Genetic Counseling for Fetal Anomalies

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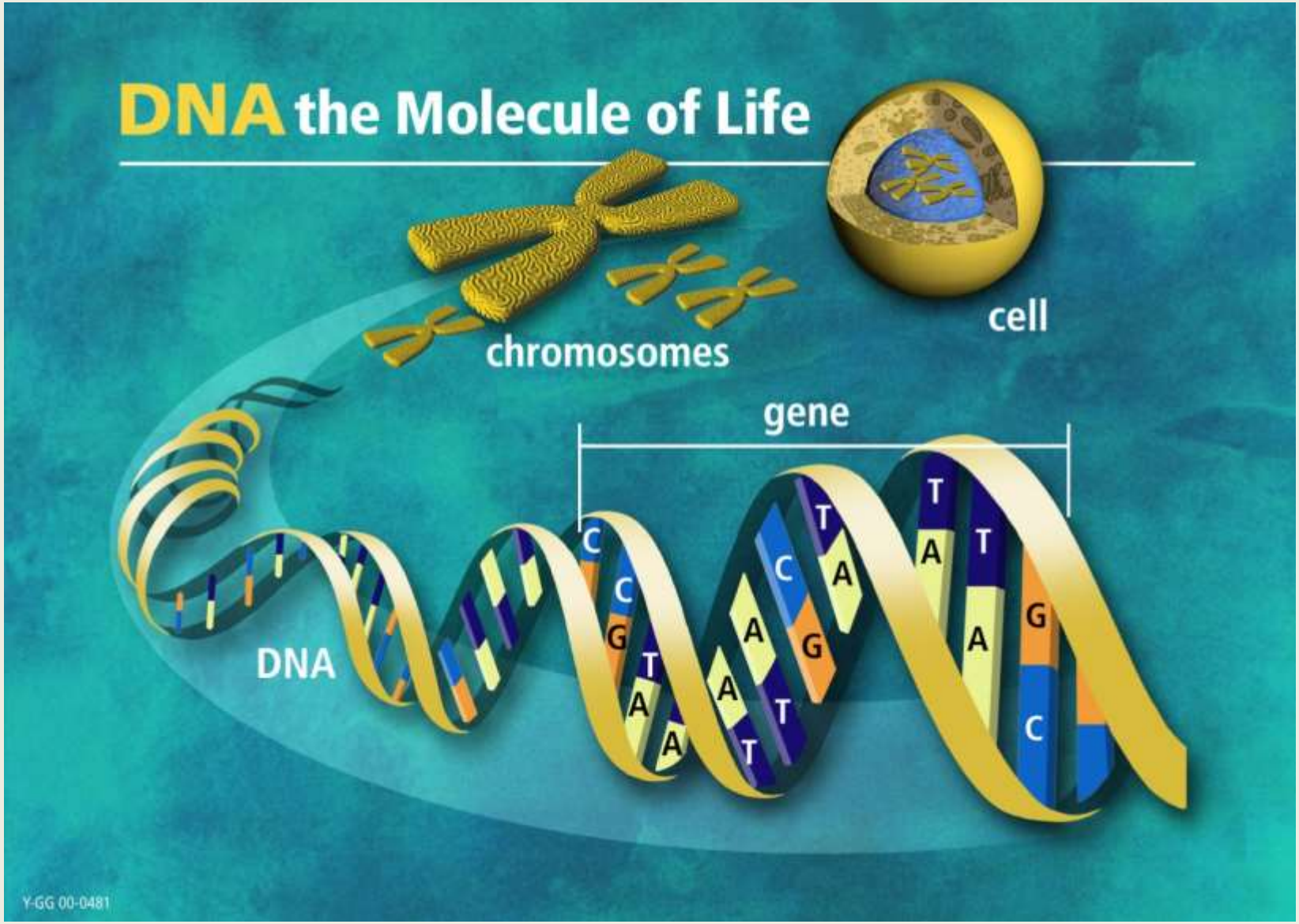
18 March 2015

Objectives

- Explain basic genetic concepts.
- Describe the role of the genetic counselor in the prenatal setting.
- Identify when genetic counseling for fetal anomalies is indicated.

BASIC GENETIC CONCEPTS


DNA the Molecule of Life
chromosomes
cell
gene
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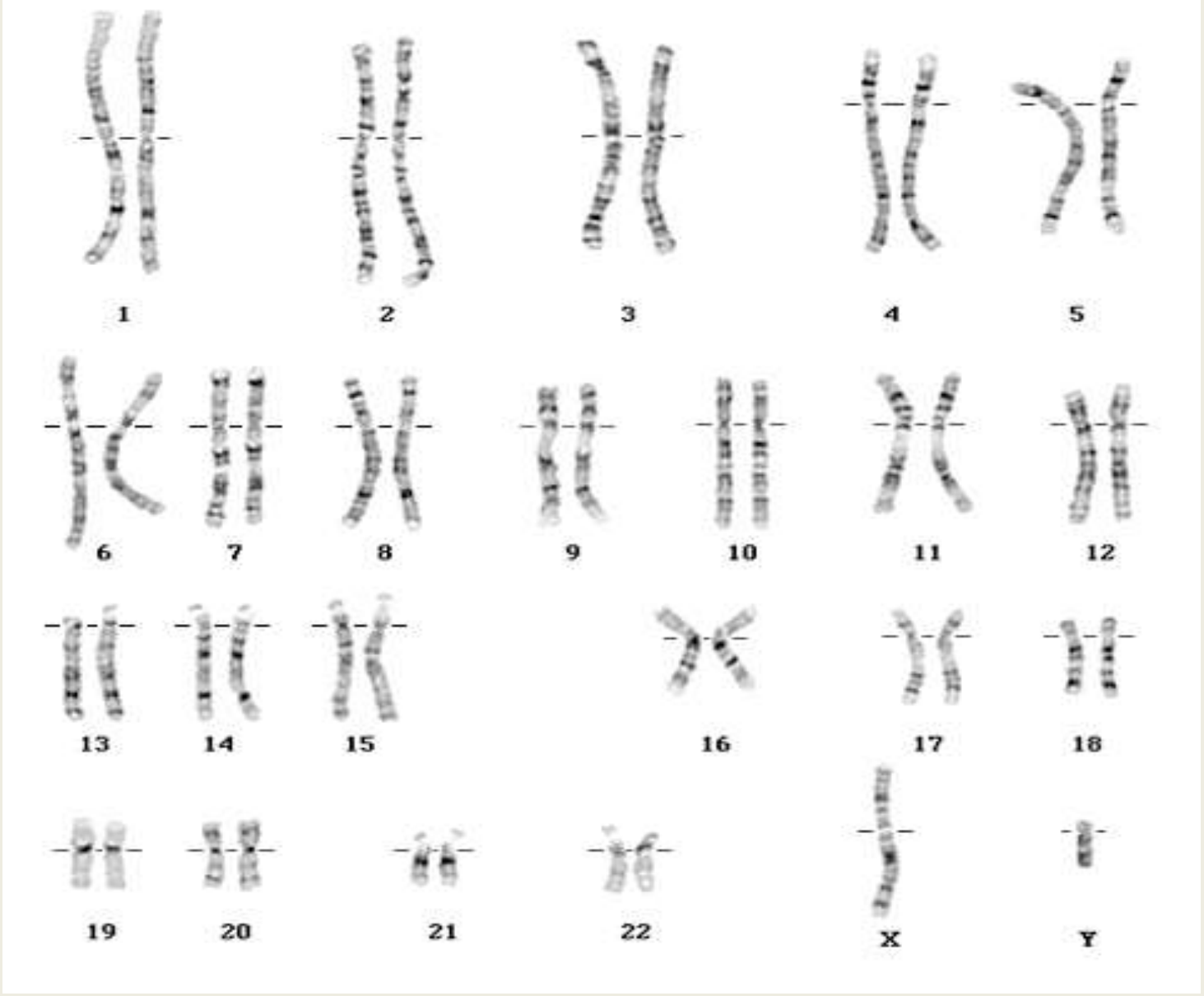
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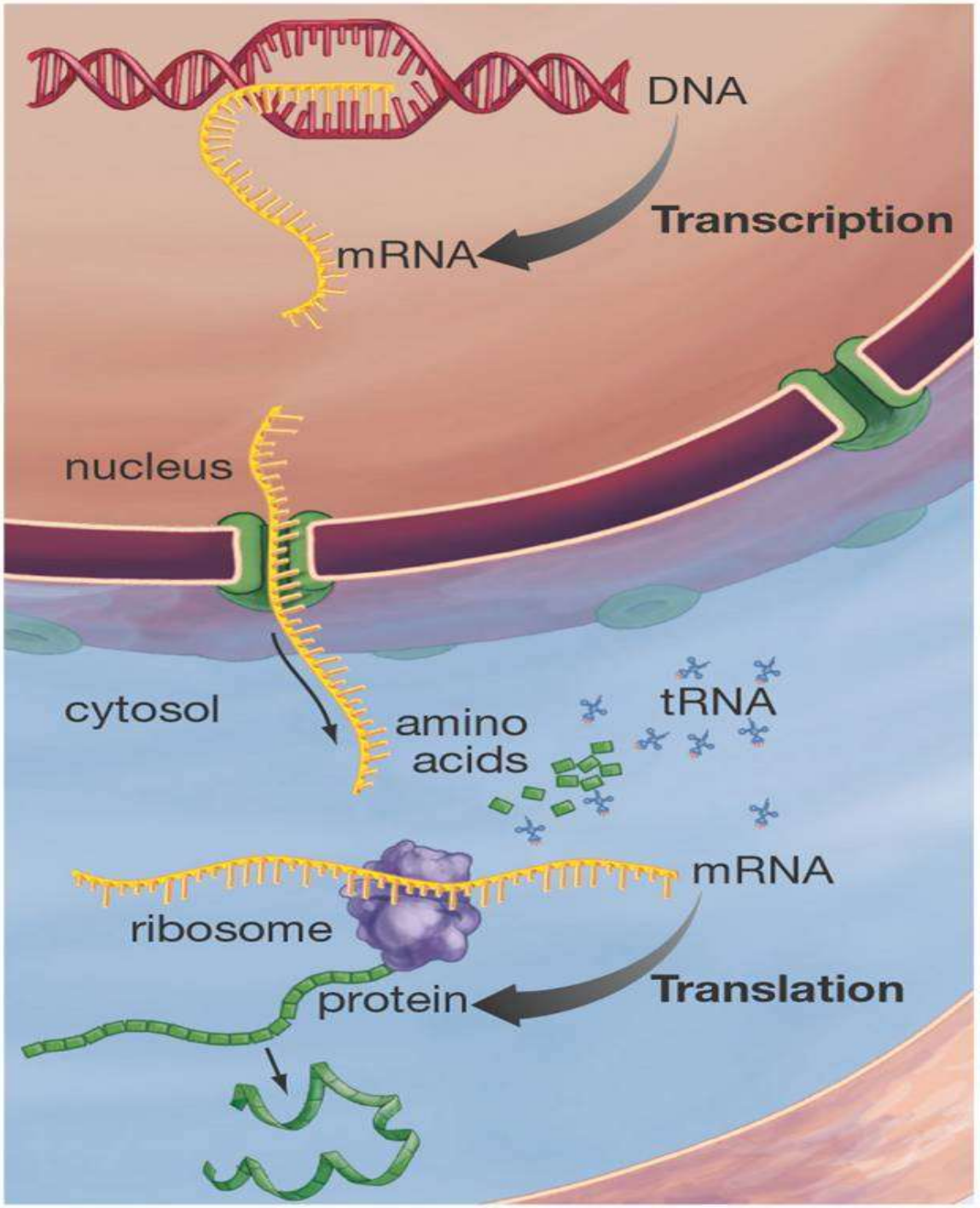
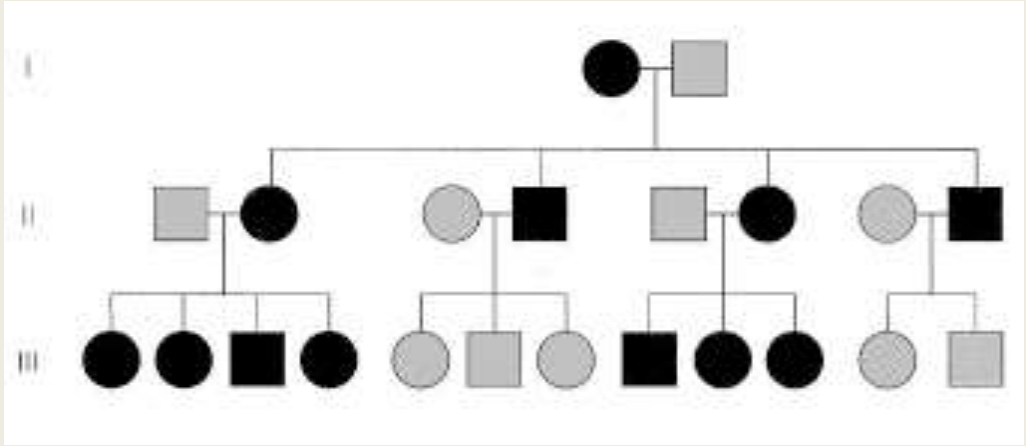
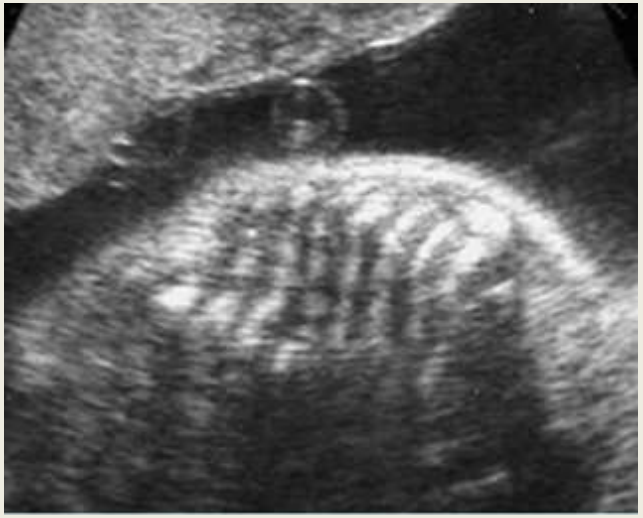

DNA
Transcription
mRNA
nucleus
cytosol
amino
acids
tRNA
mRNA
ribosome
protein
Translation

Genetic Conditions

- Inherited
  - Dominant
  - Recessive
  - X-linked
- De Novo
  - Trisomies
  - Single gene





GENETIC COUNSELING

Genetic Counseling

Genetic counseling is the process of helping people understand and adapt to the medical, psychological and familial implications of genetic contributions to disease. This process integrates:

- Interpretation of family and medical histories to assess the chance of disease occurrence or recurrence.
- Education about inheritance, testing, management, prevention, resources and research.
- Counseling to promote informed choices and adaptation to the risk or condition.

