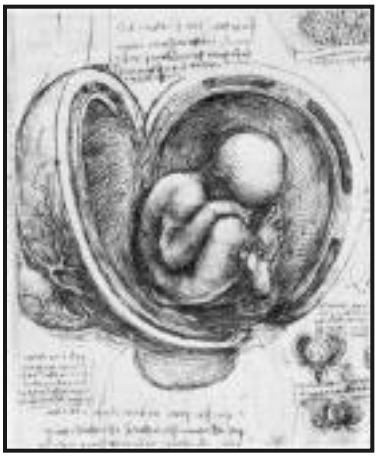
Prenatal Diagnosis Objectives

- Read/learn OBJECTIVES on web page and assigned text (pages 297-307 in Gelehrter et al.)
- Understand indications for and utility of prenatal diagnostic tests
- Know applications, risks, benefits, timing, and limitations of prenatal diagnostic techniques discussed in lecture and readings
- Understand basic elements and issues surrounding prenatal diagnosis and counseling



The goal of prenatal diagnosis is *not* to generate perfect babies.

"The are no perfect human specimens - we are all genetically flawed in some way."
- F.Collins

The goal of prenatal diagnosis is to help parents learn what *they* need to know about the health of their unborn child to help them make informed decisions for themselves and their family within the context of their own value system.

Prenatal Diagnosis

- Using a wide variety of screening and diagnostic tests to assess health of a fetus to:
  - Manage the pregnancy
  - Determine potential outcomes
  - Plan for complications at birth
  - Decide whether to continue the pregnancy
  - Discover conditions that may impact future pregnancies

General Caveats about Prenatal Diagnosis

- All couples have ~3% risk of having a child with congenital problems requiring intervention
- No 100% guarantees - even if prenatal tests are 'normal'
- All couples bring unique ethnocultural, moral, and/or religious perspectives to the process
- Use of non-judgmental, non-directive genetic counseling is important in helping families make the best choice for them
- The decision to terminate or continue a pregnancy based on prenatal diagnostic findings is *never* an easy decision

Goals of Prenatal Diagnosis and Counseling

- Assess pregnancy
- Determine specific risks to fetus
- Evaluate prenatal diagnostic options
- Diagnosis fetus when desired and possible
- Educate family about diagnosis, likely outcomes, potential and management options
- Discuss risks, benefits, and uncertainties
- Explore family concerns
- Provide risk assessment for other family members
- Provide psychosocial support and follow-up

Who benefits from prenatal diagnosis?

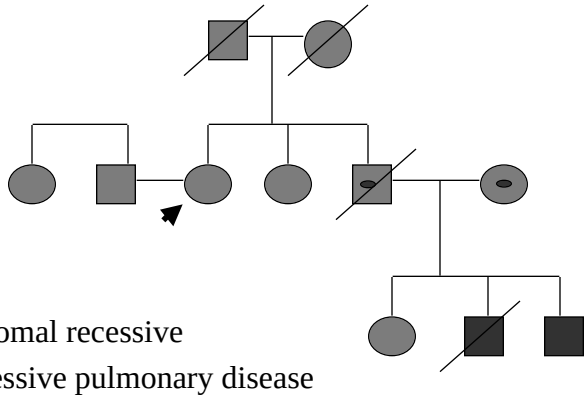
- Older women (≥ 35) at increased risk of chromosome disorders
- Individuals in populations at increased risk of a genetic disease:
  - Tay-Sachs: Ashkenazi Jews, French Canadians
  - Sickle cell anemia: Africans, Mediterraneans, Arabs, Turks, Indo-Pakistanis
  - Thalassemias: Mediterraneans, Arabs, Turks, Indo-Pakistanis, Southern and Southeast Asians
  - Cystic Fibrosis: Caucasians
  - Fragile X syndrome: All women (?)
- Family history of a genetic disease/chromosome disorder
- Maternal disease associated with increased risk of birth defects (diabetes, phenylketonuria)
- Known teratogen exposure during pregnancy
- Abnormal screening tests or ultrasounds
- Women who are concerned/worried

- What genetic tests are *AVAILABLE*?
- What genetic tests should be *OFFERED?*
- What genetic tests should be *RECOMMENDED*?

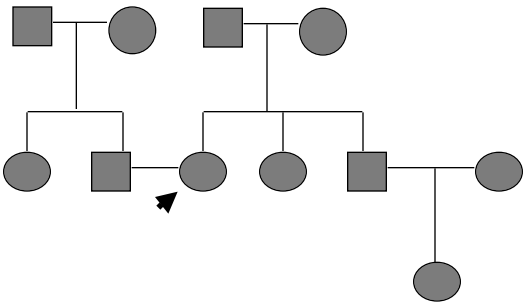
Preconception/Carrier Testing

- Couples/individuals in "high risk" populations considering pregnancy should be *offered* voluntary, informed testing prior to pregnancy
- Appropriate education and counseling about risks and benefits of tests and various reproductive options should be available prior to and after testing

Cystic Fibrosis



- Autosomal recessive
- Progressive pulmonary disease
- Exocrine pancreatic dysfunction
- Infertility
- CFTR gene identified in 1989
  - over 800 mutations reported



1 in 25 Caucasians of Northern European ancestry are carriers of a CFTR mutation

*"**<u>All</u>** Caucasians should be offered preconception or prenatal CFTR mutation carrier screening"*
ACOG 10/2001

Genotype vs. Phenotype

Severe CF - Mild CF - Male infertility?

