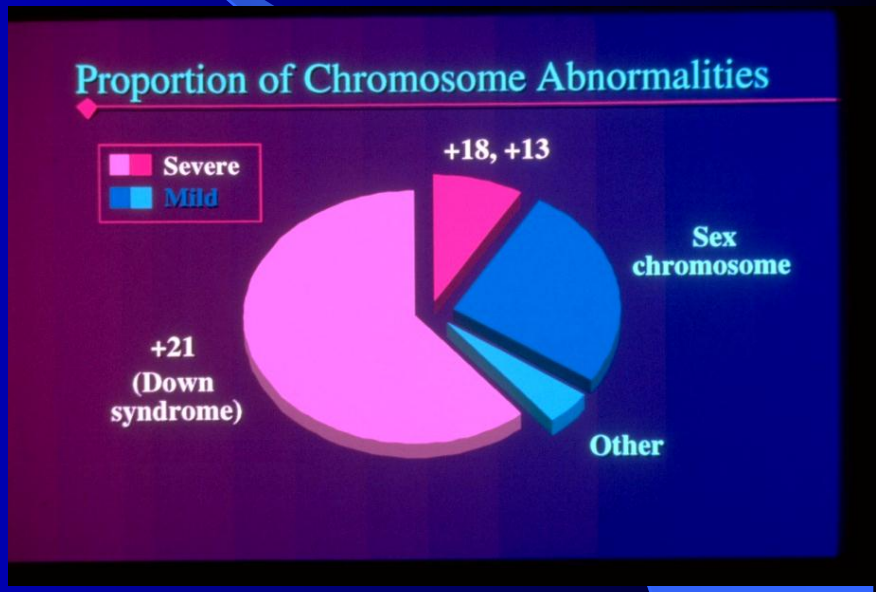
Chromosome abnormalities

- Incidence of chromosome abnormalities in newborns – 0.6%
- 60% Down syndrome (Trisomy 21)
- 10% Trisomy 18 and Trisomy 13
- 25% Sex chromosome abnormalities [45,X;47,XXY; 47,XXX; 47,XYY]
- 5% Other (del, dup, transl)



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Risk of Chromosome AbN = Risk of SA with amnio at 35YR

Maternal Age	DS	Any Chromosome Abn
20	1/1667	1/526
25	1/1200	1/476
30	1/952	1/385
35	1/378	1/192
40	1/106	1/66
45	1/30	1/21

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Age as a screen for Chromosome abnormalities

≥35 years = screen positive

- A miscarriage and a birth of a baby with a chromosome abnormality do not have the same impact.
- Risk for a miscarriage associated with amniocentesis is < 0.5%
- detection rate only 30% (depends on age of population)

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Advanced paternal age

- Association with autosomal dominant conditions: Marfan syndrome, myositis ossificans, Apert syndrome, achondroplasia, thanatophoric dysplasia, OI, NF1 etc.
- Association with ASD: In comparison to paternal age (≤29y), risk of autism increased 2.18 times for children born from fathers in their thirties, 2.71 times for fathers in their forties, and 3.22 thereafter.
- Increased risk of total childhood leukemia and ALL
- Increased risk for both schizophrenia and OCD
- Association with rare de novo CNVs not flanked by segmental duplications

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-Ultrasound

- NT
- (NB, DV, TR, fronto-maxillary angle…)

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Maternal Serum AFP Screening for ONTD & AWD

- Chance of ONTD & AWD increases with increased MS-AFP levels
- Positive screen = 2.2 MoM (~1/460)
- MS-AFP can detect 80% of the fetuses with ONTD and abdominal wall defect
- Diagnostic test - Offer detailed fetal ultrasound and amniocentesis (for AF-AFP $\pm$ AChE)

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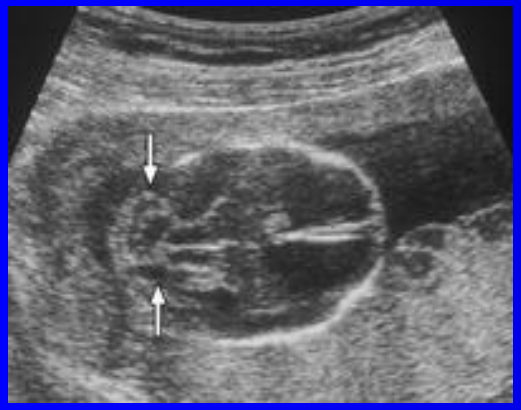
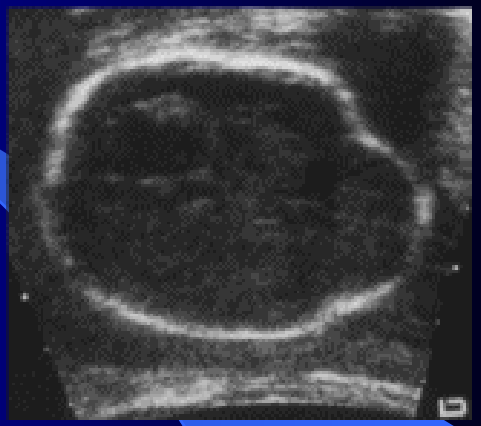
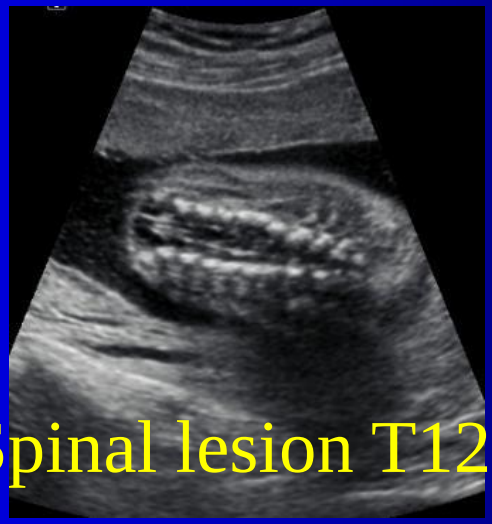
2D Ultrasound



"Banana" sign



"Lemon" sign



Spinal lesion T12-S1

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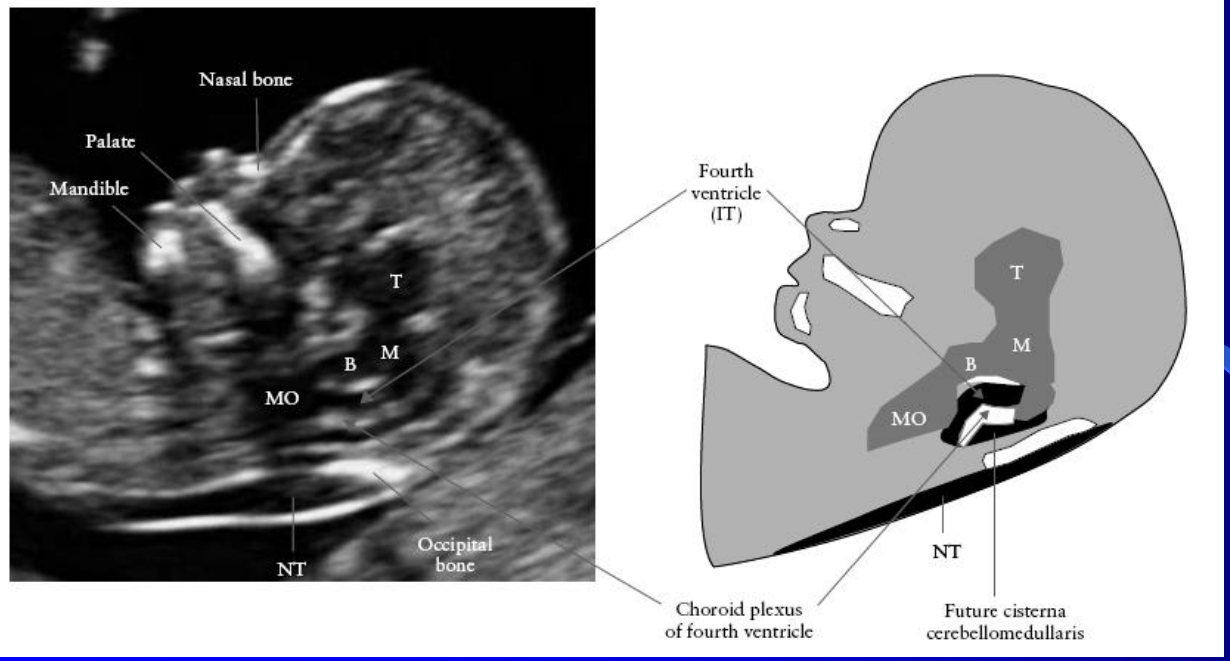
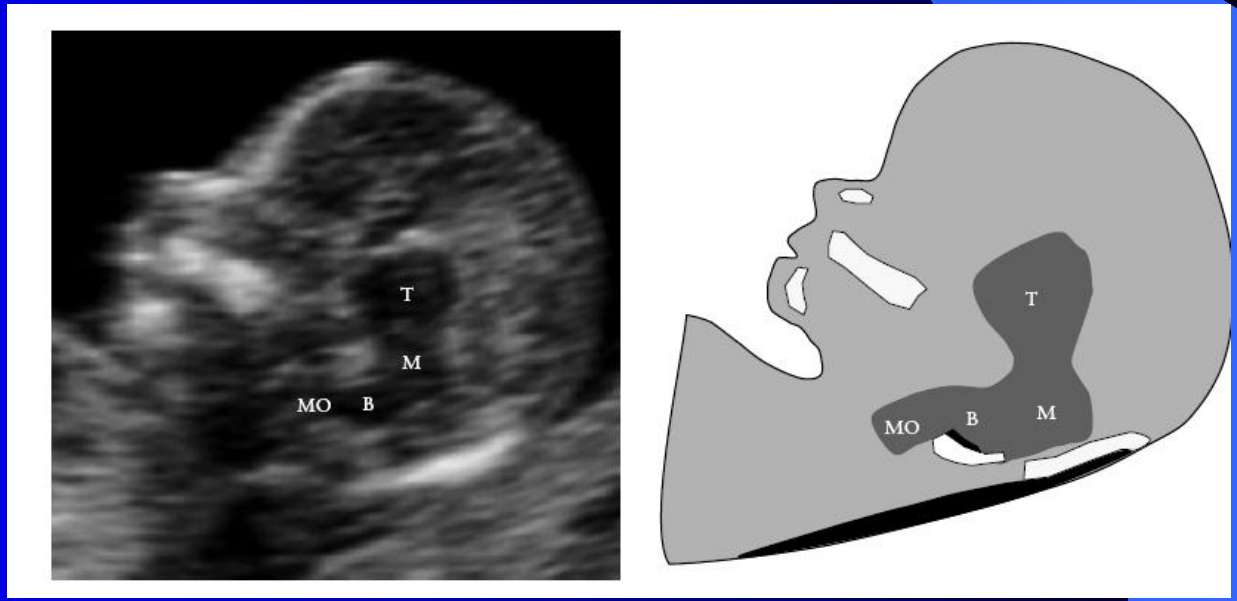