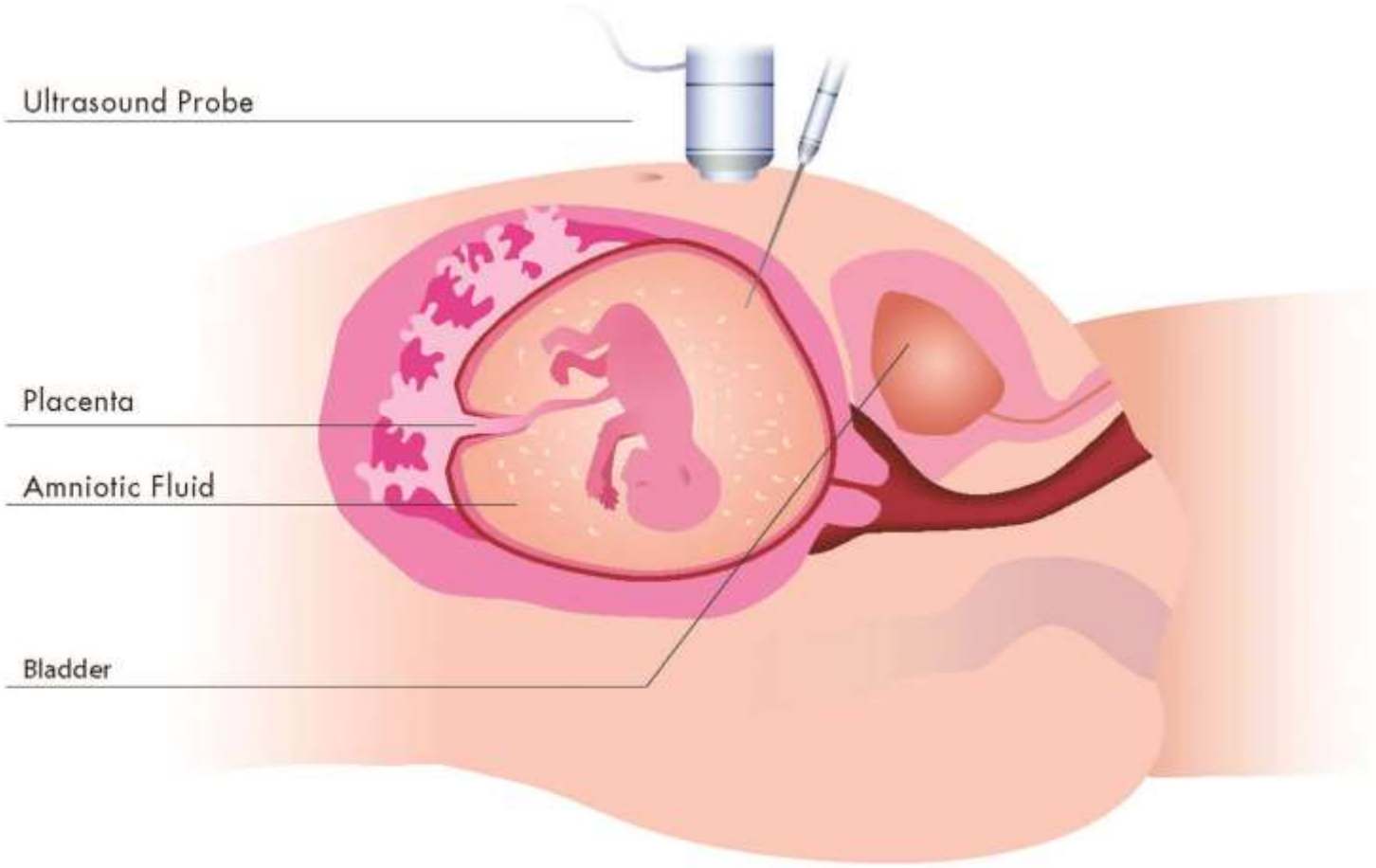
National Society of Genetic Counselors, 2005

PRENATAL DIAGNOSIS

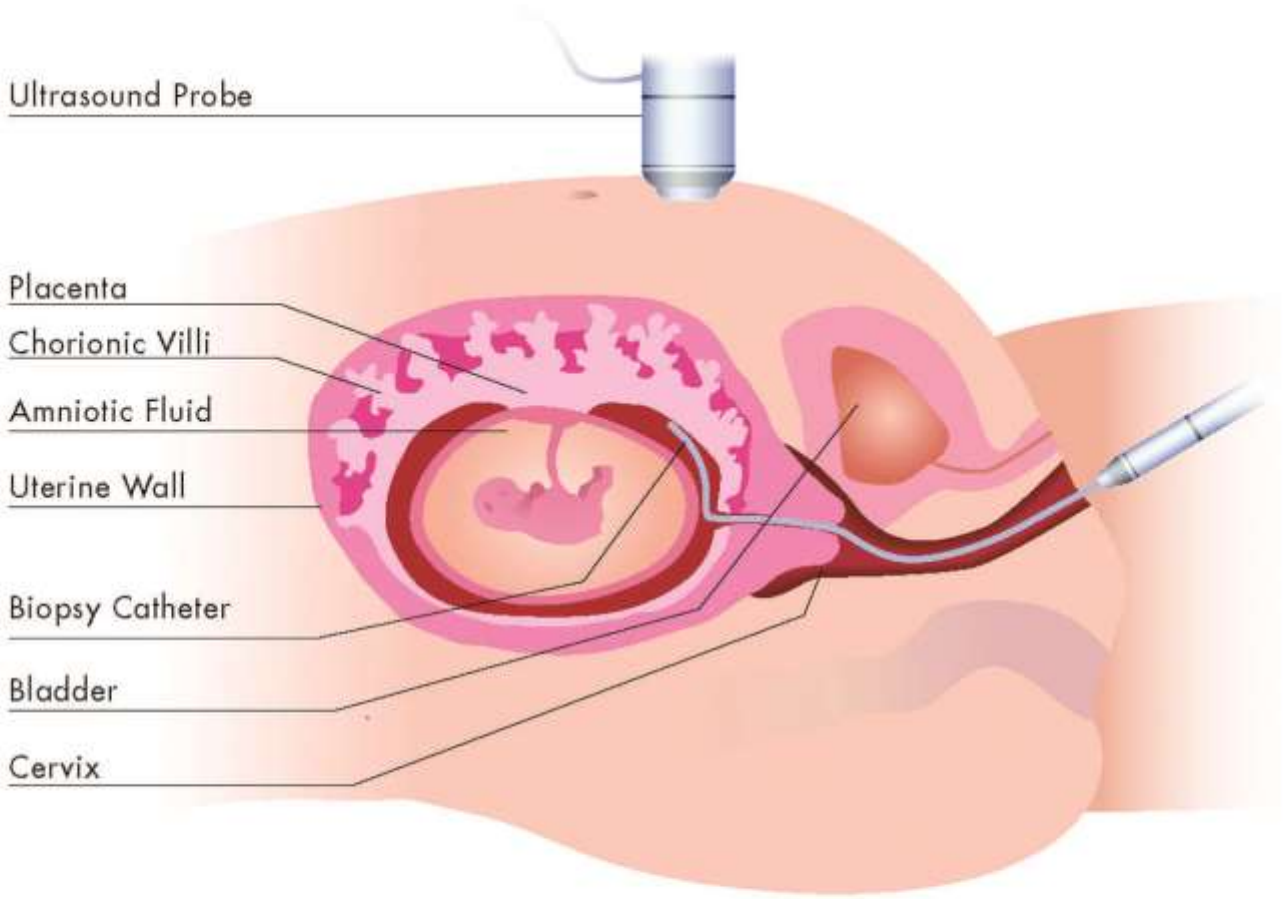
Table 15-2. Methods of Prenatal Diagnosis and Screening

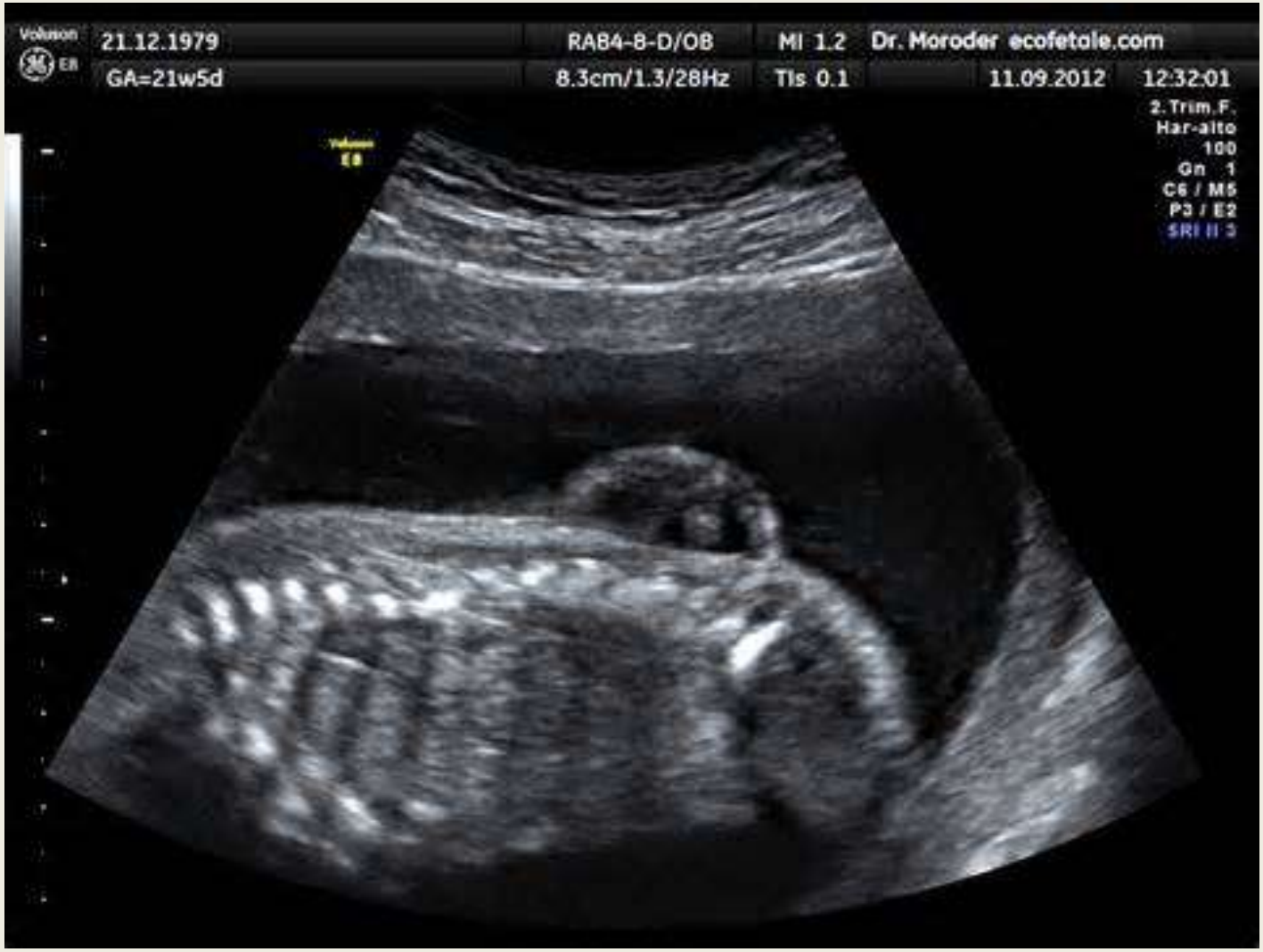
INVASIVE TESTING
Amniocentesis
Chorionic villus sampling
Cordocentesis
Preimplantation genetic diagnosis
NONINVASIVE TESTING
Maternal serum alpha-fetoprotein
First- and second-trimester maternal serum screening
Ultrasonography
Isolation of fetal cells from maternal circulation

Amniocentesis



Transcervical Chorionic Villus Sampling




Voluson E8
21.12.1979
GA=21w5d
RAB4-8-D/OB
8.3cm/1.3/28Hz
MI 1.2
TIs 0.1
Dr. Moroder ecofetale.com
11.09.2012
12:32:01
2.Trim.F.
Har-alto
100
Gn 1
C6 / M5
P3 / E2
SRI II 3