Prenatal Diagnosis Techniques

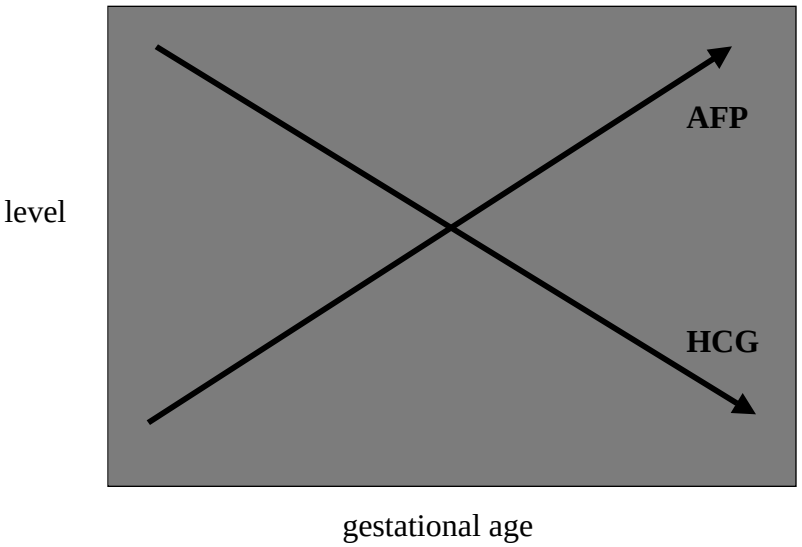
- Maternal Serum Screening Tests
  - Triple screen (alpha-fetoprotein, beta-HCG, and estriol) for neural tube defects and chromosome trisomies
- Visualization of the fetus
  - Ultrasound - 2D and 3D
  - Other (very special circumstances -X-ray, fetoscopy)
- Genetic and biochemical studies of fetal cells
  - Amniocentesis
  - Chorionic villus sampling
  - Fetal blood sample (percutaneous umbilical sample)
  - Circulating fetal cells in maternal blood

Maternal serum alpha-fetoprotein (MSAFP)

- Levels increase with gestational age in amniotic fluid and cross placenta into maternal bloodstream
- With neural tube (anencephaly, spina bifida) and body wall defects (gastroschisis, omphalocele) AFP is HIGH
- Using MSAFP along with detailed ultrasound study is sensitive to detect open body wall and neural tube defects
- MSAFP is LOWER in trisomies but using MSAFP alone to pick up trisomies is not sensitive or specific
- MSAFP most sensitive between 16-18 weeks
- To interpret must know gestational age, twin status, maternal health status(diabetes),and race - falsely high and falsely low values are often due to poor gestational dating

Maternal serum beta-human chorionic gonadotropin (MSβ−hCG)

- Produced early by trophoblasts during pregnancy
- Elevated by first missed period and used as a pregnancy test
- Elevated hCG in the mid-late 2nd trimester in trisomies
- Most sensitive when used in correlation with MSAFP level
  - eg. MSAFP low AND MSβ−hCG high suggests increased risk of a trisomy
- VERY elevated hCG in the mid-late 2nd trimester along with an absence of a fetus suggests trophoblast disease (molar pregnancy)



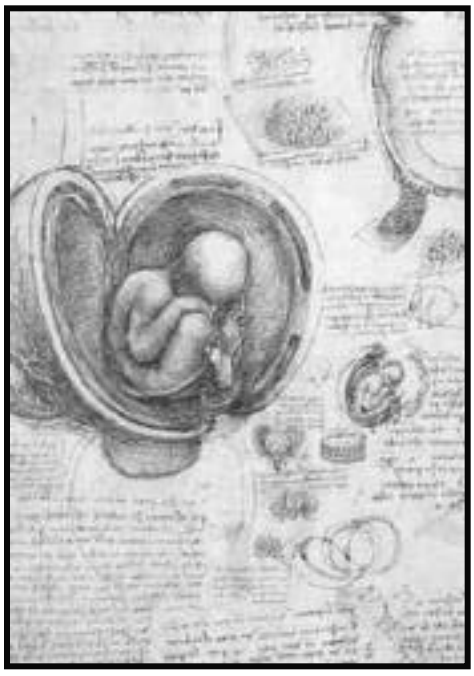
Maternal Serum Estriol

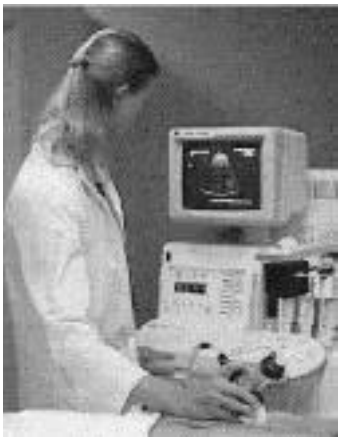
- Derived from adrenal gland hormone which is further metabolized by the placenta
- Tends to be lower in trisomies and in neural tube defects associated with adrenal hypoplasia

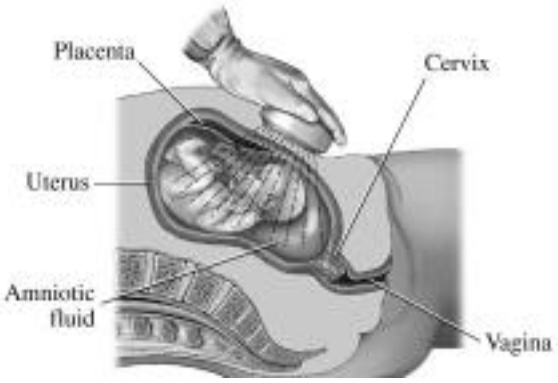
MSAFP vs "Triple Screen"

- Increased MSAFP alone is pretty sensitive for open body wall defects (eg. >95% for anencephaly, 80% for spina bifida)
- Decreased MSAFP alone is NOT very sensitive for trisomies (only 25%)
- "Triple screen" increases sensitivity (eg. to about 60% for Down syndrome)
- Use of more biomarkers further increases sensitivity, but no panel 100% sensitive or specific

Disorder	AFP	hGC	hCG/AFP ratio
Trisomy 21	↓	↑	↑
Trisomy 18	↓	↑	↑
Anencephaly	↑	N	↓↓
Spina Bifida	↑	N	↓
Twins	↑	↑	N
Fetal death	↓	↓	N ↓