Intracranial Translucency 1st trimester PND of NTD



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Maternal Serum AFP Screening for ONTD & AWD

Time for a change

	Anencephaly	Spina bifida
1st trimester TV	90%	44%
2nd trimester	100%	92-95%

- Should we continue the MS-AFP screening for ONTD and AWD???
- ONTD and AWD are not different than the other fetal abnormalities and should be detected by a detailed fetal ultrasound.

Secondary Prevention - Time for a change

- **Screening for** Down syndrome and other fetal chromosome abnormalities
- **Screening for** Open Neural Tube Defects and Abdominal wall defect
- **Screening for** structural fetal abnormalities

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-Ultrasound

- NT
- (NB, DV, TR, fronto-maxillary angle…)

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MS-AFP

- Found to be elevated in cases of ONTD and AWD
- Subsequently found to be low in pregnancies with Down syndrome and Trisomy 18
- BUT age +AFP- still not a great screen (high false positive and poor detection – 60% for 5% FPR)

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Ultrasound

- NT
- (NB, DV, TR, fronto-maxillary angle…)

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4 Biochemical Markers

- Fetal
  - AFP
  - UE3
- Placental
  - **hCG**
  - **Inhibin-A**

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Maternal Serum Triple Screen for Down syndrome (15w-20w5d)

- Maternal Age: age will ↑ chance
- AFP ↓ (fetoplacental)
- uE3 ↓ (fetoplacental)
- hCG ↑ (placenta)

Positive screen= 1/385 + chance for DS

Detection rate varies w/ age (~70% for 5% FPR)

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Maternal Serum Quad Screen for Down syndrome (15w-20w5d)

- Maternal Age: age will ↑ chance
- AFP - ↓ (fetoplacental)
- uE3 - ↓ (fetoplacental)
- hCG - ↑ (placenta)
- Inhibin A - ↑ (Placenta)

Positive screen ≥ 1/385

- Detection rate varies w/ age <35 yrs: 76%; 35 – 39 yrs: 92%; ⩾40 yrs: 97%

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Maternal Serum Quad Screen for Trisomy 18

- Maternal Age: age will ↑ chance
- AFP - ↓ (fetoplacental)
- uE3 - ↓ (fetoplacental)
- hCG - ↓ (placental)
- Inhibin A - ↓ (placental)
- measured 15w0d to 20w5d

Positive screen ≥ 1/100

Detailed ultrasound is also a good screen for Trisomy 18

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4 Biochemical Markers

- Fetal
  - AFP
  - **UE3**
- Placental
  - **hCG**
  - **Inhibin-A**

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Suggested Management for Abnormal Maternal Serum Markers

- Offer screen for aneuploidy/ONTD
- Examine serum markers as well as overall risk in consideration of placental disorders
  - PAPP-A <0.4 MoM
  - T2 AFP >2.5 MoM
  - BHCG>3 MoM
  - Inhibin >2 MoM
  - uE3 <0.5

→ Uterine a doppler

Abnormalities followed up sequentially with individualized monitoring based on level of risk

Is it necessary ?

- Although meta-analyses show that uterine artery Doppler analysis can predict women at increased risk of placental dysfunction, it is not recommended to be used for screening purposes.
- Improved identification of women at increased or decreased risk of a disease that cannot be prevented and has no treatment other than delivery is **unlikely** to improve maternal or fetal outcome.
- Furthermore, the false positive rate of these test is quite high, leading to excessive patient anxiety and health care costs.

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Ultrasound

NT

NB, DV, TR, fronto-maxillary angle…

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NT Scan

Professor Kypros Nicolaides
Founder 11 to 14 week Scan Project
Director Fetal medicine Foundation

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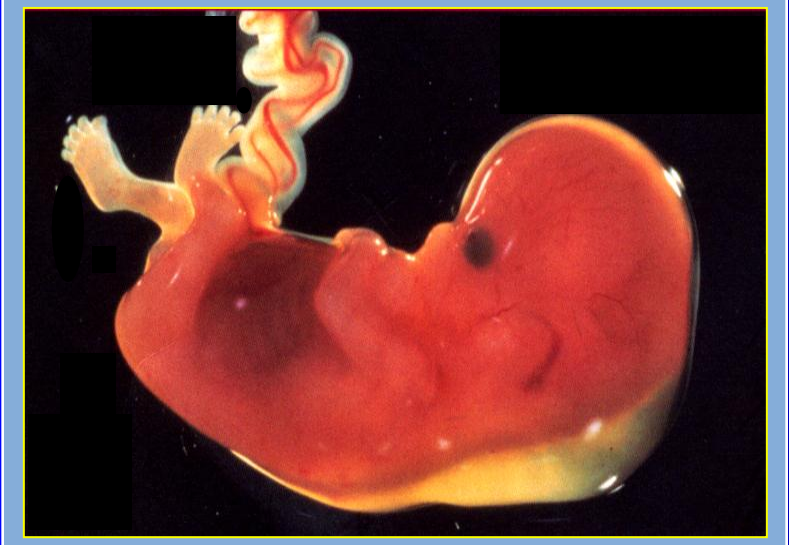
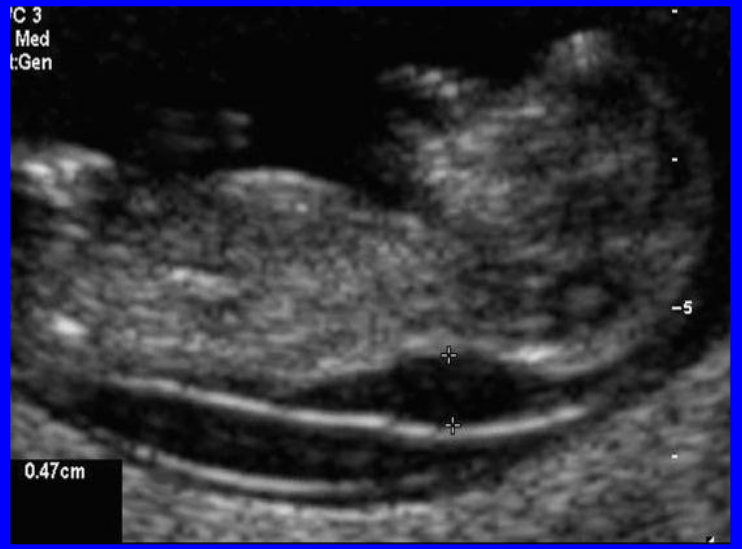
Nuchal Translucency





"the skin is deficient in elasticity. . . . . too large for the body"

Langdon Down

Observations on an ethnic classification of idiots. Clinical Lecture Reports, London Hospital 1866;3:259.

Chitayat D, Kalousek DK, Bamforth JS. Lymphatic abnormalities in fetuses with posterior cervical cystic hygroma. Am J Med Genet 1989