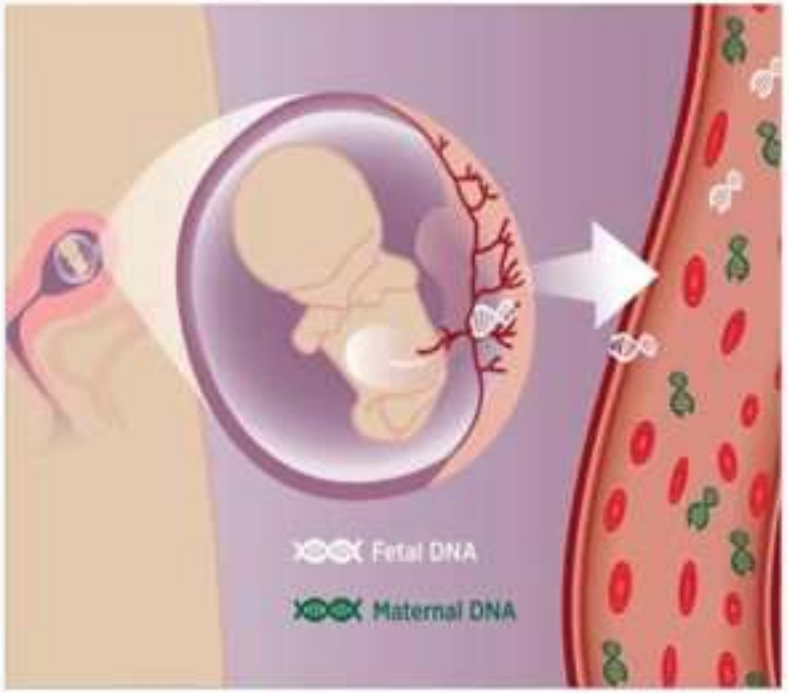
Screen	DR (%) at 5% FP*	FP (%) at 85% DR*	Offer when?
Combined	82-87	4-7	NT and CVS available; patient desires earliest risk assessment
Triple	69	14	Never. Worst performance; becoming obsolete
Quad	81	7	NT or CVS not available or patient presents in 2nd trimester
Integrated	94-96	1	NT available; patient desires lowest FPR and is willing to wait until 2nd trimester for screening result
Serum Integrated	85-88	4-5	NT not available; patient is willing to wait until 2nd trimester for screening result
Sequential	95	2	NT and CVS available; patient desires early risk assessment but willing to wait if needed

*ACOG Practice Bulletin, 2007

New possibilities: NIPT

- Cell-free DNA (cfDNA) are short DNA fragments
- In pregnancy, cfDNA from both the mom and fetus are in maternal blood
- Analysis of cfDNA allows for highly accurate genetic evaluation

Cell-free DNA



PRENATAL GENETIC COUNSELING

Common Indications for Genetic Counseling & Prenatal Diagnosis

- Advanced maternal age
- Previous pregnancy with de novo chromosome aneuploidy
- Parent with a structural chromosome abnormality
- Family history of a genetic condition that can be ruled out
- Family history of X-linked disorder with no specific prenatal diagnostic test
- Risk of a neural tube defect
- Abnormal maternal serum screen
- Abnormal cell free fetal DNA
- **Abnormal ultrasound**

Case Presentation

Lucy is a 32-year-old primigravida woman referred for ultrasound anomalies. Lucy had a routine second trimester ultrasound in her obstetrician's office that suggested a fetal arm anomaly. She was referred to our center for further evaluation. Lucy underwent a level II ultrasound and fetal echocardiogram in our clinic where a unilateral (right) absence of the fetal radius and an atrial septal defect were detected.

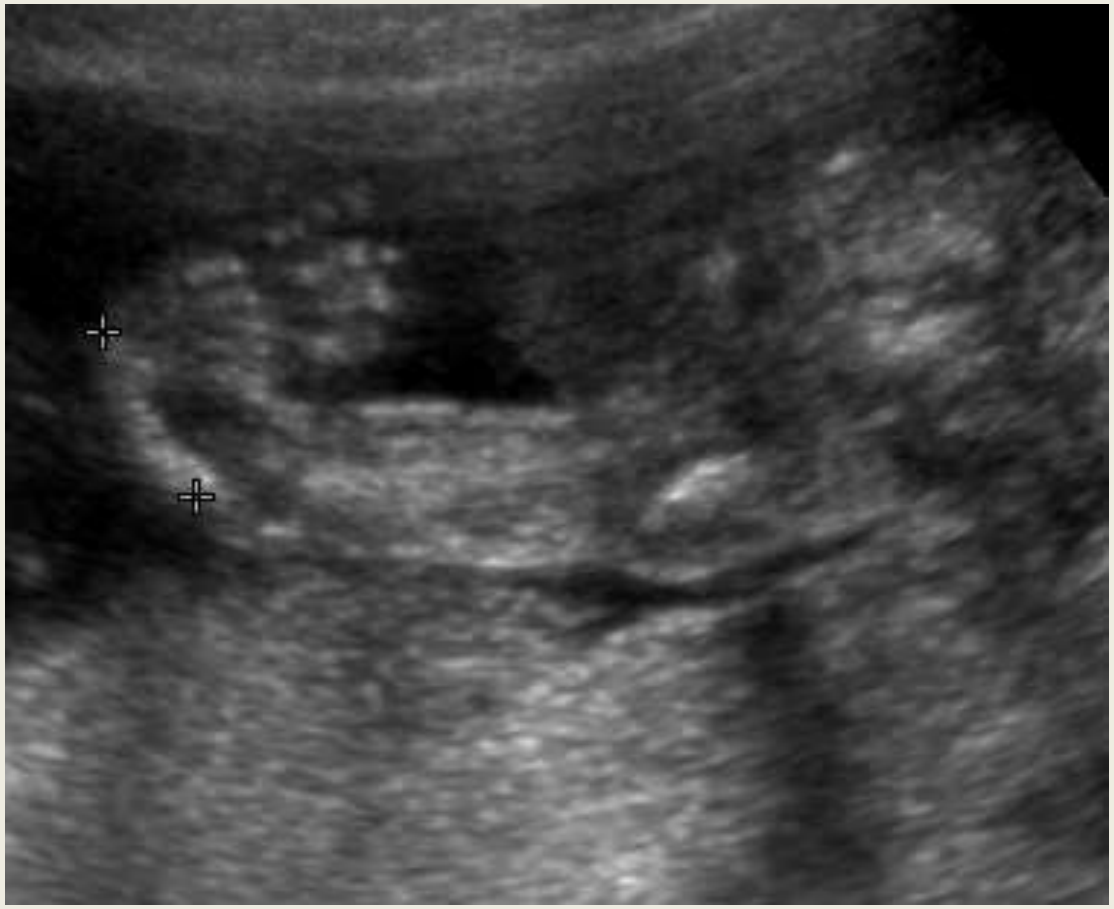
Genetic Consultation

- Any pregnancy with fetal anomalies automatically referred for genetic counseling to discuss:
  - Etiology of birth defect(s), if known
  - Chance underlying genetic syndrome
  - Benefits and limitations of genetic testing
  - Coordination of genetic testing
  - Management of pregnancy
  - Prognosis
- Always have an “on-call” counselor

Information gathering

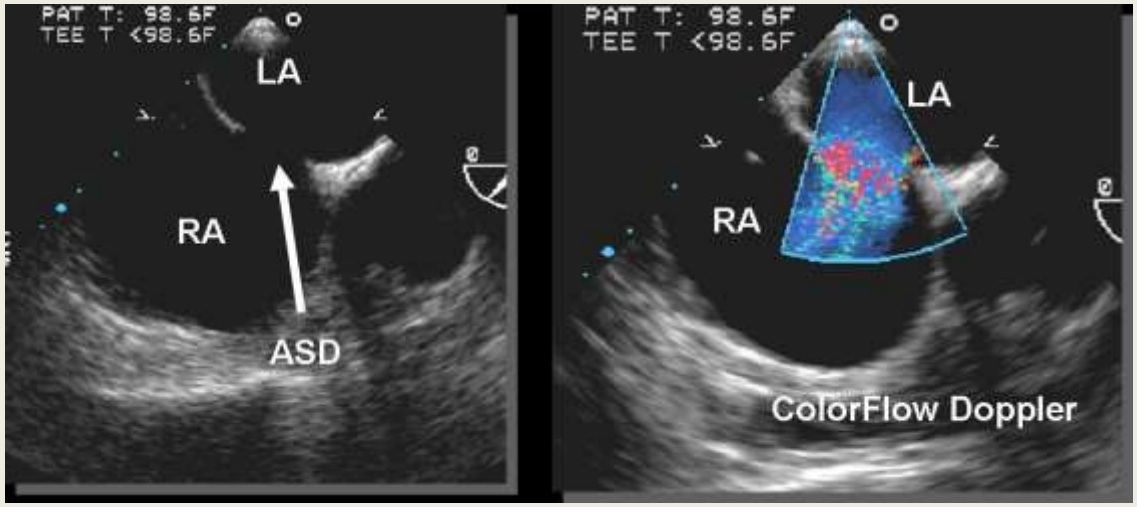
- Spoke to:
  - Sonographer
  - Maternal fetal medicine
  - Pediatric cardiologist
- Viewed ultrasound pictures and ultrasound report
- Discussed case with OB Geneticist

Level II Ultrasound



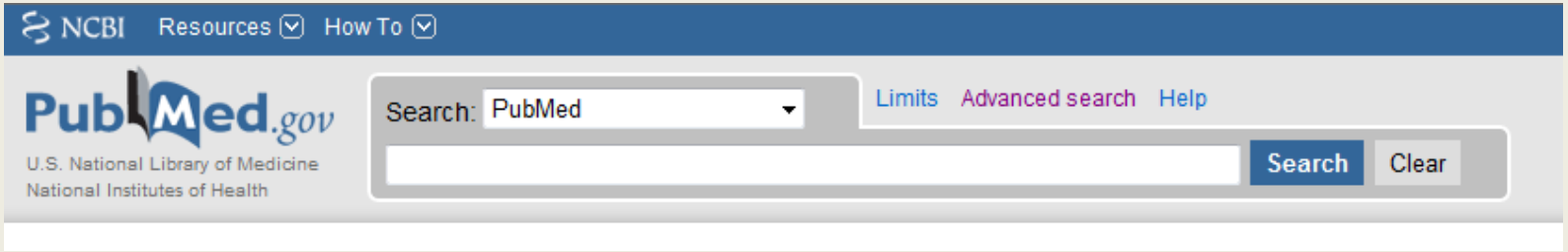
Unilateral absence of the radius

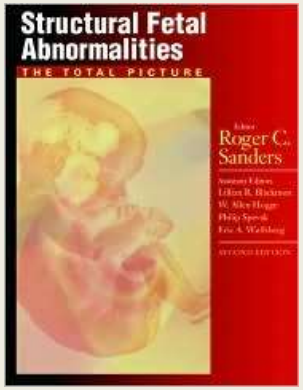
Fetal Echocardiogram



Atrial septal defect (ASD)

Information Gathering



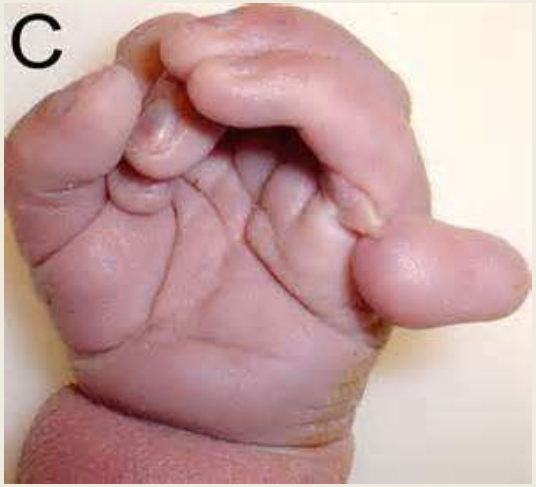


Differential Diagnosis

- More than one birth defect increases chance that fetus has a genetic condition
  - Chromosome abnormality
  - Single gene condition
  - Multifactorial genetic syndrome
- Limb anomalies and heart defects
  - Both “common”
  - Dozens of defined genetic syndromes

Trisomy 13 or 18

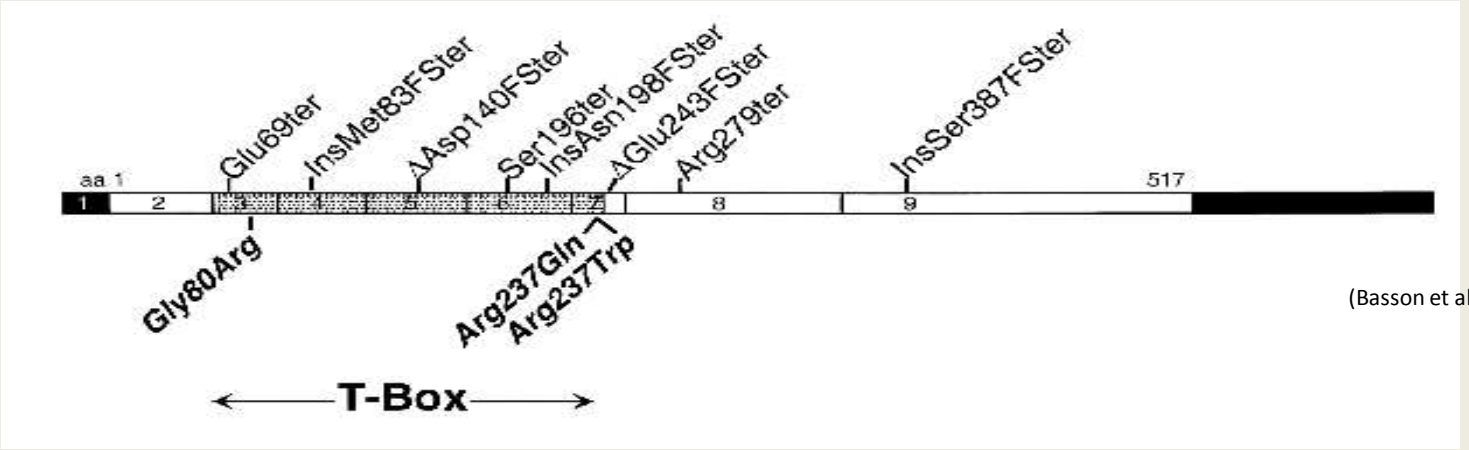
- Multiple congenital anomalies
  - Not always seen on ultrasound
- Severe mental retardation
- Most cases lethal