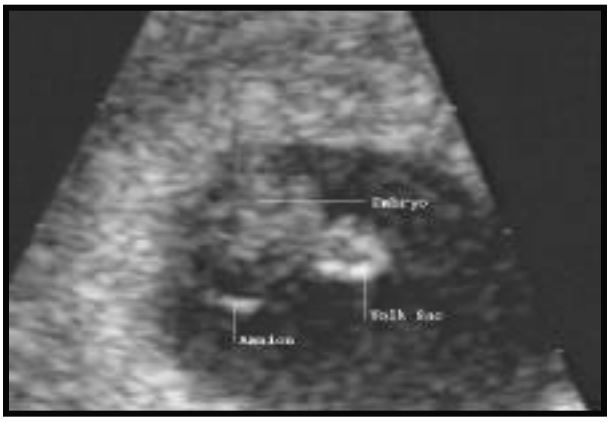


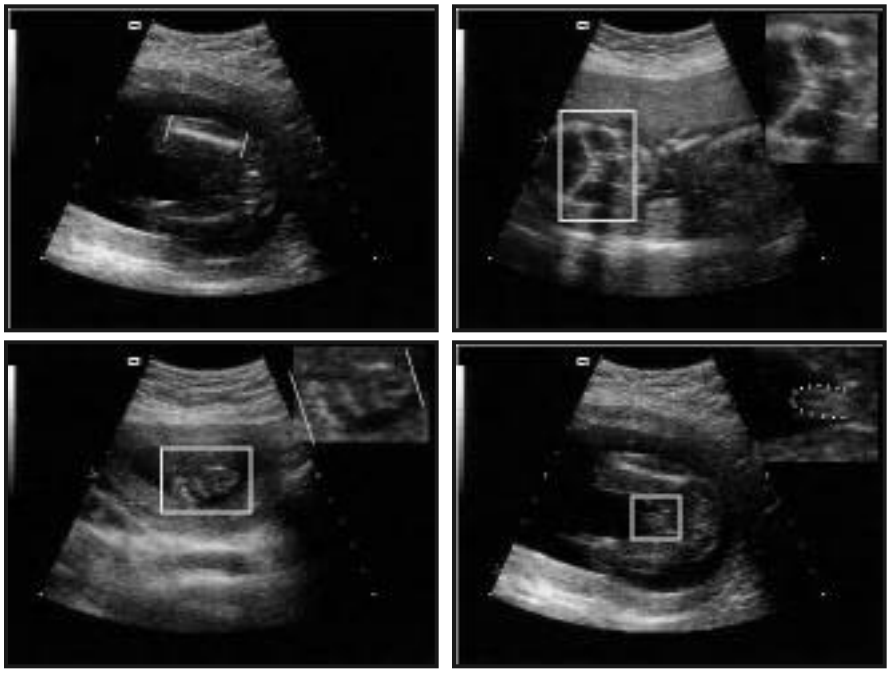


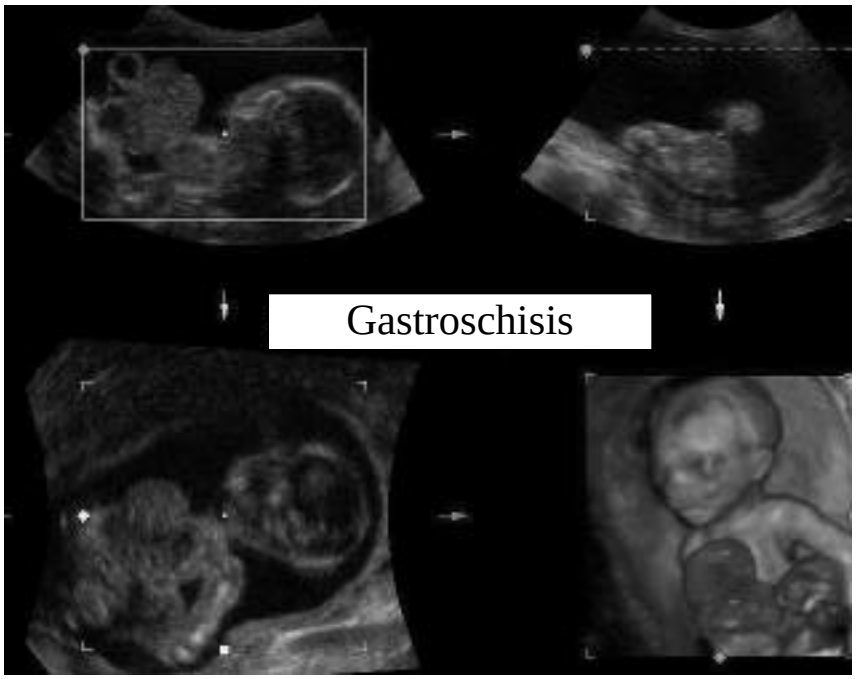


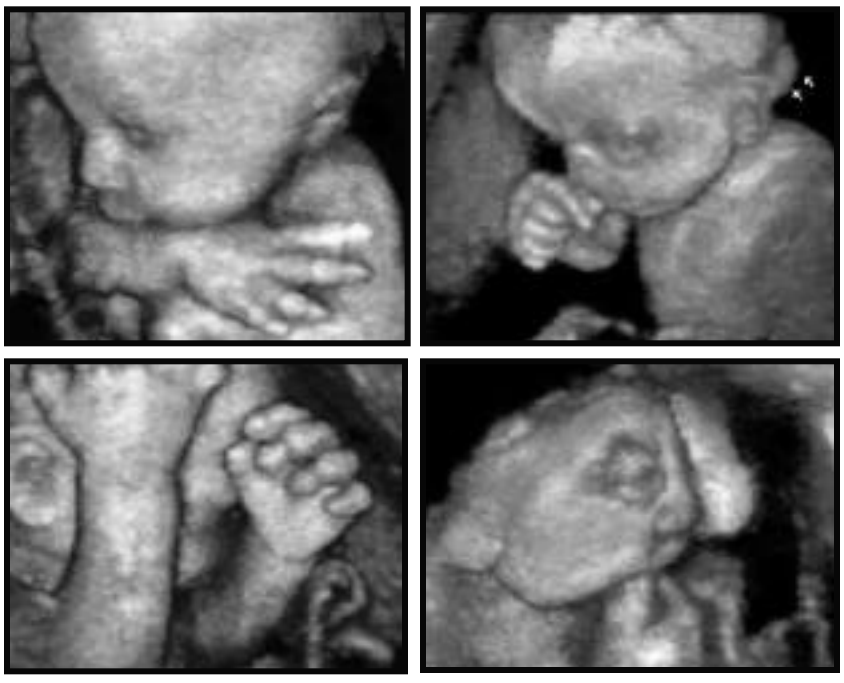
Ultrasonography

- Non-invasive - no known risks to mother or fetus
- 2-D, 3-D high resolution and fetal echocardiograms
- Assess fetal proportions, sex, position, growth; placenta, amniotic fluid
- Accurately estimate fetal age
- At 6 weeks can see developing embryo
- Between 16-20 weeks gestation is optimal time to screen for congenital anomalies for prenatal diagnosis
- False positive and false negative findings - conditions with subtle findings may be missed, (eg. trisomy 21)