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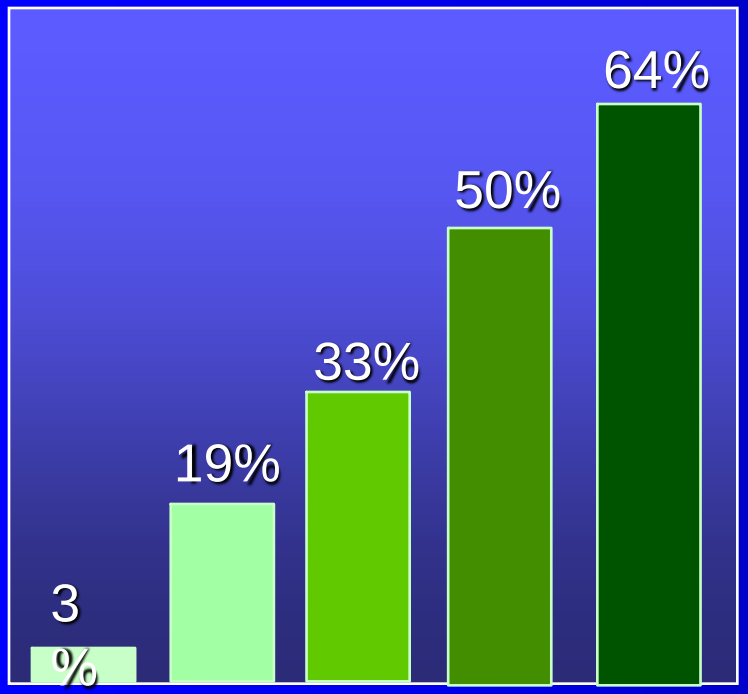
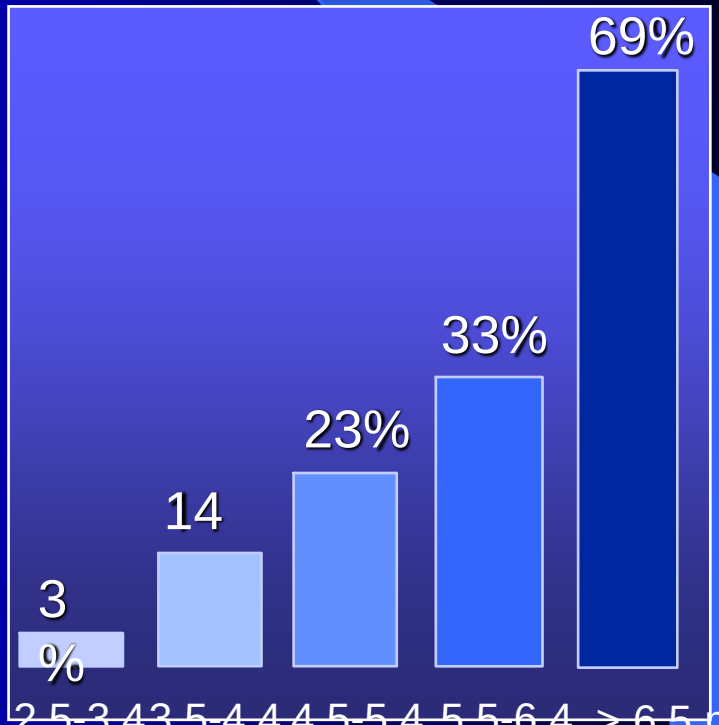
Increased NT at 11-14 wks (n=4,767)

Abnormal karyotype



Snijders et al, 1998 n=96,127

Normal Karyotype
IUD / NND / Defects



Souka et al, 2001 n=1,320

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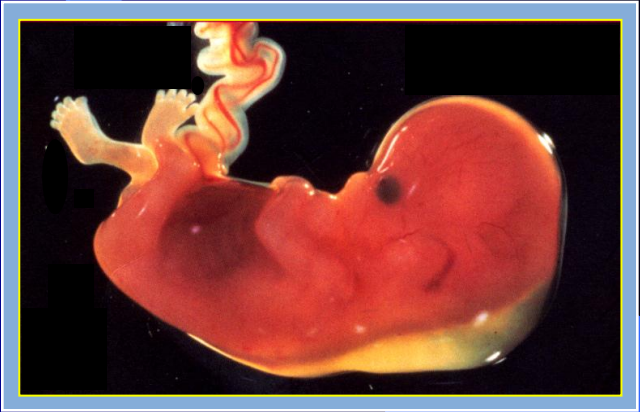
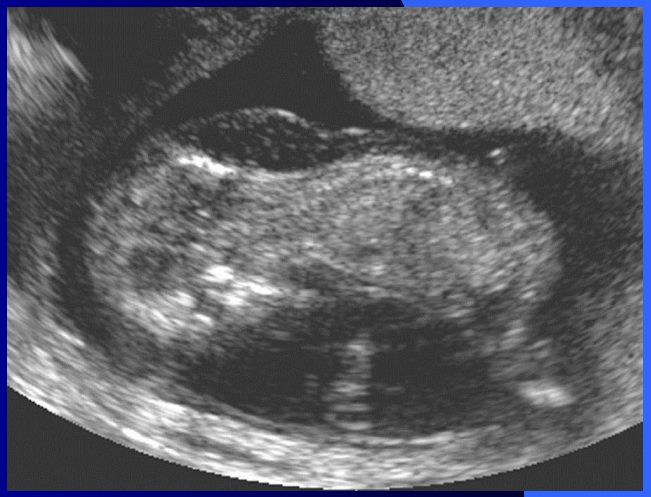
Ultrasound Detection of Fetal Anomalies in the First Trimester

- NT $\geq$ 95th centile
  - Multiple anomalies – 100%
  - Body-stalk anomalies – 100%
  - Lethal skeletal dysplasia – 50%
  - Diaphragmatic hernia – 37%
  - Cardiac defects – 28%





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Syngelaki et al, 2011
Grande et al., 2011

Pregnancy-Associated Plasma Protein - A

- A large glycoprotein tetramer produced by the trophoblast
- Metalloprotease cleaving Insulin-like growth factor binding protein-4
- Increases the bioavailability of insulin-like growth factor

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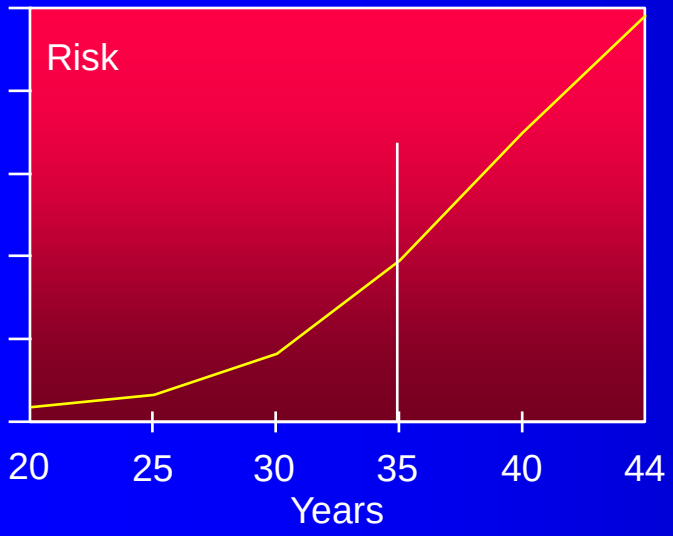
Secondary Prevention - Screening for Trisomy 21

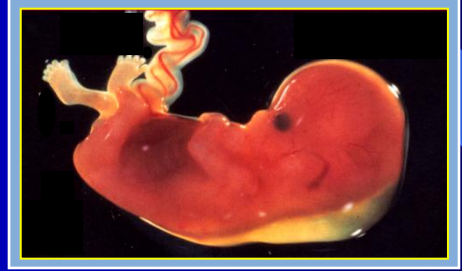
Aims

Reduce invasive testing rate & increase detection rate



ß-hCG
Estriol
AFP
Inhbin
15-20 wks

Nuchal translucency
11.5-14 wks



ß-hCG / PAPP-A
11.5-14 wks

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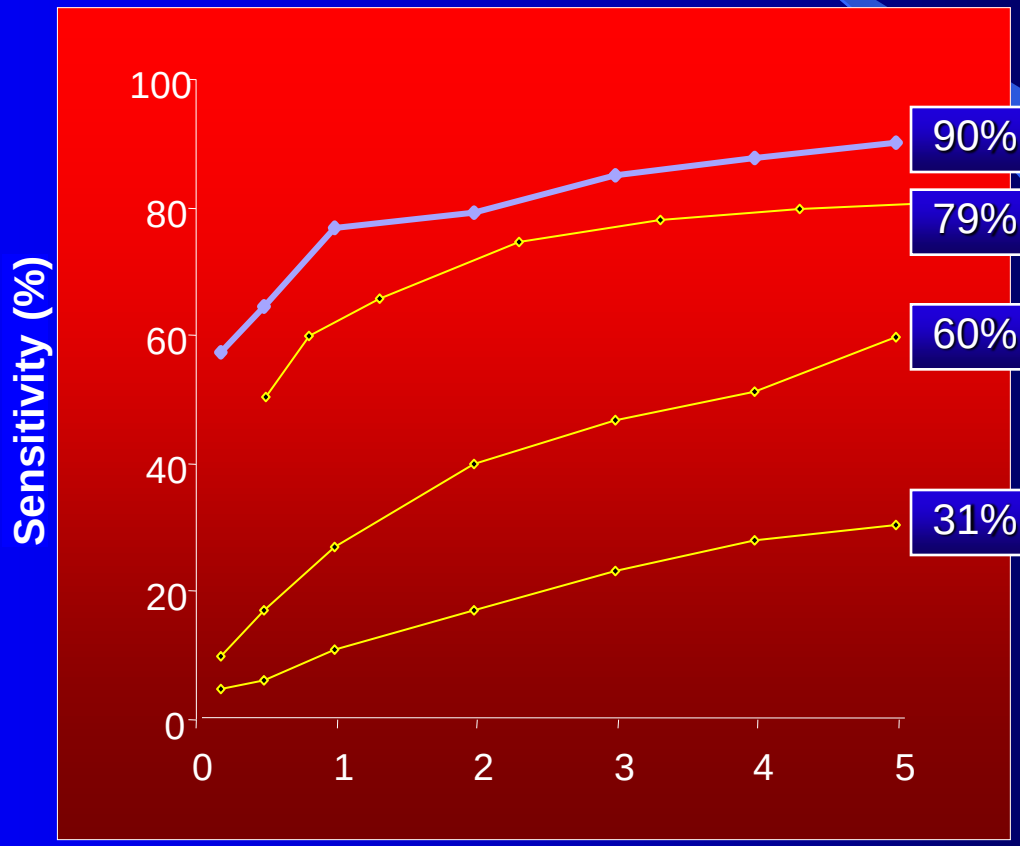
One-Stop Clinic for Assessment of Risk for Trisomy 21

Results



NT + MA+ ß-hCG + PAPP-A

NT + MA

ß-hCG + PAPP-A + MA

Maternal age

Bindra et al 2002

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Integrated Prenatal Screening