Holt-Oram syndrome

- 1 per 100,000 live births
- Autosomal dominant
  - 85% de novo mutations
  - Germline mosaicism
- Clinical features
  - Cardiovascular abnormalities
  - Bilateral asymmetric limb abnormalities

T Box Transcription Factor Gene (*TBX5* gene)



(Basson et al 1999)

- Nine coding exons
- Transcription factor
  - Cardiac septation
  - Forelimb outgrowth
- T-Box
  - DNA binding region
  - Highly conserved across species
- Over 30 mutations identified
  - Reduced *TBX5* dose

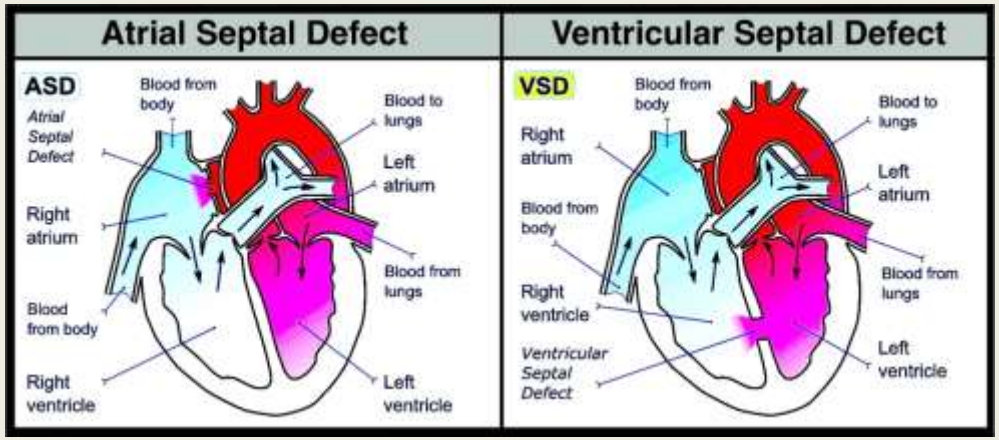
Clinical Features

Limb Abnormalities

- Radial, thenar, or carpal bones
- From thumb hypoplasia to phocomelia

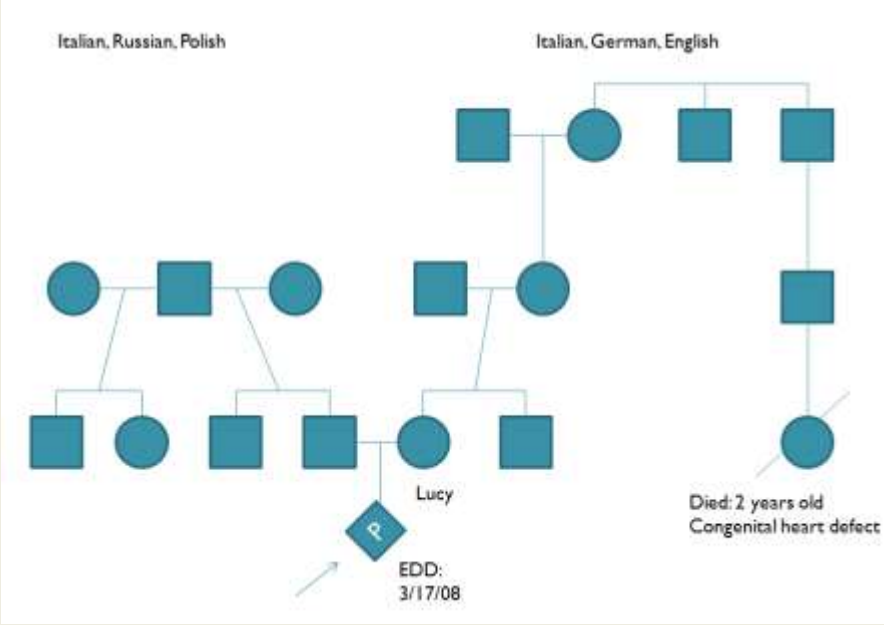
Cardiovascular Abnormalities

- Most common ASD or VSD
- From asymptomatic conduction defects to multiple structural anomalies



Consultation

- Obtained appropriate histories
  - Medical history on both patient and partner
  - Pregnancy history for patient
  - Family history for both patient and partner

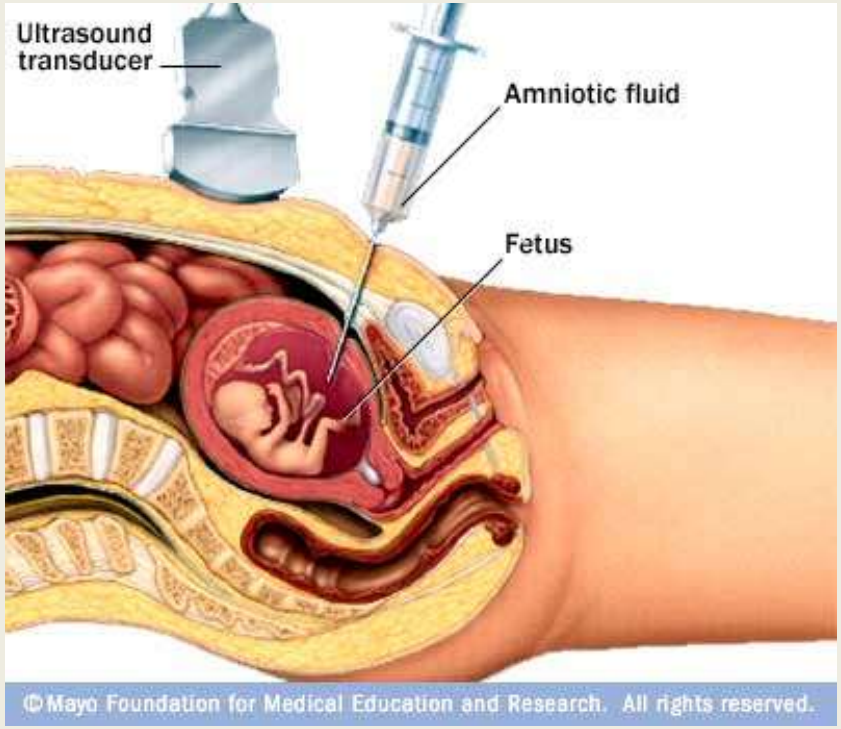


Consultation

- Discussed birth defects
  - Unable to determine etiology at this time
  - Likely we will not during pregnancy
  - Cannot predict if an other anomalies and/or mental retardation
- Options at this point
  - Continue: no additional evaluation
  - Continue: genetic testing
  - Termination

Consultation

- Genetic testing options
  - Chromosome analysis
    - Will not detect small structural changes or single gene conditions
  - TBX5 sequencing
    - 35% of patients with HOS will show mutations in this gene

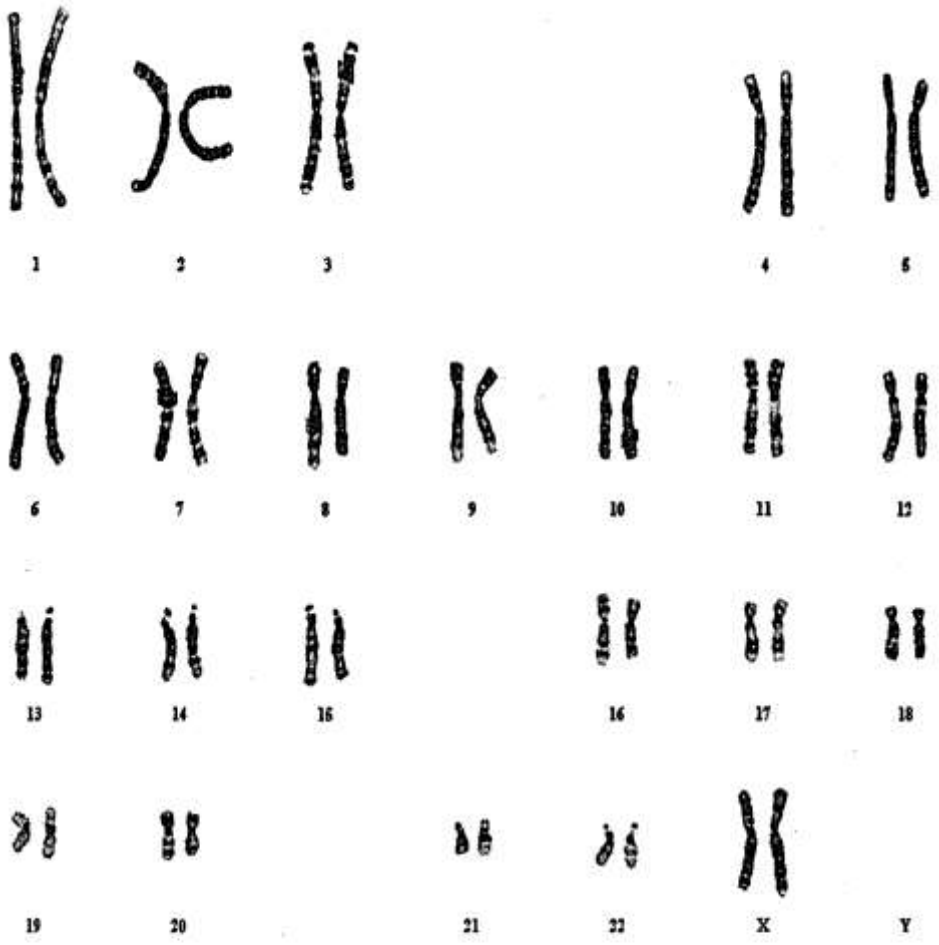


Consultation

- Psychological support
  - Throughout consultation and afterwards
    - Using counseling skills
    - Identifying personal resources
    - Referring couple to social worker specializing in pregnancy complications
    - Availability of other professionals and support groups

Coordination of Testing

- Patient chose to do testing stepwise
  - Genzyme Genetics
    - Complete chromosome analysis
      - TAT: 10 to 14 days
  - GeneDx
    - TBX5 gene sequencing
      - TAT: 2 to 3 weeks



Specimen #:
Specimen Type: AMNIO
Patient Name: FETUS of LUCY
Image ID: DKE1
Karyotype: 46,XX

Dept ID: A2
Date Received: 10/25/2007
Date Reviewed: 11/01/2007
Reviewed By: JLMC

genzyme GENERAL genetics

GeneDx

Mutation Analysis Laboratory Report

GeneDx
207 Perry Parkway
Gaithersburg, MD 20877
Phone: 301-519-2100
Fax: 301-519-2892
E-mail: genedx@genedx.com
www.genedx.com

Patient name:	LUCY (fetus of)
DOB:	
Submitters ID No:	Spec#
GeneDx Accession No:	
Specimen submitted:	Cultured amniocytes
Date sample obtained:	10-24-2007
Date sample received:	11-13-2007
Report date:	12-19-2006
Test performed:	TBX5 Gene / Prenatal testing for Holt Oram syndrome (HOS)
Result:	**POSITIVE. HETEROZYGOUS D111Y MUTATION IDENTIFIED IN TBX5 GENE.**

A heterozygous G>T nucleotide substitution was identified in exon 4 of the TBX5 gene, resulting in the replacement of an Aspartic acid codon (GAT) with a Tyrosine codon (TAT) at amino acid position 111 of the resultant protein. This mutation is denoted p.Asp111Tyr or D111Y. Analysis using polymorphic markers did not reveal evidence for significant maternal cell contamination of the fetal sample.

Interpretation:

According to the Human Gene Mutation Database (HGMD), the D111Y missense mutation in the TBX5 gene has been reported previously in association with autosomal dominant Holt Oram syndrome (Dias, 2007). Therefore, this result predicts that the fetus is **AFFECTED** with Holt Oram syndrome.

Genetic Test Results

- Provide accurate genetic counseling
  - Etiology for birth defects
  - Prognosis for this pregnancy
  - Facilitate testing on parents for accurate recurrence risk assessment
- Referrals
  - Orthopedic surgeon
  - Support groups for Holt-Oram

Additional Genetic Testing

- Most likely de novo case
  - Unremarkable family history
  - 85% cases are due to new mutation
- Parental testing available
  - If negative, still cannot rule out germline mosaicism
- Future pregnancies
  - Preimplantation genetic diagnosis
  - Prenatal diagnosis

Follow-Up Consultation

- When daughter was 8 months old, Lucy and her husband contacted me to facilitate genetic testing
- Neither had any clinical features of Holt-Oram syndrome

TBX5 genetic testing results

GeneDx
DNA DIAGNOSTIC EXPERTS

GeneDx
207 Perry Parkway
Gaithersburg, MD 20877
Phone: 301-519-2100
Fax: 301-519-2892
E-mail: genedx@genedx.com
www.genedx.com

Genetic Testing Results

Patient Name:	LUCY	*Specimen Obtained:*	11/20/2008
Date of Birth:		*Specimen Received:*	11/21/2008
GeneDx Accn.:		*Date Test(s) Started:*	11/21/2008
Specimen Type:	Blood	*Report Date:*	12/16/2008
Submitters ID No:	H43738, 2168318		

Test(s) requested: TBX5 Gene/ Evaluate for D111Y Mutation/ Holt-Oram Syndrome (HOS)

Relevant History: Affected child (GeneDx#) with a heterozygous D111Y mutation in the TBX5 gene.