Embryo
Yolk Sac
Amnion




Gastroschisis

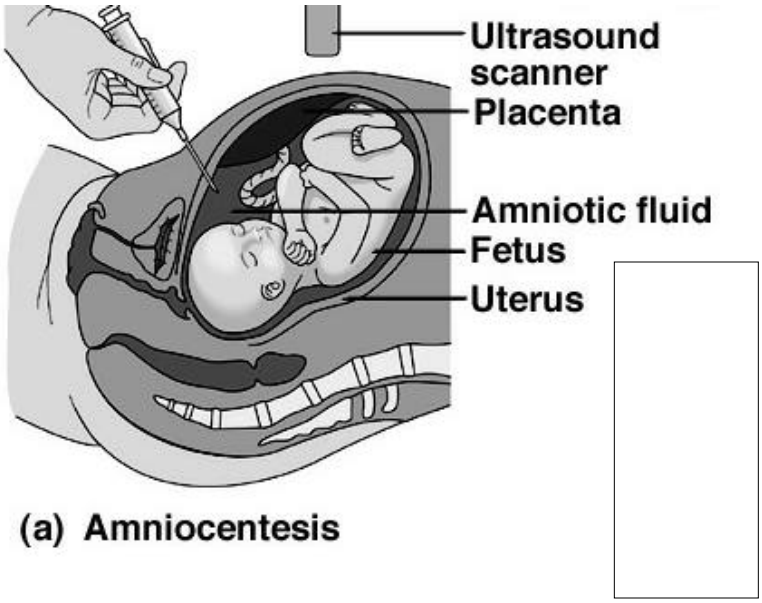


Some conditions detected by ultrasound

- Neural tube defects
- Body wall defects
- Major organ abnormalities
- Oligo- or polyhydramnios
- Major limb abnormalities
- Growth disturbances

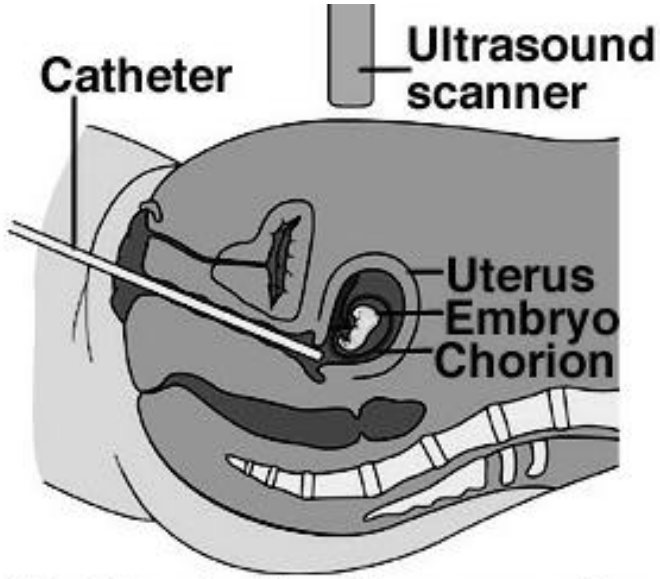
Genetic Amniocentesis

- Invasive technique to obtain fetal cells
- Study chromosomes, DNA, or biochemical profile of fetus
- Approach via mother's abdomen under ultrasound guidance
- Enough fluid after 14 weeks of gestation to perform safely
- Most often preformed between 15 and 20 weeks gestation
- Risks:
  - fetal loss - < 0.5% higher than normally expected
  - trauma and infection,
  - risk of club foot reported when done < 13 weeks
- Later in pregnancy (eg. third trimester), amniotic fluid can be taken to assess fetal lung maturity prior to a premature delivery



Chorionic Villus Sampling ★

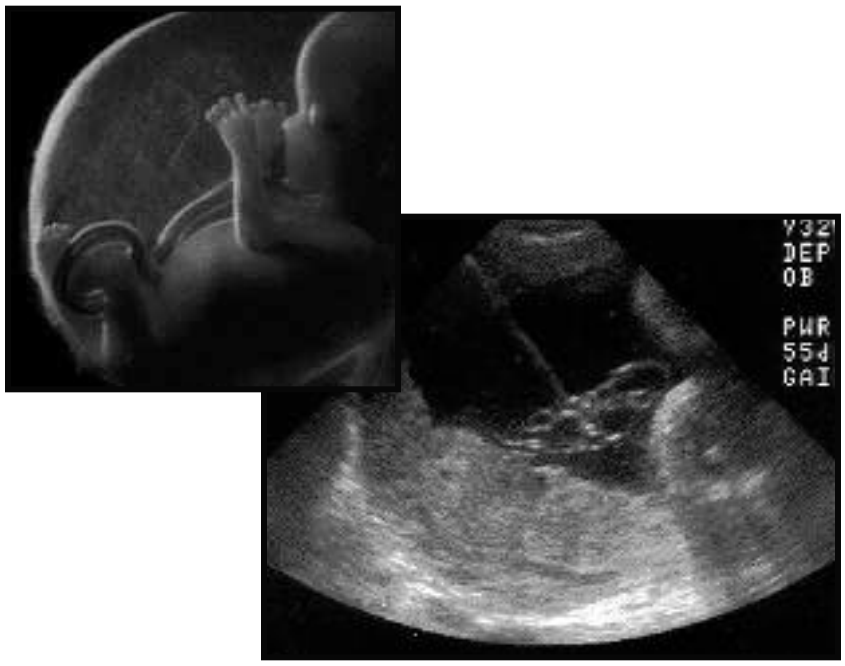
- Invasive technique to obtain fetal cells
- Study chromosomes, DNA, or biochemical profile of fetus
- Most often approached through the vagina but may be approached through the abdomen of mother
- Most often performed between 10-13 weeks gestation, but as early as 9 weeks and any time after 13 weeks
- More genetic material from cells to study right away
- Risks:
  - fetal loss rate slightly higher than amnio - about 1%
  - Very slight risk of increased limb abnormalities if done < 10 weeks
  - risk of infection