- Combine FTS w/ MSS and give one result for OSB, Down syndrome and Trisomy 18/13 (NT, PAPP-A, AFP, uE3, hCG, IA)
- benefits: more accurate- i.e. increased detection rate and less false positives
- (92% for 5% FPR)
- Timing- waiting until 2nd trimester and need woman to return

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Integrated Serum Screening (ISS)

- Papp-A, AFP, uE3, hCG, +/- Inhibin A
- benefits: more accurate- i.e. increased detection rate and less false positives
- Timing- 1st and 2nd trimester
- VERY GOOD when no access to NT
- (DR - <35 yrs: 79%; 35 – 39 yrs: 92%; cutoff 1:300; FPR 5%)

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Politics and health care in Ontario

- 5 biochemical laboratories
- Freedom to have a variety of screening tests mainly according to the HCP choice
- Lack of QA for NT decreased the detection rate
- Interaction with a commercial company and paying royalties for IPS increased the provincial expenses

Suggestions

- Prenatal Screening:
  - Screening for Down syndrome + T13/T18
    - Use FTS to provide early results and avoid having two blood tests and thus decreased compliance
  - Screening for Fetal structural abnormalities

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Ultrasound

NT

NB, Ductus venosus, TR, fronto-maxillary angle…

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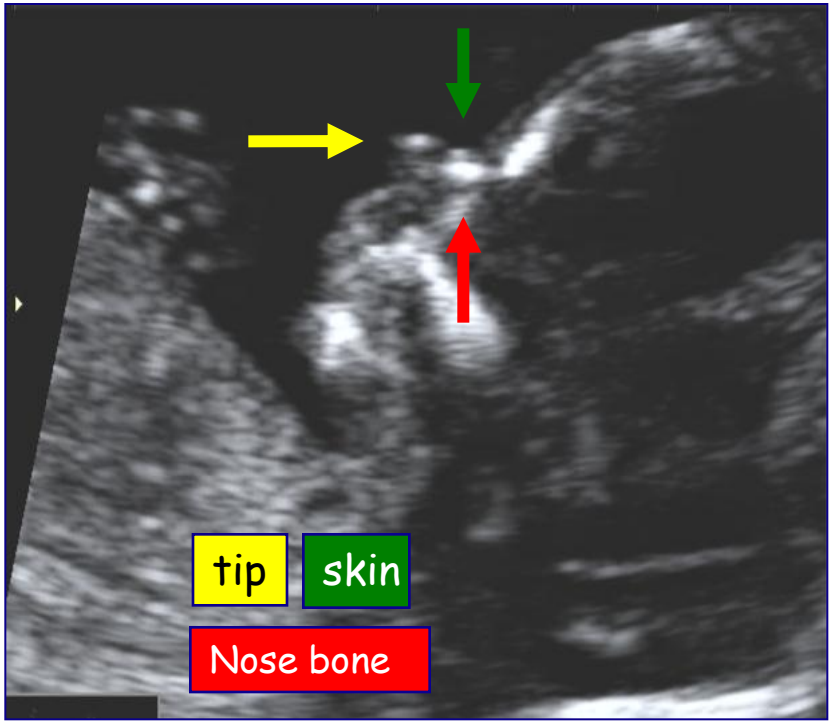
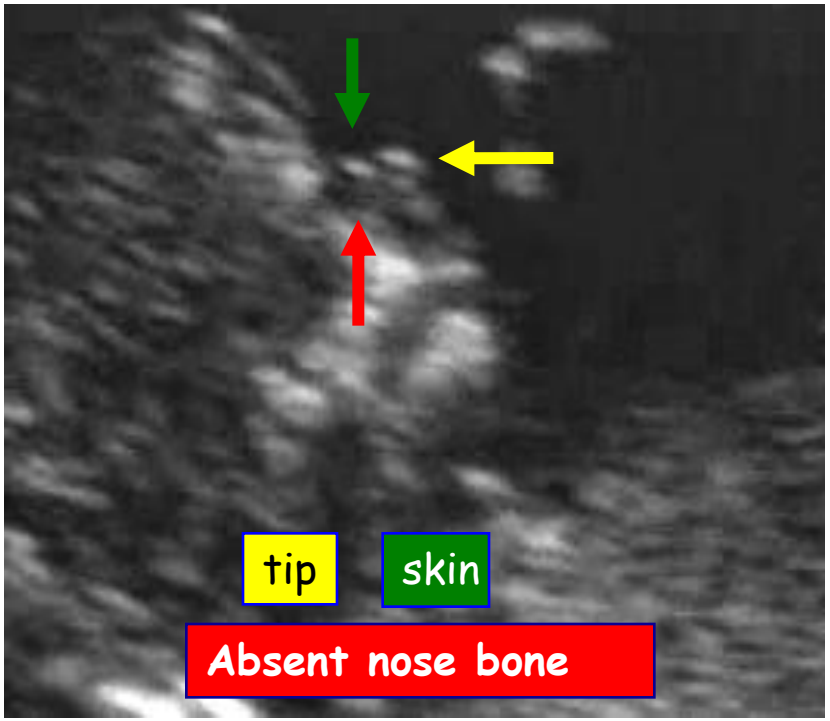
Nasal bone

Normal nasal bone



Abnormal nasal bone



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History of Prenatal Screening and Biomarkers

1960's - Maternal age associated with risk for having a baby with Down syndrome

1972 - **HIGH** AFP = anencephaly [ONTD] (Brock, Lancet)

1984 - **LOW** AFP = T18 + Down (Merkatz, AJOG)

1990's - Multiple biomarkers (AFP, uE3, hCG, DIA…)

Ultrasound

NT

NB, DV, TR, fronto-maxillary angle…

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Soft Markers LR

Table 2. Ultrasound "soft markers" performance summary in the detection of aneuploidy (trisomy 21, 18) and other genetic/congenital anomalies

Ultrasound "soft markers" (evidence and classification)[1]	Aneuploidy (LR)[2] T21	Aneuploidy (LR)[2] T18	Congenital/Anomaly Association[3]
A. Screening scan (16-20 weeks)			
Nuchal fold (III, A)	17	—	Congenital heart disease
Echogenic bowel (II-2, A)	6	—	CF2%, infection 3%, GI 6%
Ventriculomegaly (II-2, A)	9	—	AC, CNS, infection, obstruction
Echogenic cardiac focus (III, A)	2	—	—
Choroid plexus cyst (II-2, A)		7	—
Single umbilical artery (III, A)	—	—	Renal, cardiac
Enlarged cisterna magna (III, A)	—	—	OFD, MG, DiG
Renal pyelectasis (II-2, A)	—	—	Hydronephrosis; reflux
B. Comprehensive scan (calculation; detail)			
Clinodactyly (II-2, A)	5.6		—
Humerus (short) (II-2, A)	7.5		skeletal dysplasia; IUGR
Femur (short) (II-2, A)	2.7		skeletal dysplasia; IUGR
Nasal bone absent/hypo (II-2, A)	51		—
C. Research/Not useful			
Brachycephaly (III, B)	—	—	—
Iliac angle (II-2, A)	TBD	—	—
Ear length (III, B)	3–5	—	—
Sandal toe (III, B)	—	—	—

[1]Canadian Task Force on Periodic Health Examination, Health Canada; Quality of Evidence;Classification of Recommendation (Ann Intern Med 1993; 118:731-7).

[2]LR: likelihood ratio; TBD: to be determined.

[3]CF: cystic fibrosis; CNS: central nervous system; GI: gastrointestinal; OFD: oro-facial-digital syndrome; MG: Meckel Gruber Syndrome; DiG: Di George Syndrome; IUGR: intrauterine growth restriction; AC: agenesis corpus callosum

Multiple LR's can be combined

- Risk LR's can be multiplied to give new risk.

- New risk = initial x LR_1 x LR_2 x LR_3 x...x LR_n x LR modifiers*

e.g.

- Down = age risk x LR_{NT} x $LR_{PAPP\text{-}A}$ x $LR_{\beta\text{-}hCG}$ x LR modifiers*

- *LR modifiers: smoking, weight, diabetes, history, ethnicity, fetal number.

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International Trends of Down syndrome Births International Clearinghouse for Birth Defects Surveillance and Research (ICBDSR)

Year	No. Births	Maternal age >35 years	Newborn DS	Terminations	Total DS
All, 1993	1,554,529	10.89%	8.29/10,000	4.78%	13.08/10,000
All, 2004	1,564,501	18.77%	8.32/10,000	9.92%	18.24/10,000

- The mean percentage of mothers >35 years of age increased from 10.9% in 1993 to 18.8% in 2004.
- The total mean prevalence of DS (still births, live births, and ToP) increased from 13.1 to 18.2/10,000 births
- The total mean prevalence of DS births remained stable at 8.3/10,000 births, balanced by a great increase of ToP.