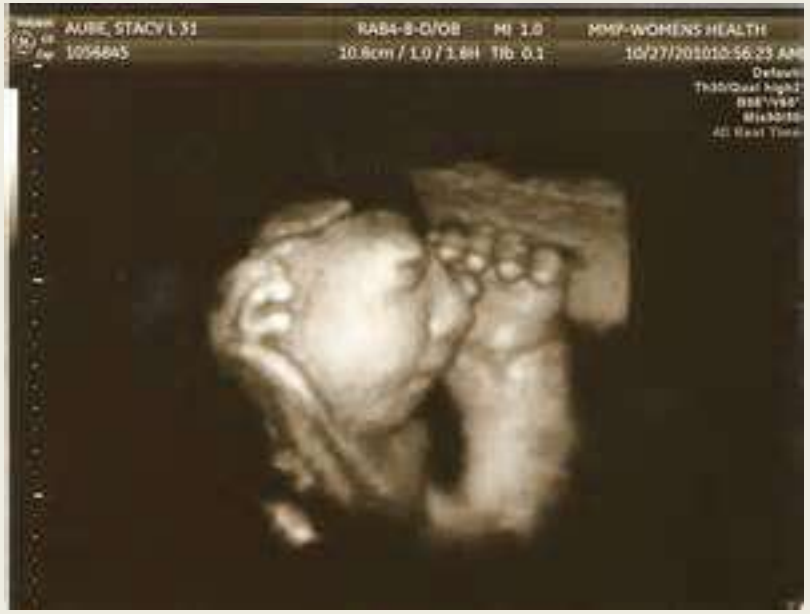
Result: **POSITIVE. The D111Y Mutation is PRESENT**

A heterozygous G>T nucleotide substitution was identified in exon 4, resulting in the replacement of an Aspartic Acid codon (GAT) with a Tyrosine codon (TAT) at amino acid position 111. This mutation is denoted c.331 G>T at the cDNA level or p.Asp111Tyr (D111Y) at the protein level.

Interpretation: This individual also harbors the D111Y missense mutation in the TBX5 gene that was previously identified in a child with Holt-Oram syndrome. According to the Human Gene Mutation Database (HGMD), D111Y has been reported previously in association with HOS (Dias et al., 2007). Mutations elsewhere in the TBX5 gene would not be identified by this targeted analysis.

GENETIC COUNSELING FOR FETAL ANOMALIES

Ultrasound Results



Genetic Consultation

- Any pregnancy with fetal anomalies referred for genetic counseling to discuss:
  - Etiology of birth defect(s), if known
  - Chance underlying genetic syndrome
  - Benefits and limitations of genetic testing
  - Coordination of genetic testing
  - Management of pregnancy
  - Prognosis

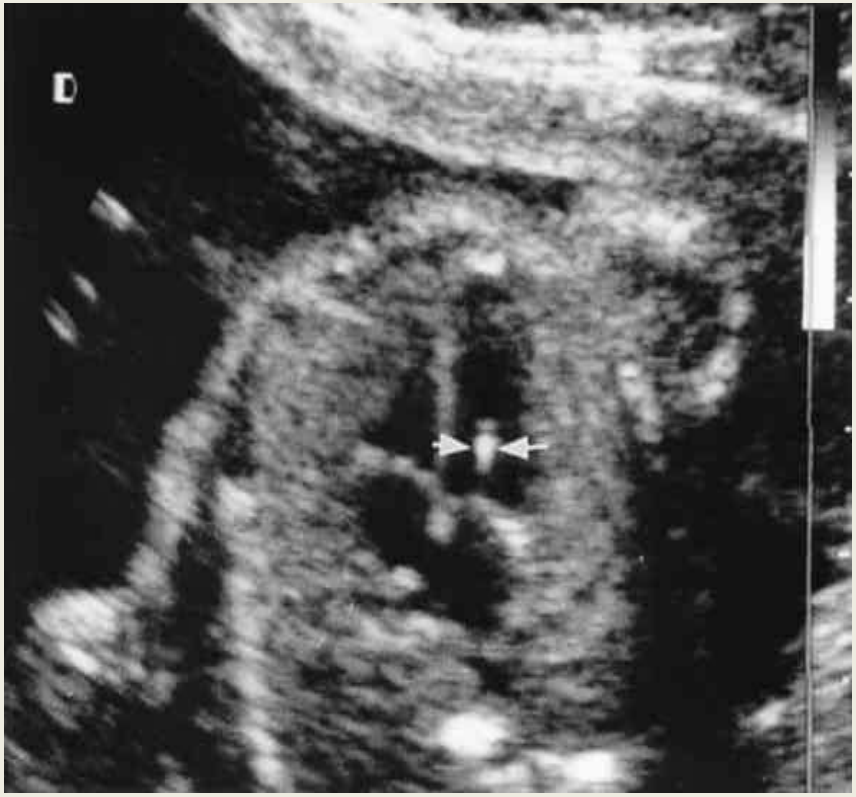
“Soft Signs”

- Variations on ultrasound
  - NOT structural abnormalities
  - Detected with increased frequency due to advanced ultrasound resolution
- Each soft sign is identified in 1-2% of ***normal*** pregnancies
- Each occurs more often in fetuses with a chromosome abnormality

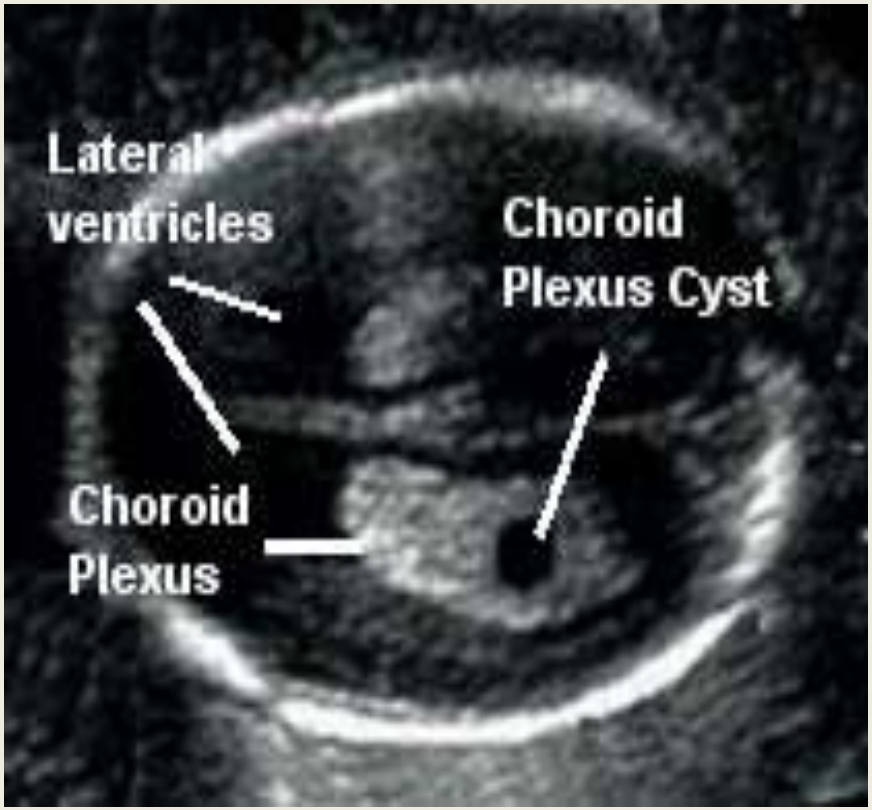
Examples of Soft Signs

- Echogenic intracardiac focus (EIF)
  - Hyperechoic spot on the fetal heart
  - Hypothesized to be calcium deposits in the muscle
  - Associated with an increased risk for Down syndrome
- Choroid plexus cyst (CPC)
  - The choroid plexus is the portion of the brain responsible for creating cerebral spinal fluid
  - Associated with increased risk for Trisomy 18

EIF



CPC

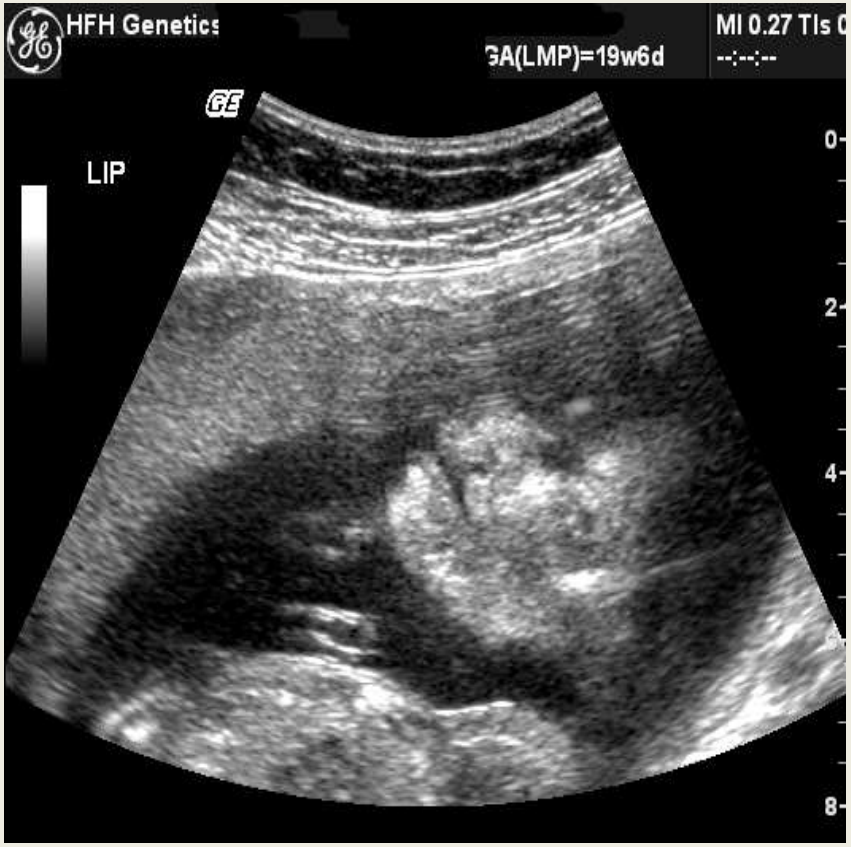


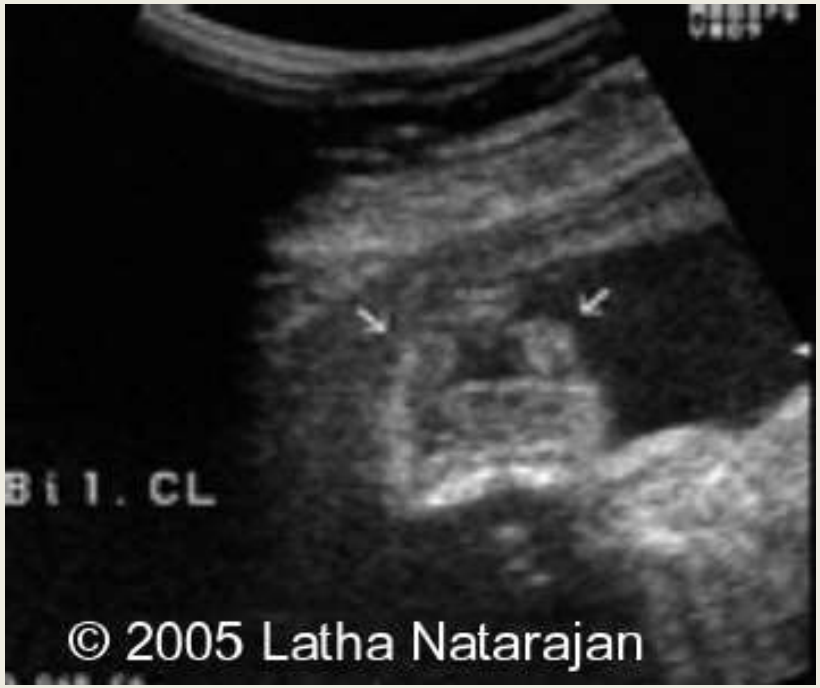
What if a soft sign is visualized?

- Are there other risk factors?
  - Advanced maternal age?
  - Multiple markers?
  - Abnormal maternal serum screen result?
  - Family history?
- Prenatal diagnostic testing
- If chromosomes are normal then the markers are considered normal variants

Unknown to the rest of the world, members of the scientific community have been making their own babies to order for quite some time now.