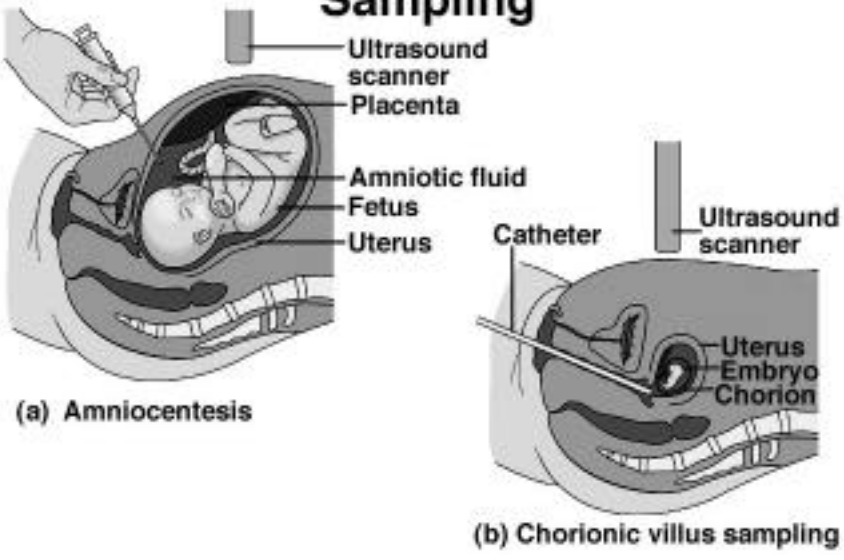
(b) Chorionic villus sampling

Percutaneous Umbilical Blood sampling

- Invasive procedure to obtain fetal blood cells
- Study chromosomes, DNA, blood chemistries, or biochemical
- Needle under ultrasound guidance to obtain blood from umbilical vein
- Risks:
  - Fetal loss rate higher than amnio or CVS (at least 2% mid-2nd trimester)
- Rarely needed except in special circumstances where results can not be obtained by amniocentesis or CVS techniques



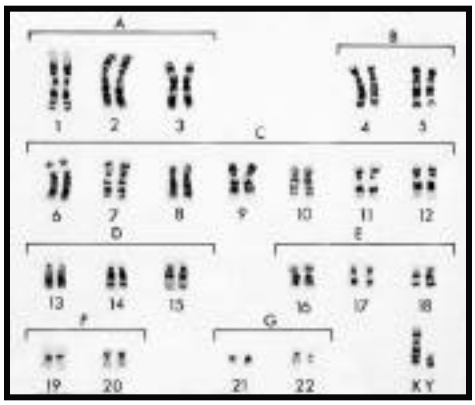
Amniocentesis & Chorionic Villus Sampling

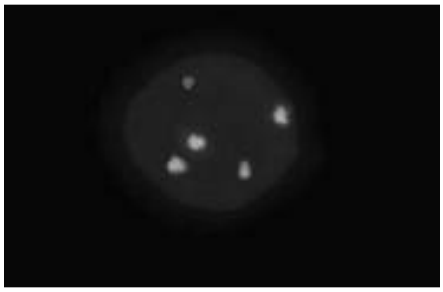


Indications for *Offering* Amniocentesis or Chorionic Villus Sampling

- Advanced maternal age
- Abnormal maternal serum marker test
- Family history of chromosome abnormality
- Genetic disease detectable by biochemical or DNA analysis
- Concerns of patient

Maternal Age	**Trisomy 21**	**Trisomy 18**	**Trisomy 13**
15 - 19	1:1600	1:17000	1:33000
20 - 24	1:1400	1:14000	1:25000
25 - 29	1:1100	1:11000	1:20000
30 - 34	1:700	1:7100	1:14000
35 - 39	1:240	1:2400	1:4800
40 - 44	1:70	1:700	1:1600
45 - 49	1:20	1:650	1:1500





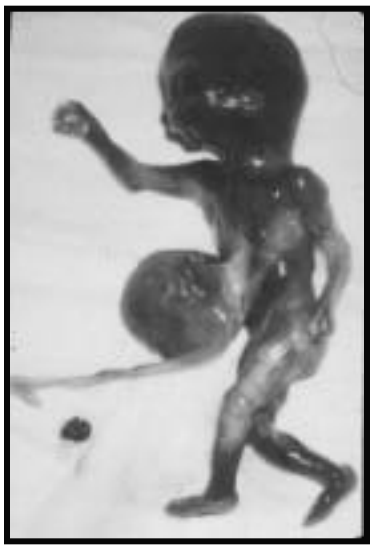
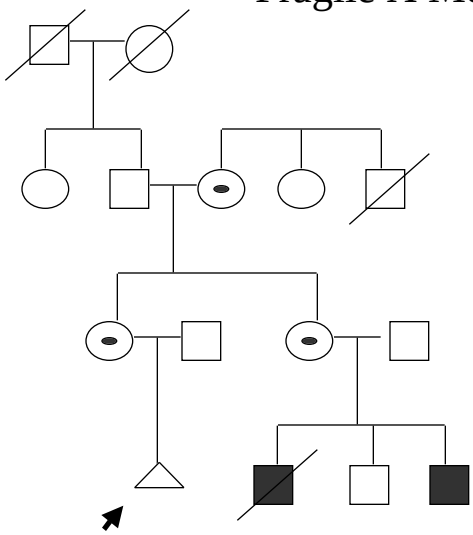


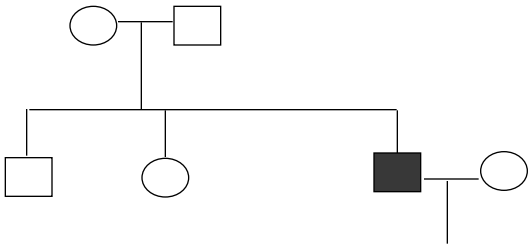
Table 12.12. Selected Single-Gene Diseases Amenable to Prenatal or Presymptomatic Diagnosis by DNA Analysis

Autosomal dominant
Myotonic dystrophy
Adult polycystic kidney disease
Huntington disease
Neurofibromatosis 1
Familial breast cancer
Autosomal recessive
Sickle cell anemia
β-thalassemia, α-thalassemia
Cystic fibrosis
Phenylketonuria
α_1-Antitrypsin deficiency
Tay-Sachs disease
X-linked recessive
Hemophilia A and B
Duchenne and Becker muscular dystrophy
Fragile X syndrome
Ornithine transcarbamylase deficiency