Prenatal Diagnosis
Secondary "Prevention"

- Screening for Down syndrome and other fetal chromosome abnormalities
- Screening for Open Neural Tube Defects
  - Spina bifida, Anencephaly
    and
  - Abdominal wall defect
- Screening for structural fetal abnormalities

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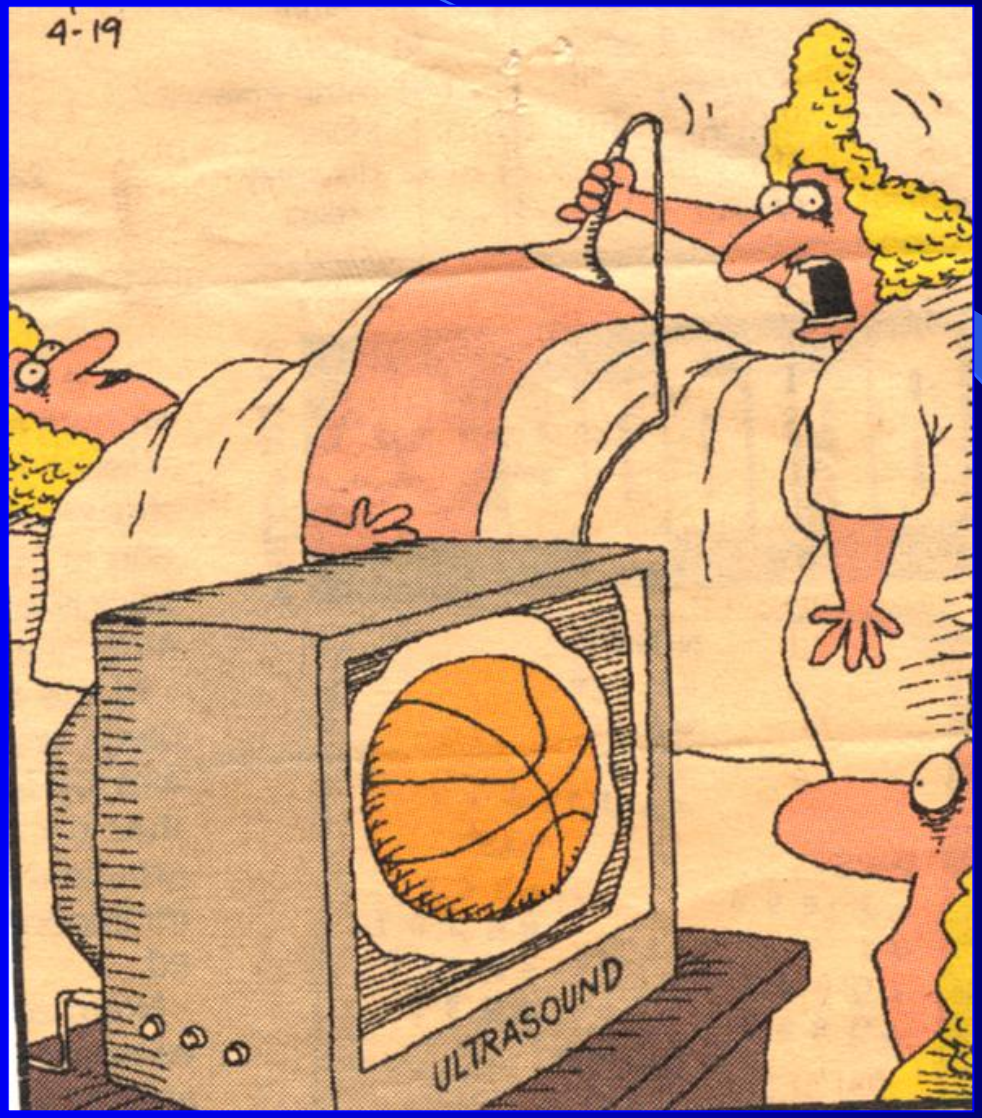
Ultrasound



Should we tell her?

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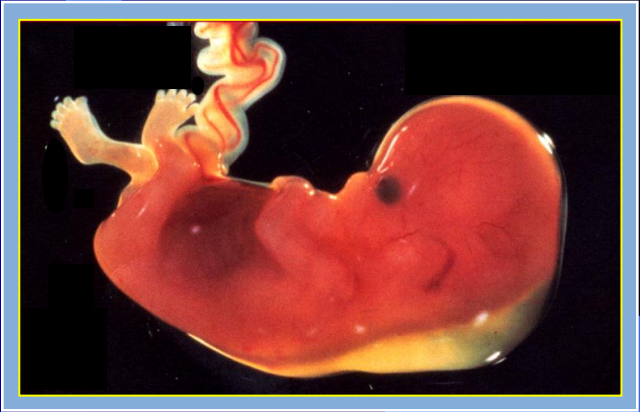
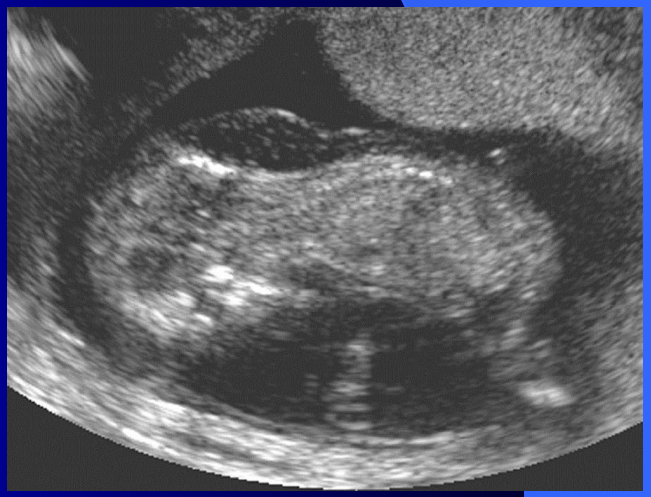
Ultrasound Detection of Fetal Anomalies

First Trimester

Among 45,191 studied pregnancies, 44% of the anomalies (213/488) were detected in the first trimester

Syngelaki et al, 2011
Grande et al., 2011





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The 18 - 20 week ultrasound scan

- Standard of care in Canada
- Screen for birth defects

"***The Genetic Sonogram***"

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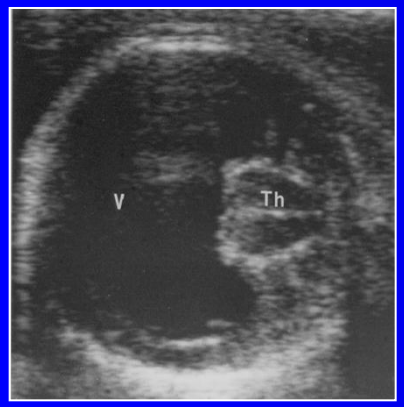
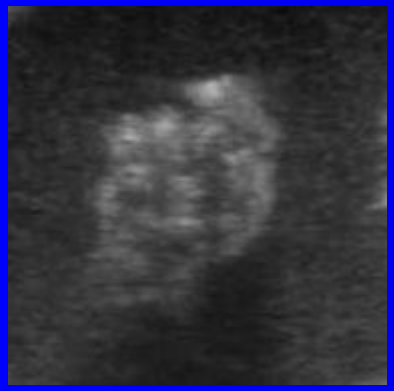
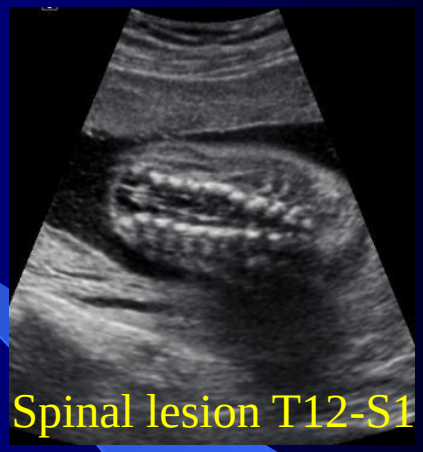
Major Defects



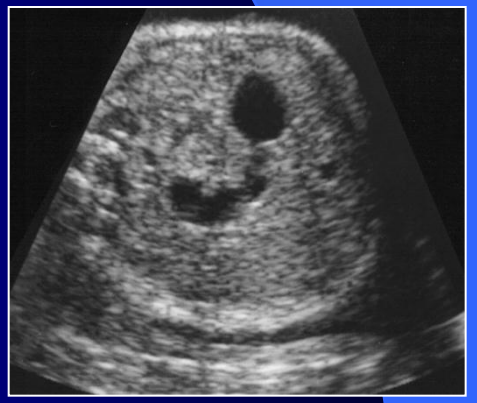
Trisomy 13



Trisomy 18



Normal karyotype



Trisomy 21

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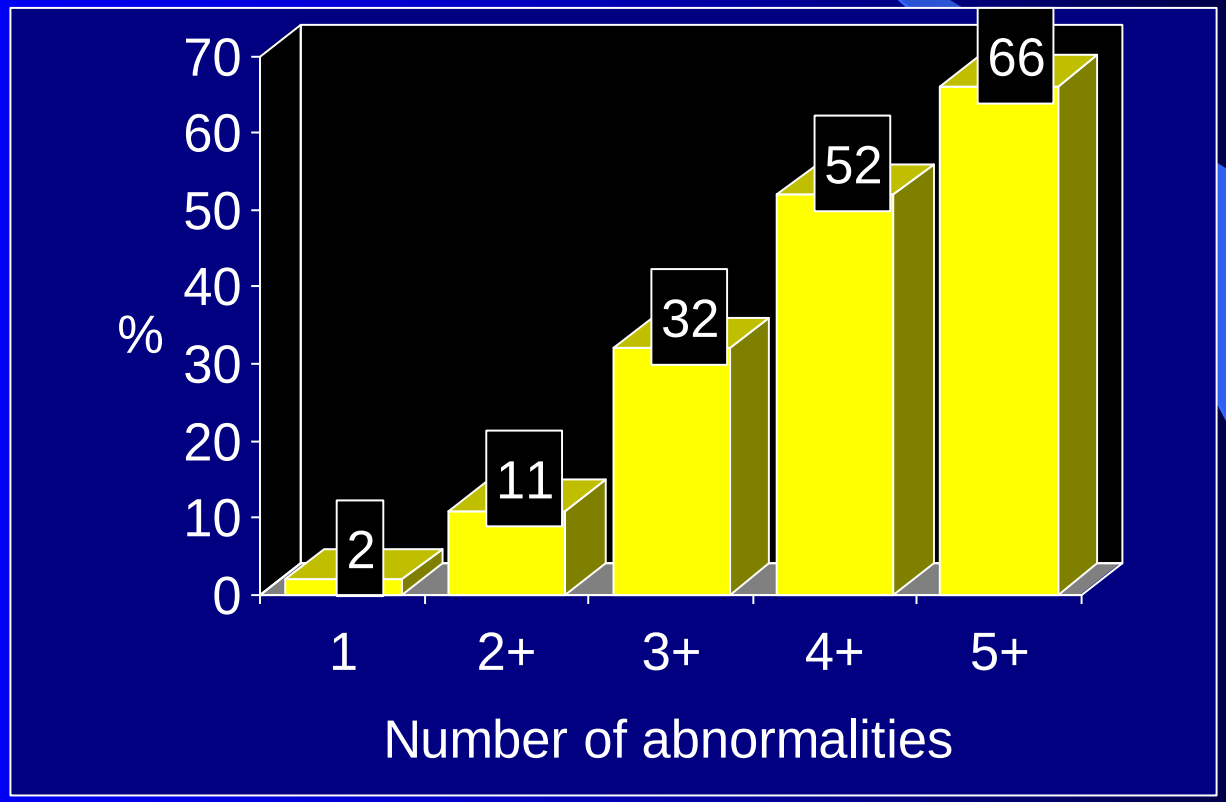
Assessment of Risk