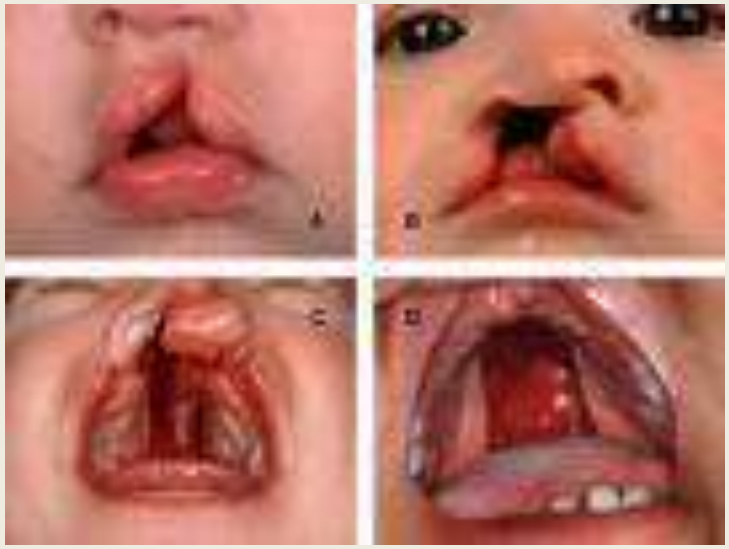
Cleft Lip & Cleft Palate





Cleft Lip & Cleft Palate

- Facial cleft involving the upper lip and/or palate, usually to the right or left of midline
- May occur as an isolated malformation or part of a multiple malformation syndrome
- Seen in 1:500 – 1:1000 livebirths
- Cleft lip and/or palate (M>F)
- Isolated cleft palate (F>M)



Cleft Lip & Cleft Palate

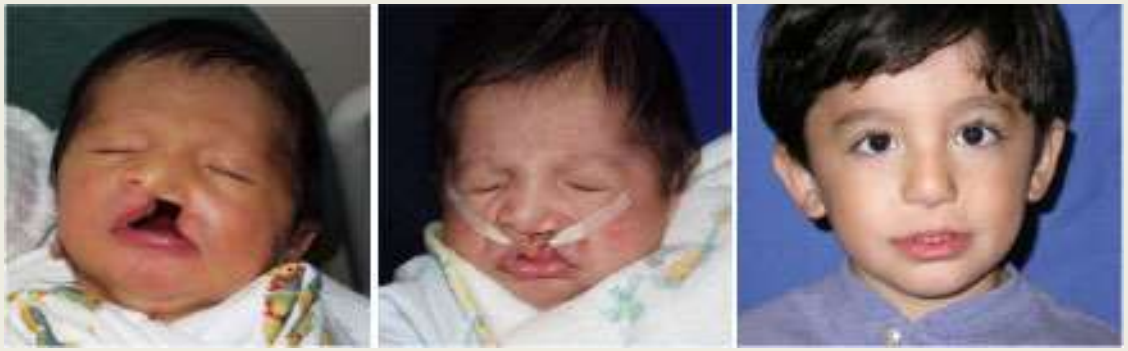
- Prenatal Testing / Management of Pregnancy
  - Detailed medical history, exposure history, family history
  - Detailed fetal ultrasound to look for additional abnormalities
  - Fetal echocardiogram
  - Fetal karyotype
    - Consider additional genetic testing if findings are suggestive of specific genetic syndrome (FISH for 22q11.2 deletion)
  - Serial ultrasounds for polyhydramnios
  - Meet with neonatologist and pediatric surgeon prior to delivery

Cleft Lip & Cleft Palate

- After Delivery
  - Genetics evaluation to look for additional abnormalities
  - Echocardiogram
  - Feeding difficulties – failure to gain weight appropriately
  - Surgical repair of the defect
  - Hearing evaluation
  - Long term concerns include appearance (and related psychological problems), dental abnormalities, speech disorders, and reduced body growth

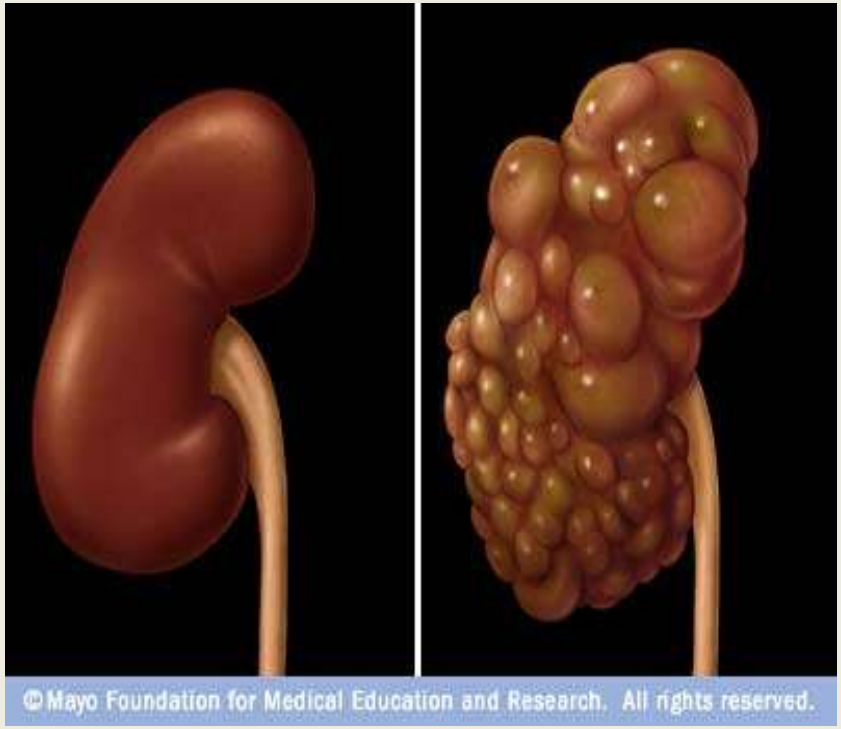
Cleft Lip & Cleft Palate

- Recurrence Risks
  - Aneuploidy: slightly higher than a woman's age-related risk for aneuploidy
  - Genetic syndrome: depends on the syndrome and type of inheritance, but may potentially be as high as 50%
  - Isolated cleft lip and palate:
    - Risk to offspring of affected: 4.3%
    - Risk to siblings of affected: 4-10%



Cystic Kidneys

- Group of disorders ranging from:
  - Solitary cysts
  - Multicystic kidneys
  - Polycystic kidneys
- Findings:
  - Enlarged and hyperechogenic
  - Uni- or bi-lateral involvement
  - Absent or reduced levels of amniotic fluid
  - Small/absent bladder
- Genetic, developmental, and systemic etiologies



Complications/Prognosis

- The cysts replace most of the normal structure of the kidneys reducing function

- Unilateral
  - Good prognosis if associated abnormalities are excluded and amniotic fluid volume is preserved
  - Chronic concerns: high blood pressure, pain, infections, kidney failure
  - Usually requires dialysis and/or transplant later in life

- Bilateral
  - Typically considered lethal condition because of oligohydramnios leading to pulmonary hypoplasia
  - Need to make decisions about resuscitation at birth

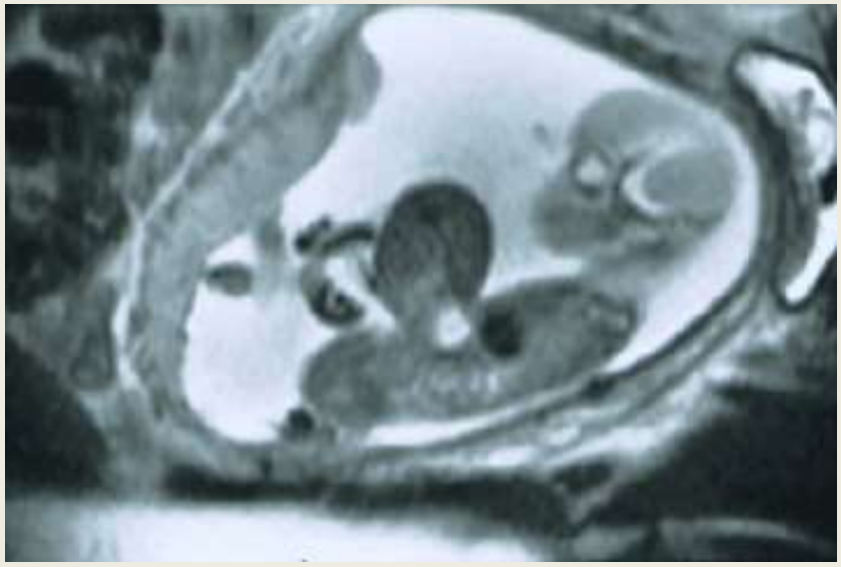
- Depends on diagnosis; other associated abnormalities?
  - ***Many times, a diagnosis is not made prenatally***

Differential Diagnoses/Ultrasound Findings

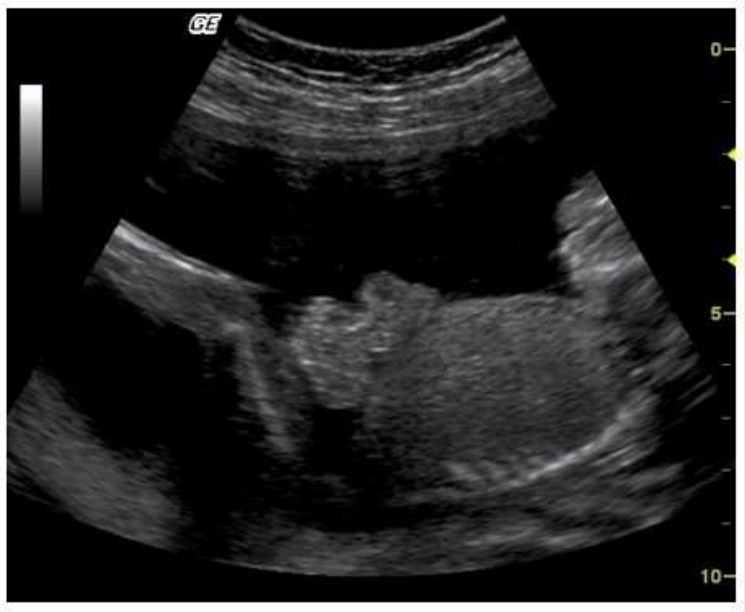
Disease	Cysts (size, location, and number)	AFI	Associated abnormalities
AD Polycystic KD	Randomly distributed cysts	Normal or reduced	Uncommon
AR Polycystic KD	Greatly enlarged kidneys with no visible cysts	Reduced	Uncommon
Trisomy 13	Enlarged echogenic kidneys; randomly dispersed small cysts	Normal or reduced	Heart defects, brain abnl., IUGR, facial clefts
Meckel-Gruber syndrome	Small cysts, same size, scattered throughout	Normal or reduced	Encephalocele, polydactyly
Multicystic Dysplastic Kidney	Cysts grouped at the periphery of the kidney	If bilateral then no fluid; unilateral then normal	GI-defects, other urologic abnl., cranial defects

Ventral Wall Defects
Omphalocele & Gastroschisis

Fetal MRI: Omphalocele



Gastroschisis

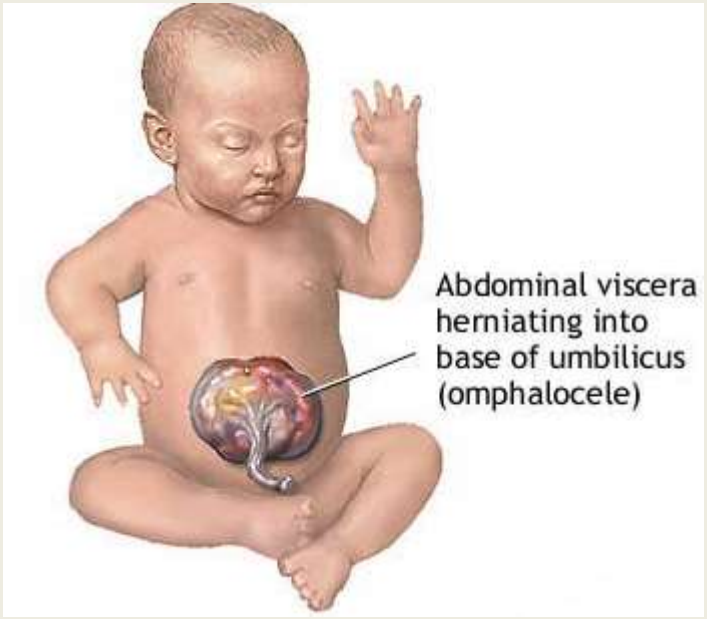


Ventral Wall Defects

- Omphalocele is a transparent sac of amnion attached to the umbilical ring that contains herniated intestines
- Gastroschisis is the finding of exposed intestines that protrude through a defect that is typically located on the right side of the abdomen
- Both occur in 1:4000 births
  - Gastroschisis (M:F)
  - Omphalocele (M1:F5)

Ventral Wall Defects

- Omphalocele
  - Associated abnormalities are seen in ~66% of cases, including congenital heart defects, bladder exstrophy, imperforate anus, neural tube defects, cleft lip +/- cleft palate, and diaphragmatic hernia
  - Approximately 25% have associated chromosomal abnormalities
  - Other genetic syndromes



Ventral Wall Defects

- Gastroschisis
  - Primary concern: vascular compromise from kinking of the blood vessels coming through the defect which can lead to necrosis
  - Intestinal atresias and other GI disruptions are found in approximately 5-10% of cases
  - Extraintestinal abnormalities occur in less than 5% of cases
  - Usually not associated with chromosomal abnormalities or genetic syndromes
  - Associated with young maternal age and maternal cigarette smoking