Fragile X Mental Retardation

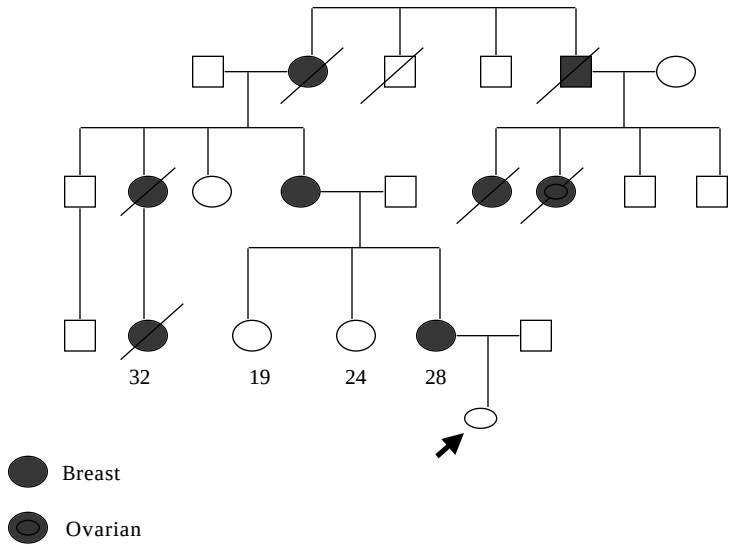


- X-linked disorder
- Most common heritable form of MR
- Affects 1 in 1,500 males
- Sensitive genetic diagnostic tests available



Achondroplasia

A single predominant mutation in *FGFR3* gene on chromosome 4p identified as cause in most cases - often a new mutation



Prenatal testing of minors for adult-onset conditions only....

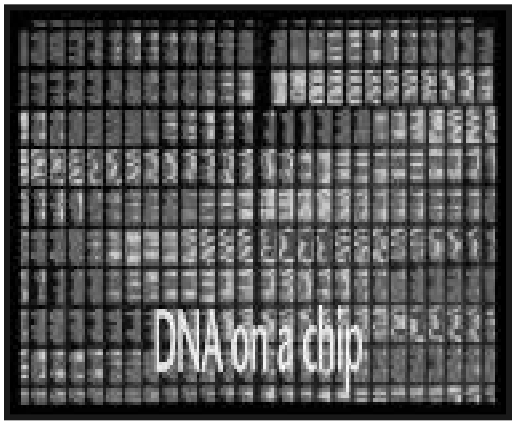
- When there is an effective, curative, or preventive treatment that should be instituted early in life to achieve benefit
- If parents want to terminate pregnancy if child would have this disease

Prenatal genetic testing is a process, not just a laboratory procedure

- Pre-testing evaluation, education, genetic counseling, and informed consent
- Laboratory analysis
- Accurate interpretation of results
- Follow-up must include support, education, and management

Foundations for "good" genetic testing

- High-quality (sensitive and specific)
- Cost-effective, clear benefit
- Ethically justifiable
- Informed Consent

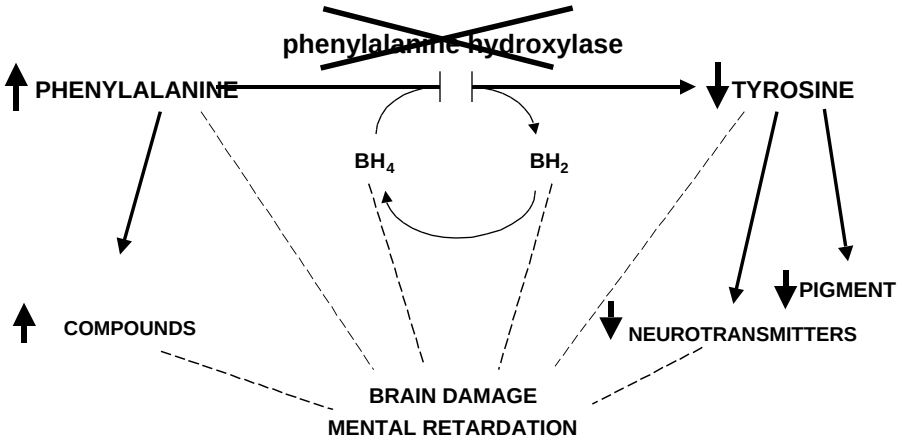


Teratogens

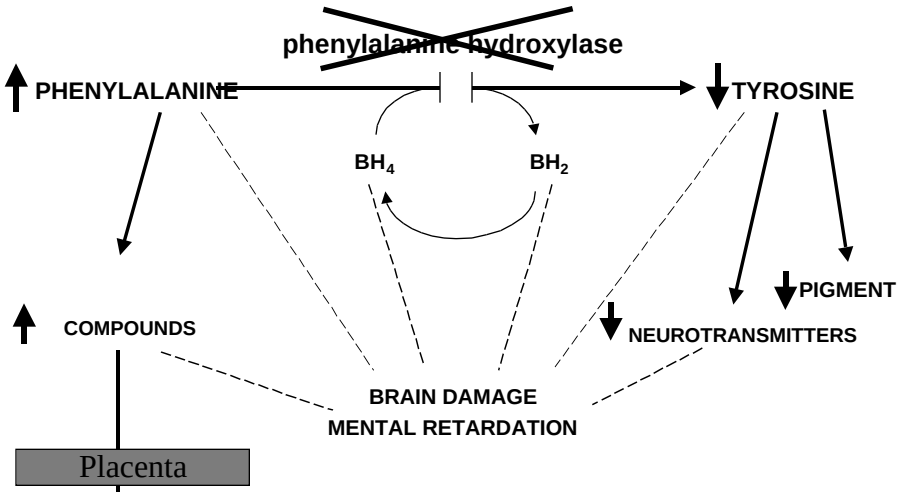
- Agent that may cause birth defects or alterations of normal function when present in utero
- Timing is critical - teratogenic only when exposure takes place during a critical time period
- Mechanisms of teratogenicity are agent specific with characteristic abnormalities
- Variability among the degree of problems may be secondary to differences in dose, timing of the exposure, differences in genetic susceptibility, interactions among other exposures
- For most agents, limited information is available - often only animal studies and limited case reports

Established Teratogens

- Some Maternal Diseases
  - Diabetes
  - Phenylketonuria
  - systemic lupus erythematosus
  - Grave's disease
- Ionizing radiation
- Some Maternal Infections (TORCH)
- Certain Drugs