18 - 20 wk scan - Number of abnormalities

Chromosomal Defect 301/2086 (14%)



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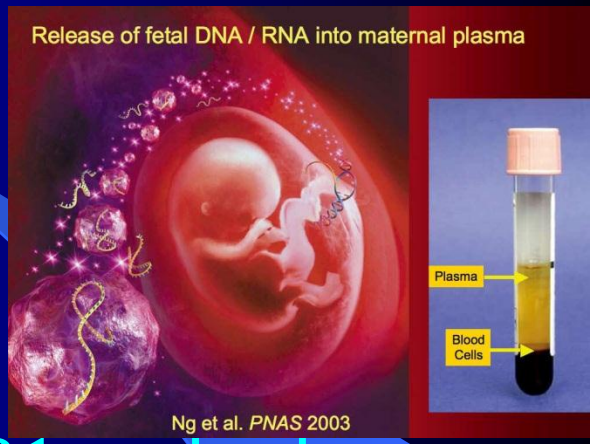
Nicolaides et al 1992

Noninvasive Prenatal Diagnosis



- Fetal Cells in Maternal Blood
- Cell-free DNA in Maternal Blood
  - Chromosome abnormalities - T21 and others
  - Rh Disease
  - Sex determination for X – linked & X-limited disorders
  - Single Gene disorders

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Sequenom launched MaterniT21 Down Syndrome Test as LDT, Publishes Clinical Validation Study

October 19, 2011

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Private Sector

华大基因 BGI

Harmony™ PRENATAL TEST

verifi™ prenatal test

natera™

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NIPT - Performance

Table 1. A comparison of aneuploidy screening options

	First trimester screen traditional	Second trimester maternal serum screening	NIPT
When is the test performed?	11–14 weeks	15–23 weeks	After 9 weeks
Who is the test available to?	All patients	All patients	Patients with a risk factor
What does it screen for?	Down syndrome	Down syndrome	Down syndrome
	Trisomy 18	Trisomy 18	Trisomy 18
	Trisomy 13	Open spina bifida	Trisomy 13
			Sex chromosome aneuploidy
			Triploidy (SNP-based)
			Microdeletion syndromes, trisomy 16, trisomy 22 clinically available.
What is the detection rate?	Down syndrome: 85% [14]	Down syndrome: 80% [14]	Down syndrome: ~99% [8▪]
	Trisomy 18/13: 90% [14]	Trisomy 18: 60% [14]	Trisomy 18: ~97% [8▪]
		Open spina bifida: 80% [14]	Trisomy 13: 92% [8▪]
			Monosomy X: ~88% [8▪]
What is the screen positive rate?	5%	5%	<1% [7]

NIPT, noninvasive prenatal testing; SNP, single nucleotide polymorphism.

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Hardisty and Vora, 2014

NIPT not only for common aneuploidy
Submicroscopic deletions

- 22q deletion syndrome (**DiGeorge**)
- 5p (**Cri-du-chat syndrome**)
- 15q (**Prader-Willi/Angelman syndromes**)
- **1p36 deletion syndrome**
- 4p (**Wolf-Hirschhorn syndrome**)
- 8q (**Langer-Giedion syndrome**)
- 11q (**Jacobsen syndrome**)
- **Trisomy 16**
- **Trisomy 22**

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NIPT – Points to remember

- It is a screening test
- Pre and post-test counselling is essential including discussion of false positive and false negative
- The PPV is at the most 85%
- No irrevocable obstetrical decision should be made in pregnancies with a positive NIPT result without confirmatory invasive diagnostic testing.
- Further consideration needed regarding:
  - Test performance on multiples
  - Turnaround times
  - Economic aspects

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NIPT – Indications/suggestions

- Maternal age ≥ 40 at delivery

  (we should we go for 35)
- Ultrasound anomalies associated with an increased risk for aneuploidy (with the low risk associated with CVS/amniocentesis we should offer invasive testing in these cases)
- A prior pregnancy with aneuploidy
- Parent is a known carrier of a translocation involving chromosome 13 or 21
- High risk result for aneuploidy on FTS, IPS, SIPS, MSS (including adjusted risk with soft signs)

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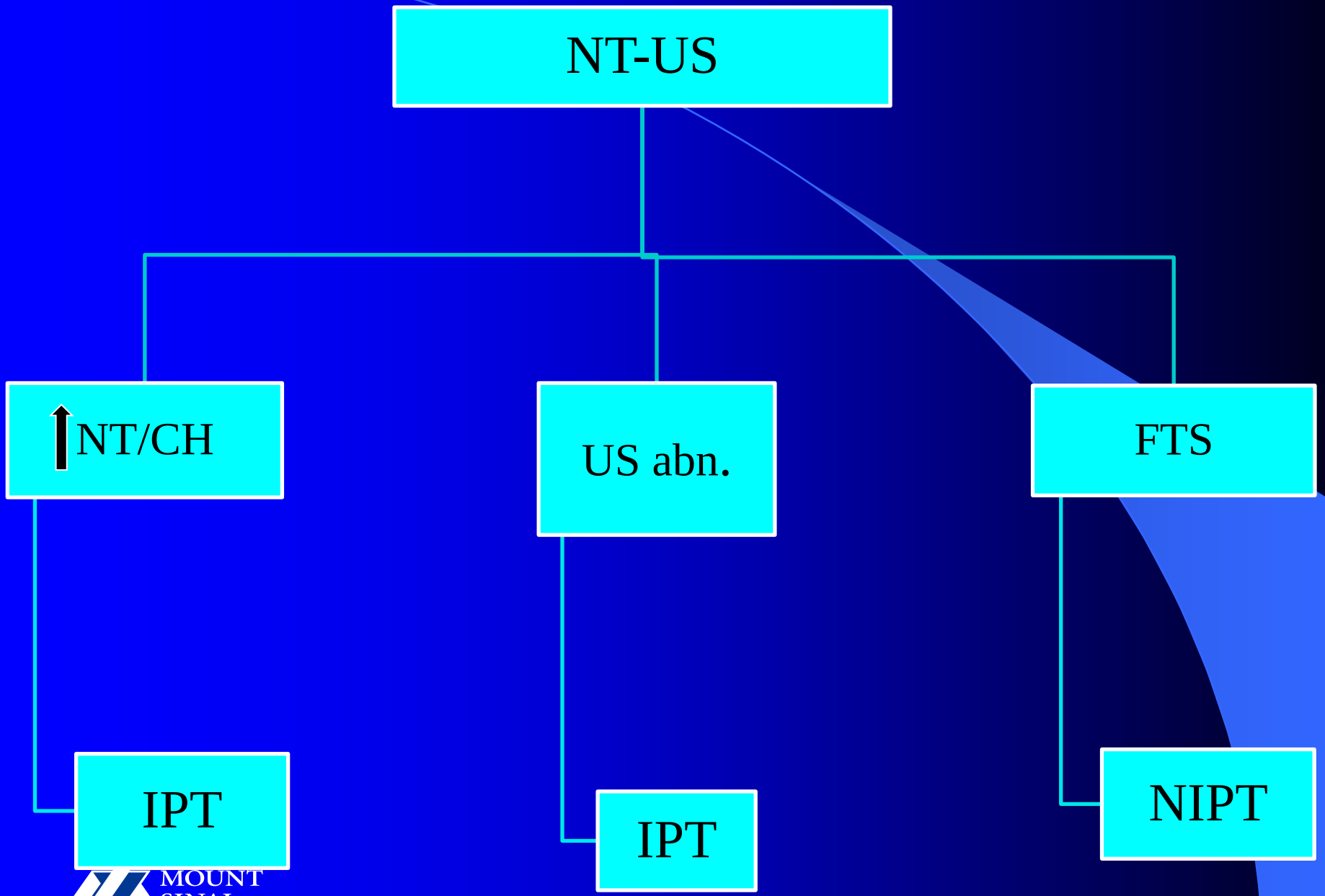