Ventral Wall Defects

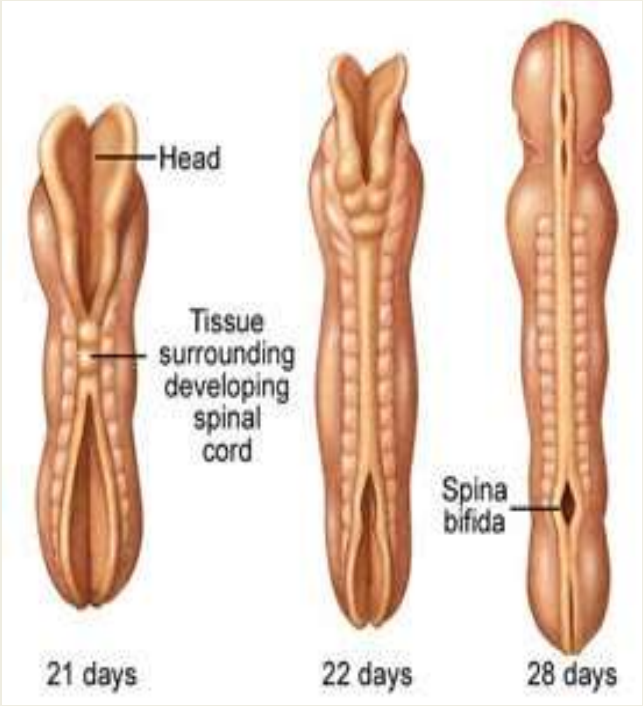
- Prenatal Testing / Management of Pregnancy
  - Omphalocele
    - Detailed fetal ultrasound examination
    - Fetal karyotype
    - Fetal echocardiogram
    - Consultation with neonatologist and pediatric surgeon
    - Serial ultrasounds to monitor growth
    - Preterm delivery and IUGR frequently complicate cases
    - High rate of emergency C-sections due to fetal distress
    - Delivery at hospital with tertiary-care center

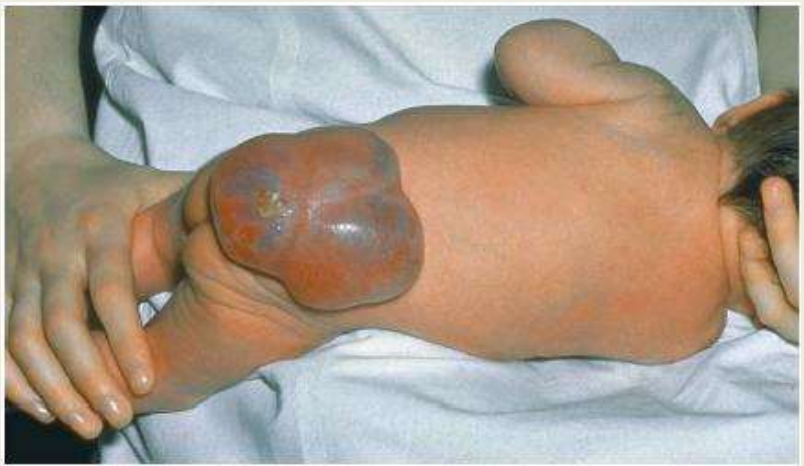
Ventral Wall Defects

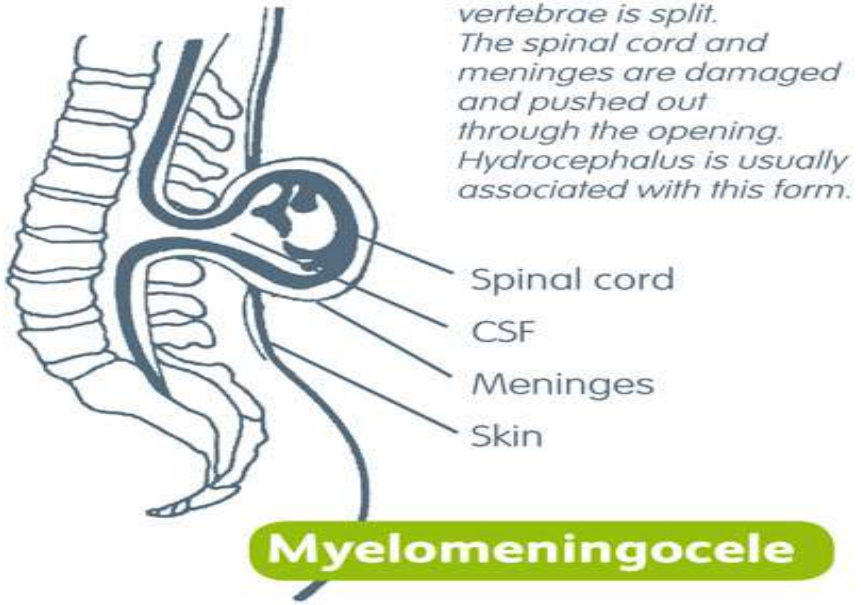
- Prenatal Testing / Management of Pregnancy
  - Gastroschisis
    - Detailed fetal ultrasound examination
    - Fetal karyotype can be considered
    - Fetal echocardiogram
    - Consultation with neonatologist and pediatric surgeon
    - Serial ultrasounds to detect thickening and/or dilation of the fetal bowel and assess fetal growth
    - Preterm delivery and IUGR frequently complicate cases
    - Delivery at tertiary-care center

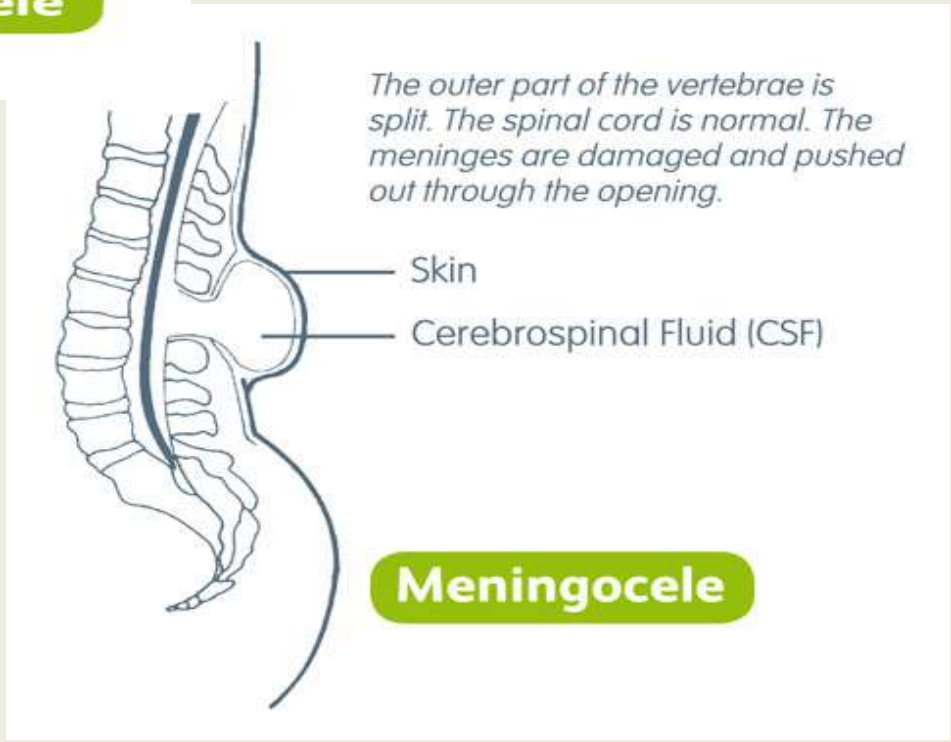
Neural Tube Defects (NTDs)

- Population incidence: 1/1000 births
- Failure of closure of the neural tube @ ~28 days post conception
- Includes
  - Anencephaly
  - Spina bifida
    - Myelomeningocele
    - Meningocele
- Caused by
  - Multifactorial inheritance
  - Diabetes
  - Medications (anti-seizure medications)
  - Chromosomal or single gene disorders

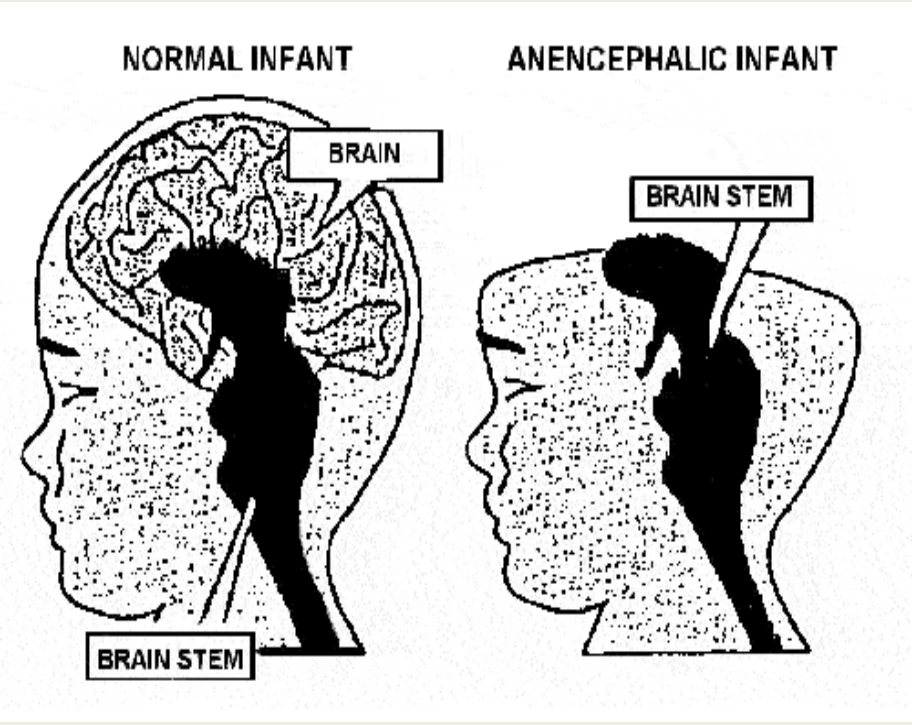


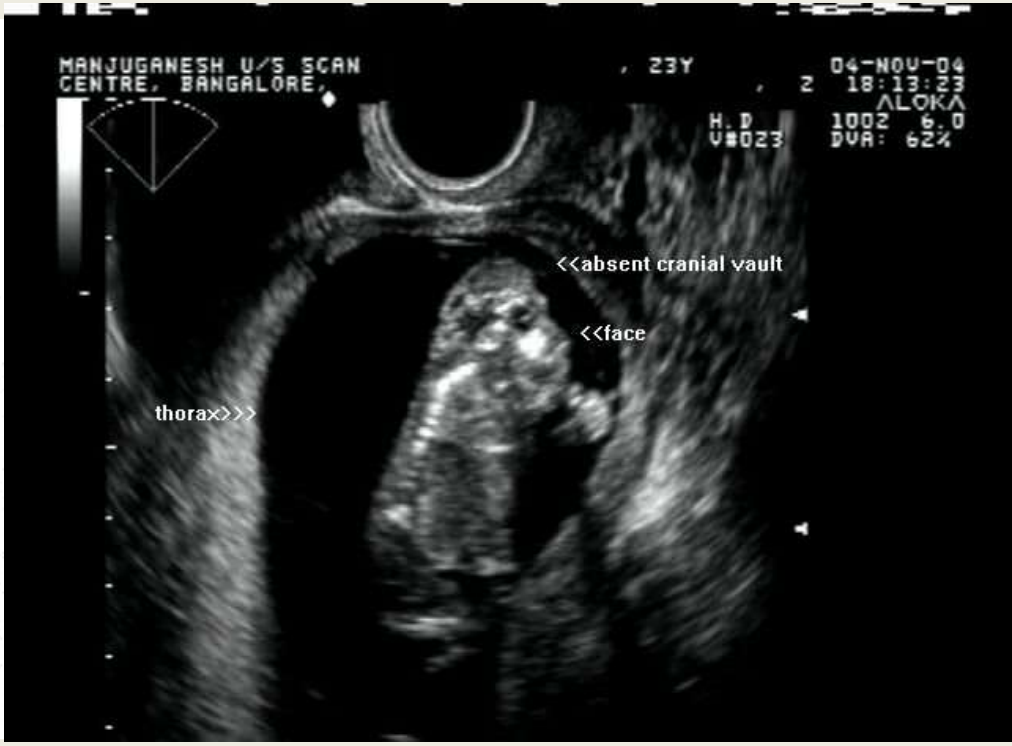



The outer part of the vertebrae is split. The spinal cord and meninges are damaged and pushed out through the opening. Hydrocephalus is usually associated with this form.
Spinal cord
CSF
Meninges
Skin
Myelomeningocele


The outer part of the vertebrae is split. The spinal cord is normal. The meninges are damaged and pushed out through the opening.
Skin
Cerebrospinal Fluid (CSF)
Meningocele