Person with untreated PKU



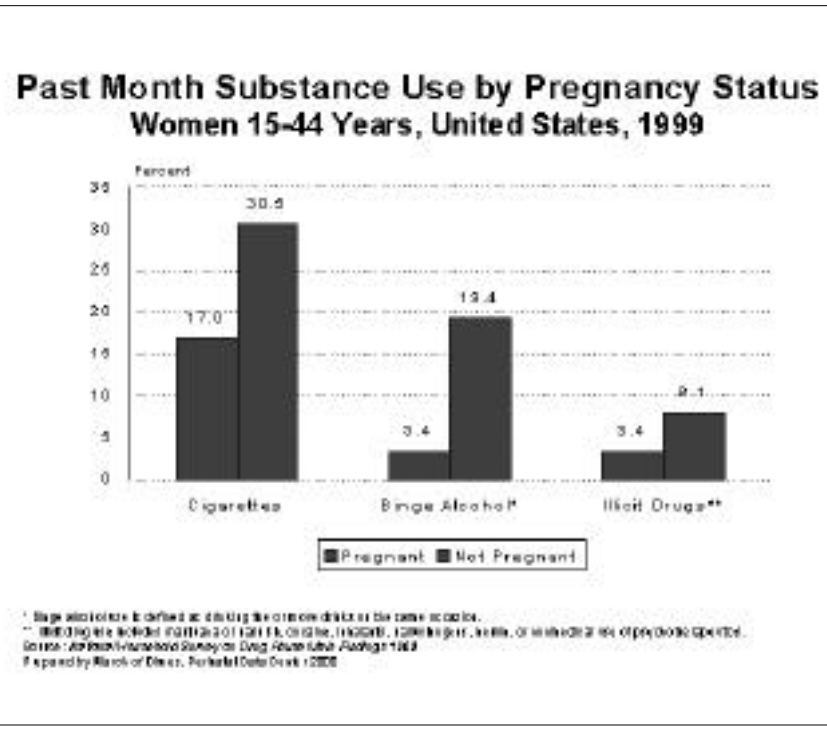
Placenta

Microcephaly
Congential cardiac defect
Growth retardation
Mental retardation

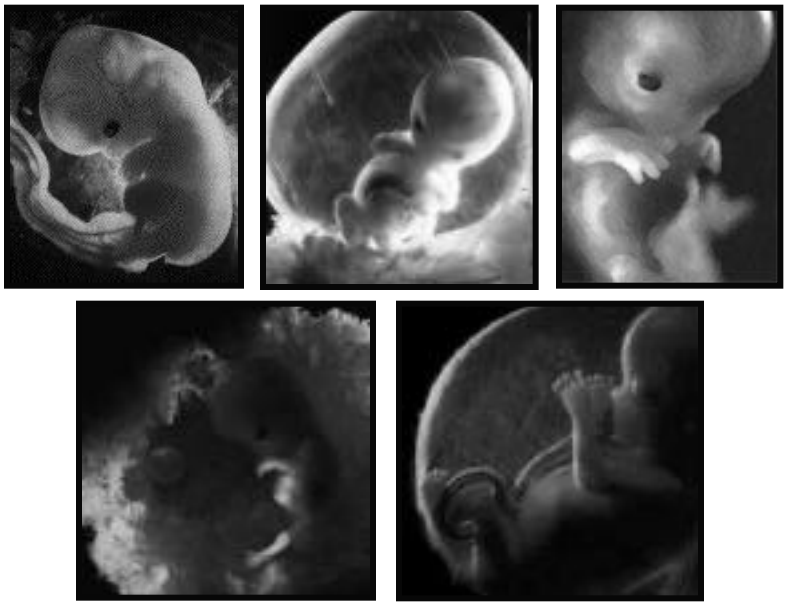
Baby with Maternal PKU effects, is most cases baby will NOT have PKU

Maternal Infections

- T- toxoplasmosis
- O - other such as group B strep, syphillis, parvovorus
- R - rubella
- C - cytomegalovirus
- H - herpes simplex or HIV



When was the exposure? Timing is everything...



Drug	Problems	Timing	%
Isotretinoin	Death, CNS defects, absent ears and thymus, heart defects, small jaw	>15 days	45-50%
Phenytoin	Craniofacial abnormalities, hypoplastic digits and nails	1st trimester	10-30%
Thalidomide	Limb hypoplasia, ear anomalies	38-50 days	15-25%
Alcohol, chronic	Craniofacial abnormalities, CNS abnormalities, heart defects, low birth weight, developmental problems	<12 weeks anytime	10-15%
Valproic acid	Spina bifida Craniofacial abnormalities, preaxial defects	< 30 days 1st trimester	< 1%
Streptomycin	Hearing loss	3rd trimester	?
Lithium	Ebstein abnormality	< 8 weeks	< 1%

Common questions:

- What are the risks to fetus if I stay on these medications?
- What are the risks to myself if I stop these medications?
- What, if any, medications can I safely stay on?
- What are the risks that my child will inherit my disease?
- Is there any way you can test prenatally to see if my child will have this disease? Problems due to the medications?

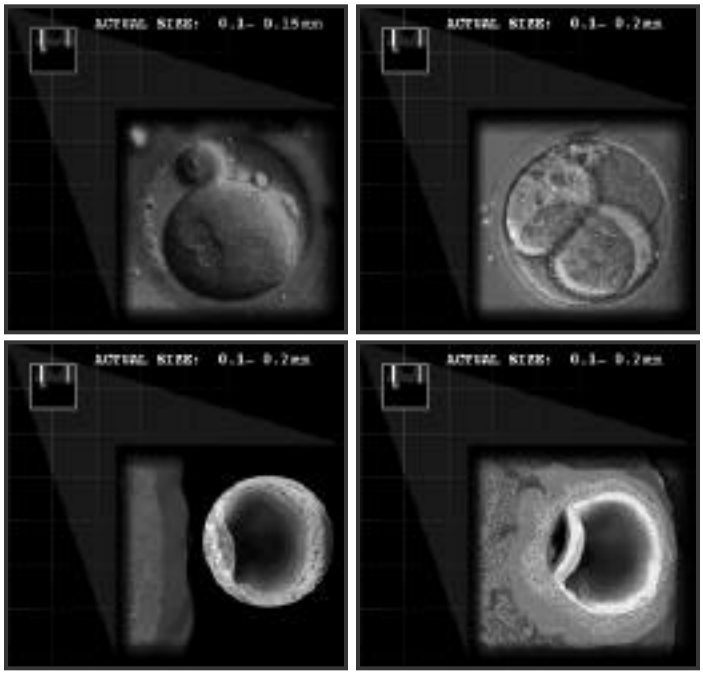
Reduce risk for birth defects without pregnancy termination