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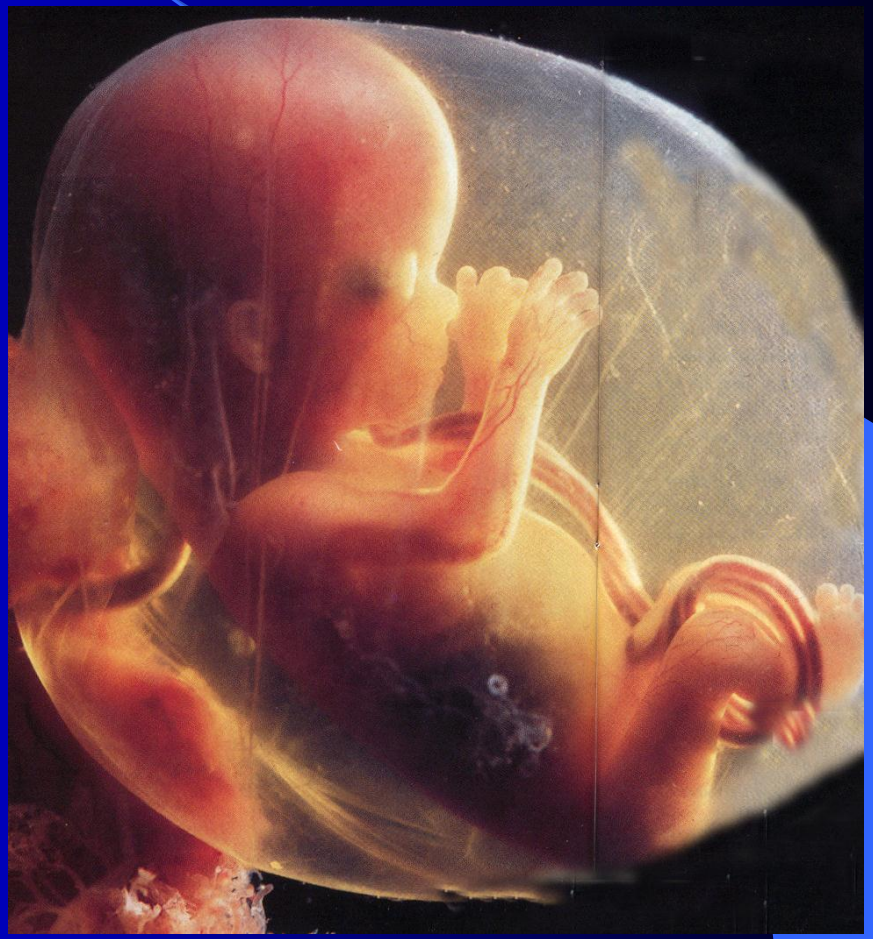
Prenatal Diagnosis



Prevention

- Primary
- Secondary

- **Diagnosis**
- **Treatment**

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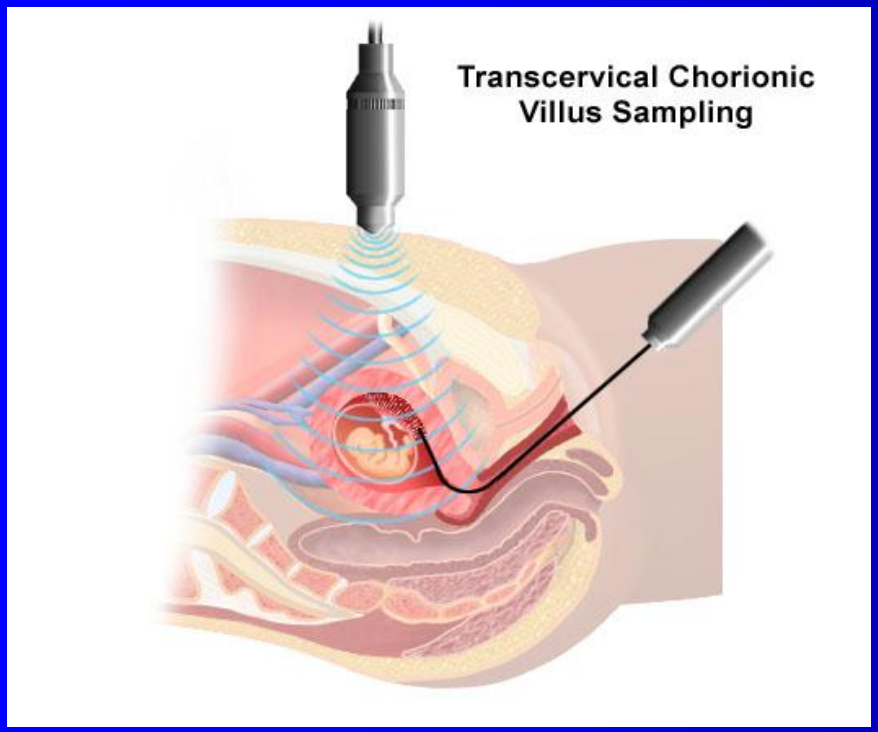
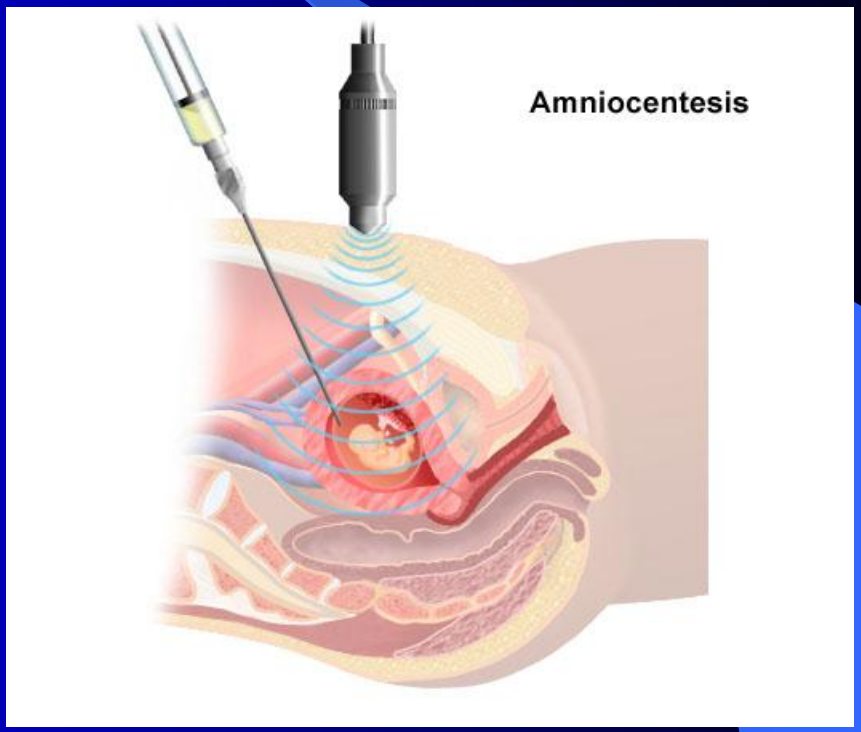
Invasive testing in pregnancy





Risk of miscarriage up to 1%

Risk of miscarriage < 0.5%

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Procedure-related risk of miscarriage following amniocentesis and chorionic villus sampling: a systematic review and meta-analysis. Akolekar et al., UoG 2014

The weighted pooled procedure-related risks of miscarriage:

- Amniocentesis - 0.11% (95% CI, -0.04 to 0.26)
- CVS - 0.22% (95% CI, -0.71 to 1.16)

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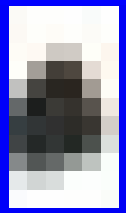
Metaphase Spread

Advantage of ACGH

- Much higher resolution



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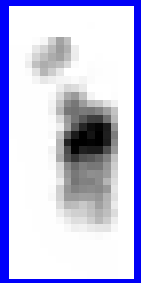

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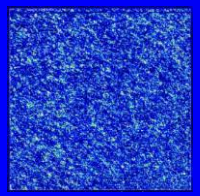

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Detection of pathogenic, benign and unclear CNVs by aCGH in PND specimen

Reference	Number of cases studied	Cases with pathogenic CNV	Cases with unclear CNV (VOUS)
Fiorentino et al., 2011	1037	9 (0.9%)	0 (0)
Shaffer et al., 2012	4406	207 (5.3%)	163 (4.2%)
Wapner etl al., 2012	3822	35 (0.9%) US Abn – 6% LMA/Abn screening – 1.7%	61 (1.6%)
Scott et al., 2013	1049	13 (1.2%) US Abn – 4.8% LMA/Abn screening – 1.2%	3 (0.3%)
Fiorentino et al., 2013	3000	7/120 (6%) 17/2880 (0.6%)	1 (0.03%)

US Abn – 6%; LMA/Abn screening – 1.7%

0.8% = 1/125 cases sampled for AMA or positive screening had CNVs associated with cognitive impairment and psychiatric diseases

All Pregnancies are High Risk

Wapner et al., 2012

	By Predeterm Listings	VOUS Adjudicated by CAC or Clinical Geneticist			Total
	Pathogenic	Total	Likely Benign	Report to Patient	Clinically Relevant
AMA N=1965	9 (0.5%)	62 (3.2%)	37 (1.9%)	25 (1.3%)	34 (1.7%)
Positive Screen N=727	3 (0.4%)	22 (3.0%)	13 (1.8%)	9 (1.2%)	12 (1.6%)
US Anomaly N=757	21 (2.8%)	40 (5.3%)	16 (2.1%)	24 (3.2%)	45 (5.9%)

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Wapner etl al., 2012

Additional value of prenatal genomic array testing in fetuses with isolated structural ultrasound abnormalities and a normal karyotype: a systematic review of the literature

De Wit et al., UOG 2014

Pooled prevalence of pathogenic submicroscopic CNVs in a specific anatomical system

	Isolated anomalies				
	Cardiac	**Resp**	**CNS**	**Facial**	**MSK**
Pooled prevalence (95% CI)	22/476 4.6% (2.7-6.5)	5/81 6.2% (0.9-11.4)	35/563 6.2% (4.2-8.2)	6/113 5.3% (1.2-9.4)	24/305 7.9% (4.8-10.9)

	Isolated anomalies				
	GIT	**Urogenital**	**NT >3.5 mm**	**Cystic hygroma**	**Total**
Pooled prevalence (95% CI)	7/105 6.7% (1.9-11.4)	9/153 5.9% (2.2-9.6)	5/162 3.1% (0.4-5.7)	12/262 4.6% (2.0-7.1)	**125/2220** **5.6%** **(4.7-6.6)**

The Use of Microarray Analysis in the Prenatal Setting

- The use of microarrays has not only increased the identification of pathogenic CNV (chromosome abnormalities), it has also identified copy number variants (CNVs) that are clearly benign.