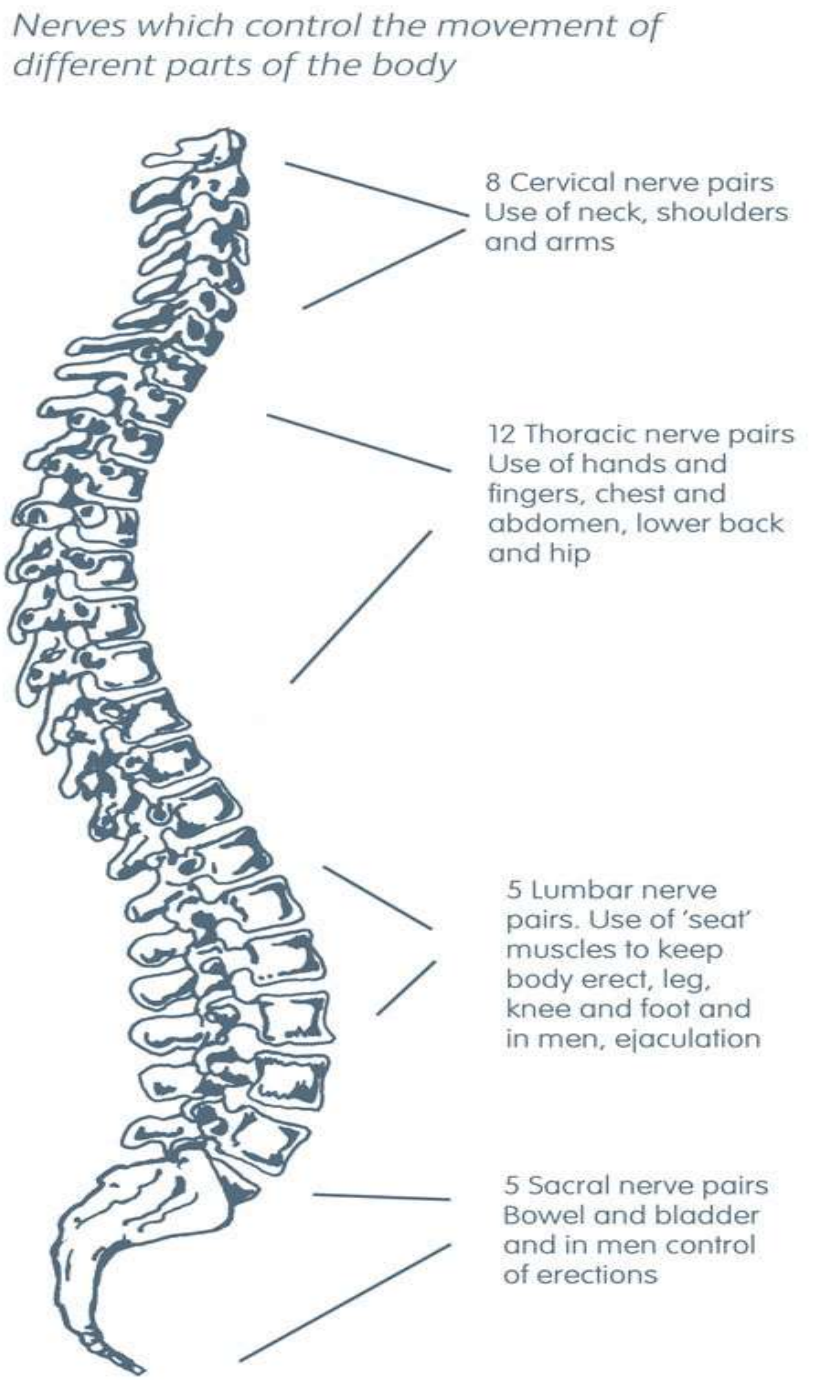
Anencephaly





Medical Issues

- During and after birth, the exposed nerves can become damaged and infecte
- Anencephaly is lethal
- Other forms show variable severity depending on :
  - Presence of neural tissue
  - Size and location of the malformation (the higher, th more severe)
  - Whether it is covered



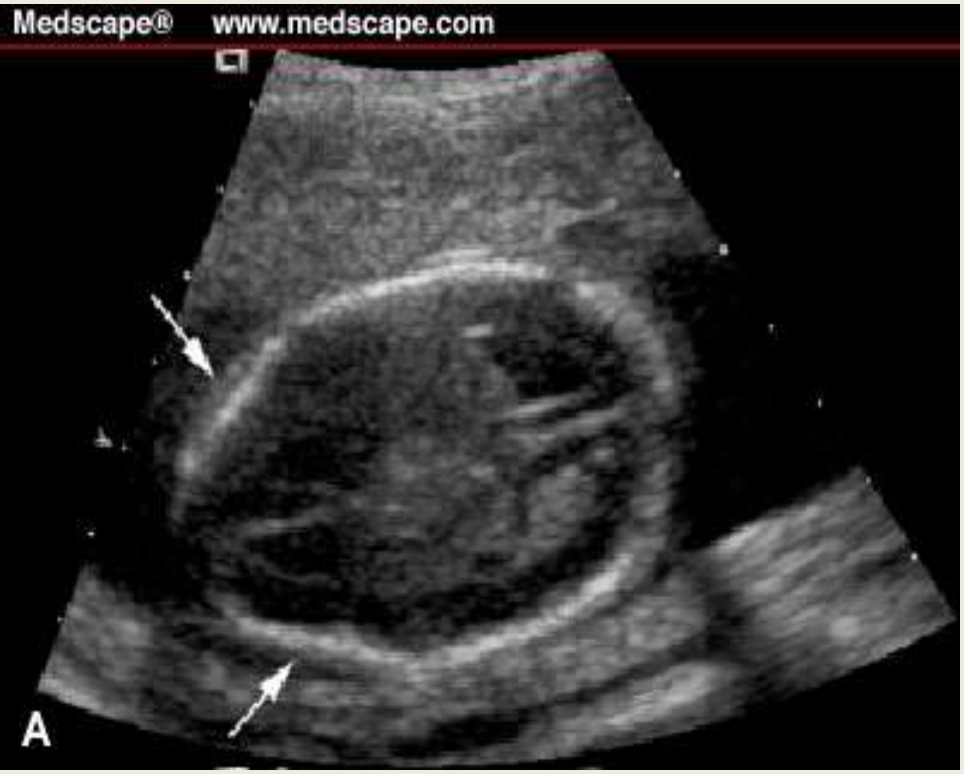
Medical Issues

- Spine:
  - Loss of sensation and paralysis
  - Loss of control of muscles served by damaged nerves
  - Tethered cord
  - Sexual dysfunction
- Brain
  - Hydrocephalus
  - Chiari II malformation
  - Learning disabilities
- Urologic issues:
  - Loss of bowel and bladder control
  - Kidney infections and damage
  - Gastrointestinal issues
- Orthopedic issues
  - Paralysis can lead to dislocated joints, misshapen bones, scoliosis

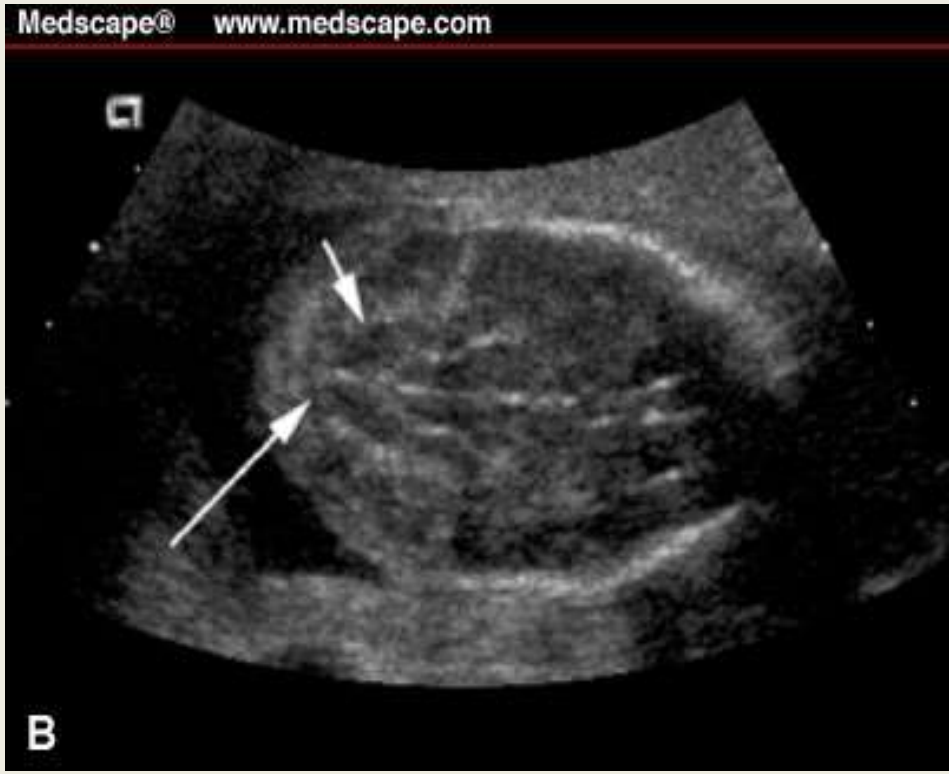
Diagnostic Options

- Ultrasound
  - A detailed ultrasound at 18-20 weeks can detect 90% of open neural tube defects
  - Anencephaly as early as 12 weeks
  - Open defects are associated with specific head findings
    - *Lemon sign:* 98% of fetuses with open defects when scanned <24 weeks and 13% of fetuses scanned after 24 weeks
    - *Banana sign:* 95% of fetuses with open defects
    - Ventriculomegaly

Cranial Ultrasound Findings Associated with Open Spina Bifida



Inward scalloping of the frontal bones (arrows), also known as the "lemon sign."



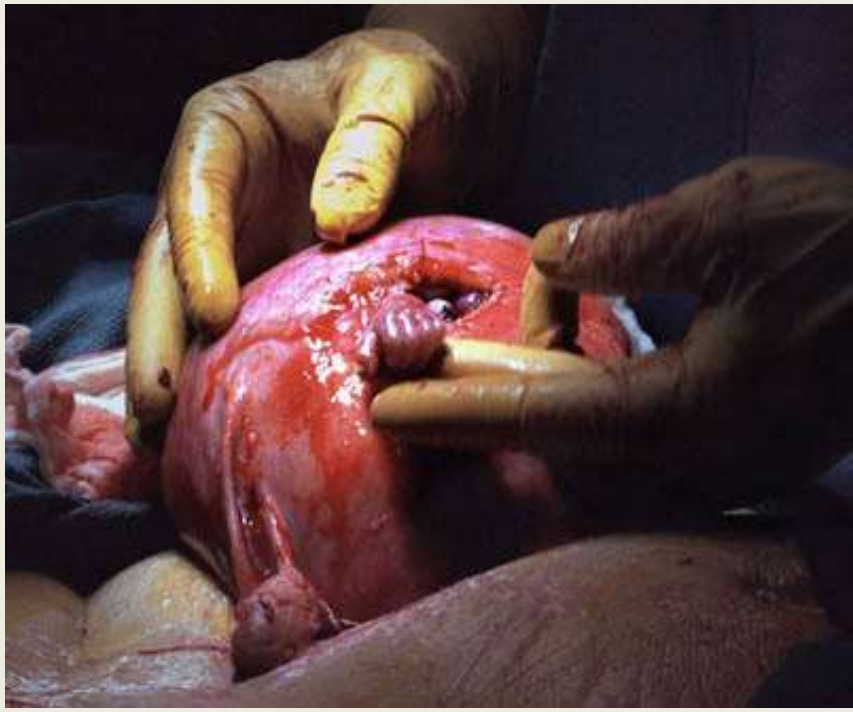
Small posterior fossa and banana-shaped cerebellum ("banana sign") (short arrow) and effaced cisterna magna (long arrow).

Other Diagnostic Options

- Maternal serum screening (MSS)
  - Elevated alphafetoprotein (AFP) in mom's blood
  - Can detect 85% of ONTDs if drawn after 15 0/7 weeks

- Amniocentesis
  - Elevated AFP
  - Can detect 95% of ONTDs
  - Acteylcholinesterase (ACHE) level can detect greater than 99% of *open* NTDs.
  - Recommended when:
    - Abnormal ultrasound
    - Abnormal MSS result
    - Prior history of ONTD
    - History of medication exposure

Pregnancy Management



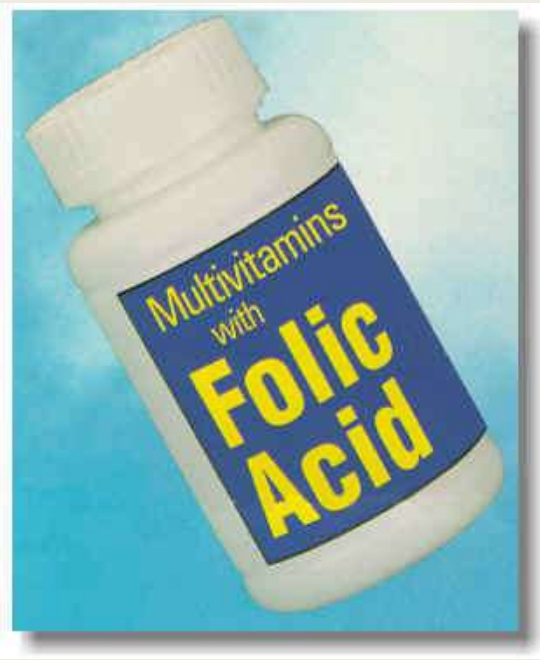
- Continuation versus termination
- Follow-up ultrasounds to watch progression
- Fetal MRI
- Fetal echocardiogram
- Discuss delivery plan
- Surgery
  - Earlier the better (before 25 weeks)
  - Cannot restore lost function but can prevent further damage
  - Risks to mother and fetus

Medical Management/Prognosis

- Prevent infection
- Surgery
- Shunt to correct hydrocephalus
- Long-term multidisciplinary care (neurosurgeon, orthopedic surgeon, urolo dietician, physical therapist)
- Assistive devices
- Early developmental intervention
- Prognosis is variable but better when chil get early intervention

Recurrence Risks

- Recurrence depends on the cause
  - Genetic condition: risk as high as 50%
    - Other abnormalities?
    - Family history?
  - Chromosomal: risk <1%
  - Isolated: 3-5% risk to siblings
- Recurrence risks for all types
- Folic Acid supplementation can reduce the risk of NTDs by 50%



Thank You

Elizabeth Cameron, MS, CGC
Lauren Mohnach, MS, CGC

For use of their slides on fetal anomalies.