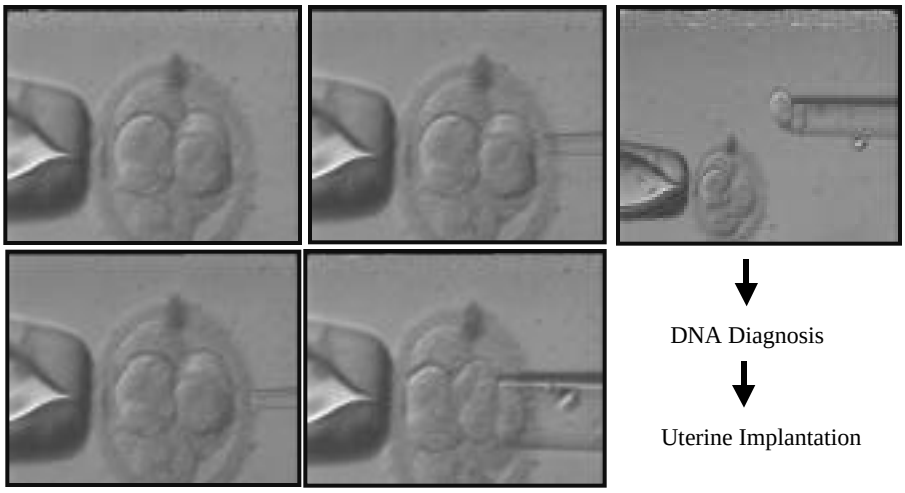
- Avoid teratogens!
- Get good early prenatal care
- Manage maternal medical problems
- FOLIC ACID supplementation BEFORE and during pregnancy
  - Sexually active women of childbearing age who might become pregnant
  - Reduces NTD and other birth defects
- Use assisted reproductive technologies

Assisted Reproductive Technologies

- Artificial/assisted insemination with donor sperm
- Sex selection prior to insemination by sorting X and Y sperm
- Donor ovum with or without surrogate mother
- In vitro fertilization
- Intracytoplasmic sperm recovery in men low sperm count/sperm motility followed by in vitro fertilization (eg. congenital absence of the vas deferens, Klinefelter syndrome)
- Preimplantation diagnosis followed by in vitro fertilization

In vitro fertilization techniques can be expensive, require significant medical and hormonal treatments, multiple attempts, and may result in multiple births - raising many ethical issues

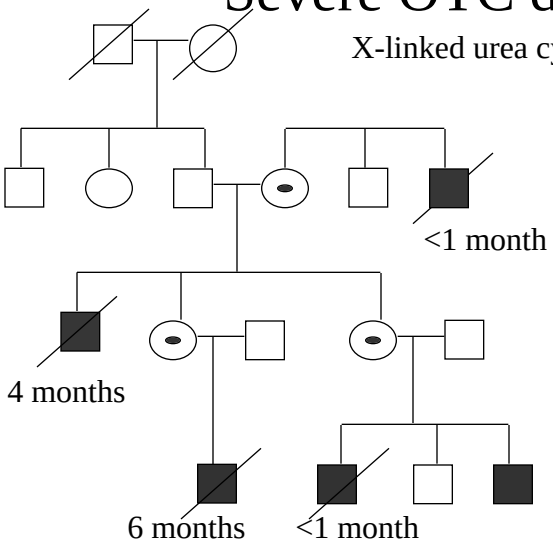




In vitro Fertilization and Preimplantation Diagnosis

Severe OTC deficiency

X-linked urea cycle disorder



Every pregnancy should be assessed for risk of birth defects

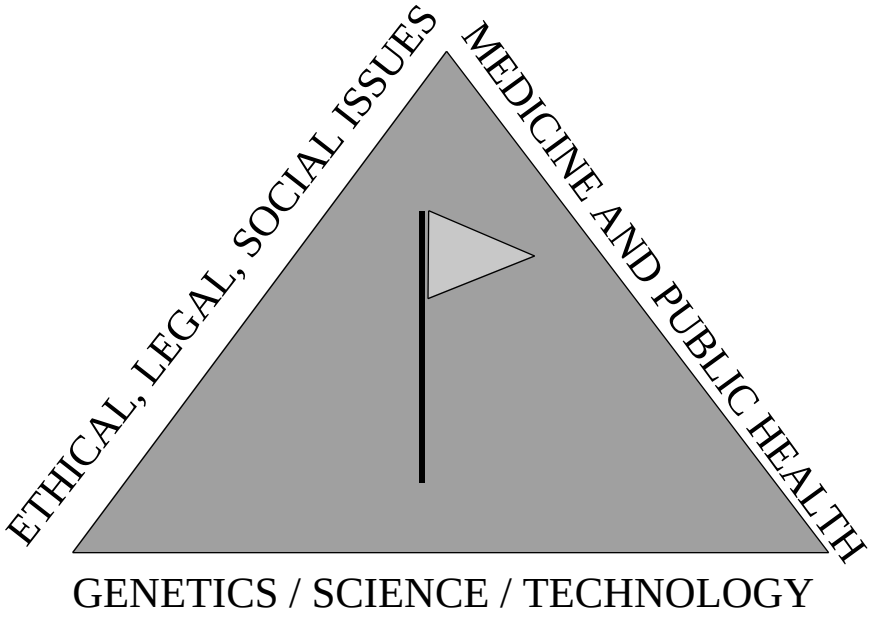
- Obtain family history of birth defects or genetic disorders
- Determine if there recurrent pregnancy losses?
- Look for signs of fetal abnormalities - IUGR, poly- or oligo-hydramnios?
- Offer screening for NTDs, aneuploidy
- Offer screening for age and ethnicity based increased risks
- Minimize risk with optimal preconception care, prenatal care and avoidance of teratogenic agents
- Check for maternal illnesses or exposures

High Fetal Risk Pregnancy Management

- Conduct appropriate diagnostic studies and genetics evaluation as needed
  - Chromosome, biochemical, molecular studies...
  - Consults
- Look for associated malformations
  - Ultrasounds, echocardiograms...
- Carefully discuss diagnostic, prognostic, and therapeutic issues and options with parents as non-directively as appropriate

Management After Loss of a Fetus due to Miscarriage and Termination

- Conduct clinical evaluation/autopsy to confirm diagnosis
- Offer parents an opportunity to see fetus if miscarriage , still birth or late termination due to genetic problems
  - Name, photograph,obtain hair, memorialize, bury...
- Provide referrals to social work/psychological services and support groups as appropriate
- Arrange follow-up genetic counseling
- Most importantly be aware, available, and sensitive to needs - all people will deal loss in different ways



Primum non nocere

"I will apply treatment for the benefit of the sick according to my ability and judgment; I will keep them from harm and injustice"

3rd paragraph
Physician's Hippocratic Oath