- The identification and classification of these novel alterations have become challenging, especially in the prenatal setting.

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Counselling issues

Variants Of Uncertain Clinical Significance

	VOUS	Pathogenic	Likely Benign
2007 Study Classification	94 (2.5%)	35 (0.9%)	-
2012 Classification	57 (1.5%)	64 (1.7%)	8

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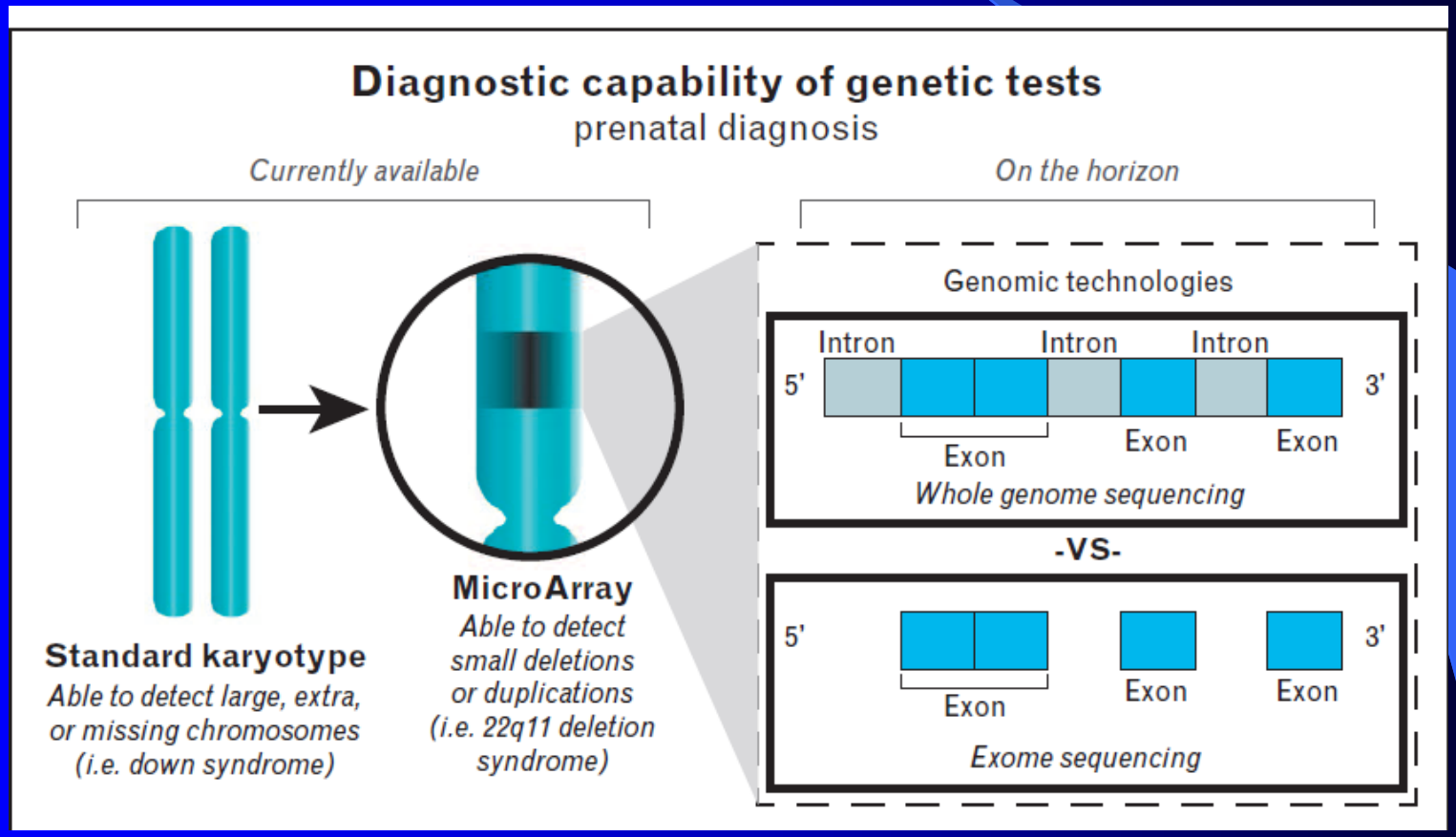
On the Horizon



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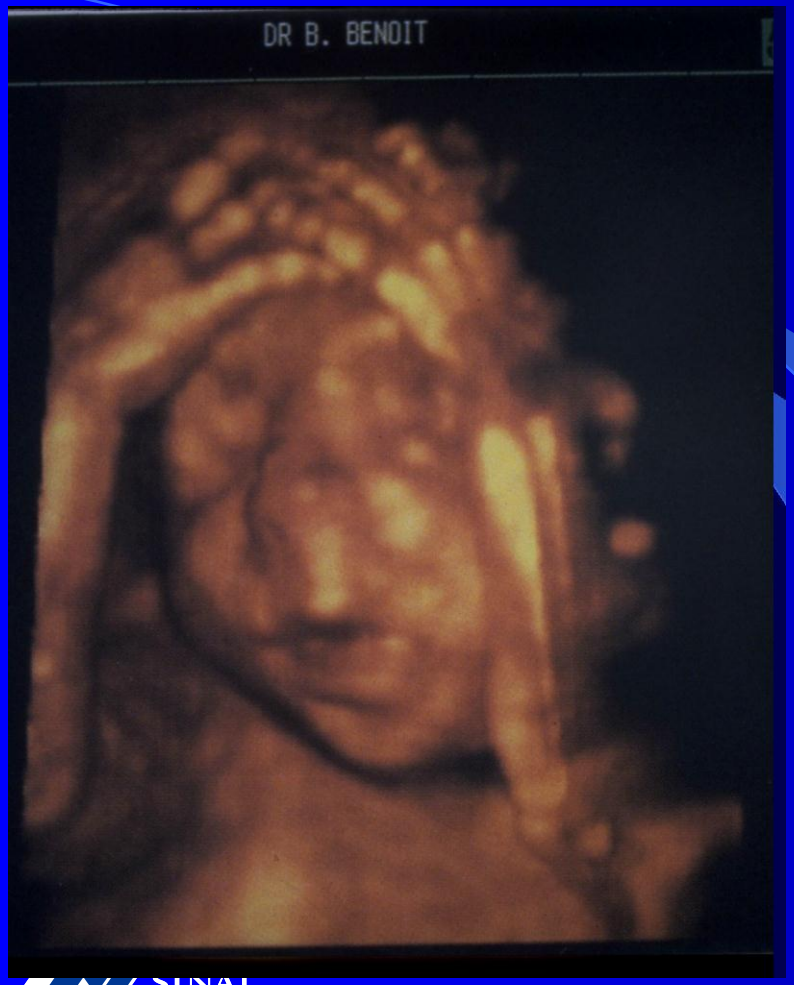
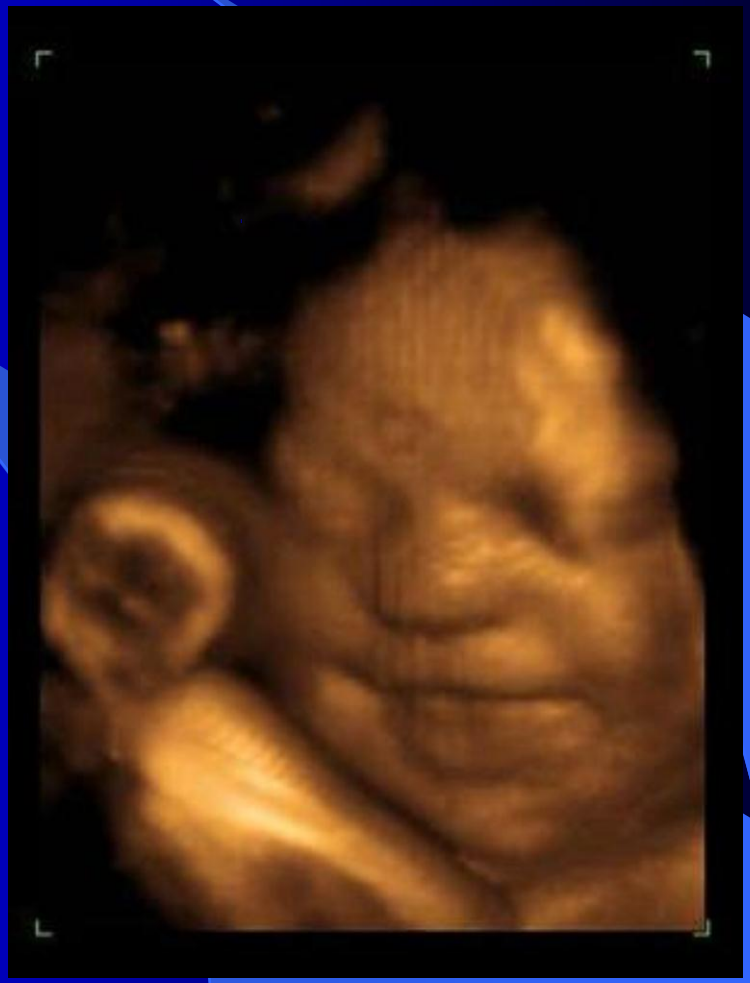
Hardisty and Vora, 2014

Thank You





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