


1. Prenatal Diagnosis Diana W. Bianchi, M.D.

**Prenatal Diagnosis**  
Diana W. Bianchi, M.D.



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2. Case Scenarios

**Case Scenarios**

- Couple 1: Advanced parental ages, history of infertility, at risk for Down syndrome in fetus. To test or not to test? How invasive?
- Couple 2: Previous child identified by newborn screening as having cystic fibrosis (CF). Both parents are carriers of cystic fibrosis mutations. Prenatal diagnosis? Pre-implantation diagnosis?
- Couple 3: Fetal ultrasound reveals neural tube defect. In utero surgery? Postnatal treatment? Terminate?

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3. Objectives of Prenatal Diagnosis

**Objectives of Prenatal Diagnosis**

- Provide information to prospective parents regarding fetal diagnosis
- Counseling and support for prospective parents for reproductive decisions
- To be able to offer fetal therapy and ideally, prevent postnatal medical complications seen in infants

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4. Techniques of Prenatal Diagnosis

**Techniques of Prenatal Diagnosis**

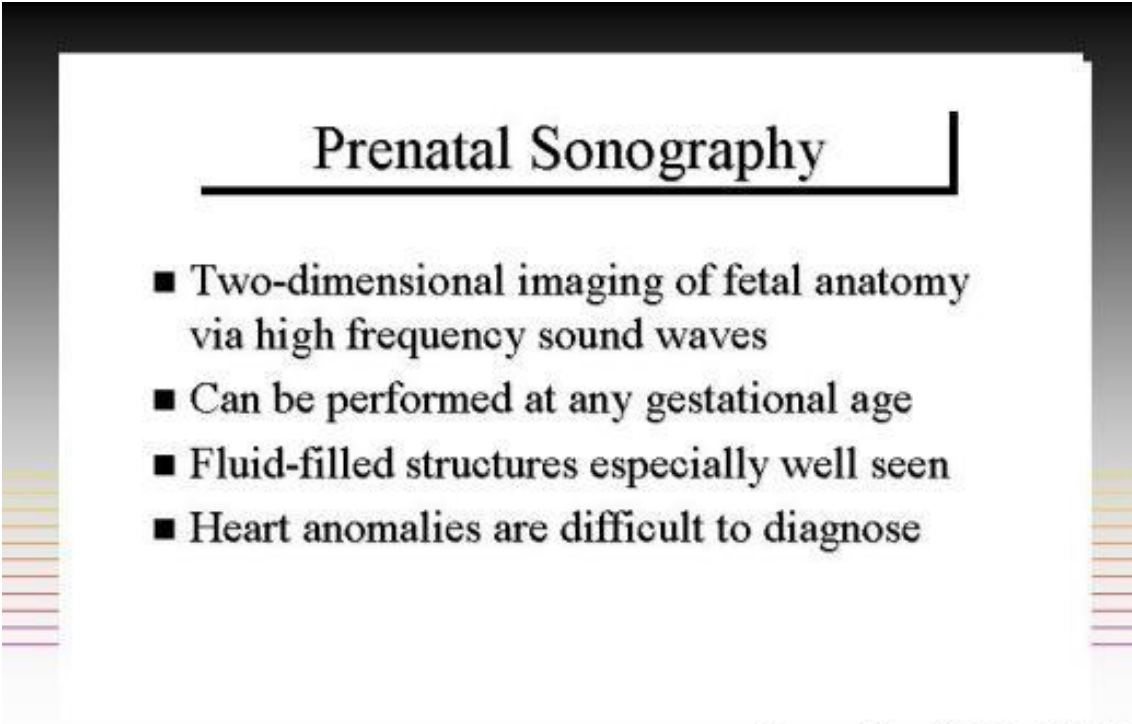
(We will progress from noninvasive to invasive)

- Fetal Imaging
- Maternal serum screening
- Analysis of fetal cells and nucleic acids in maternal blood
- Amniocentesis
- Chorionic Villus Sampling (CVS)
- Preimplantation Diagnosis

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5.

## Prenatal Sonography



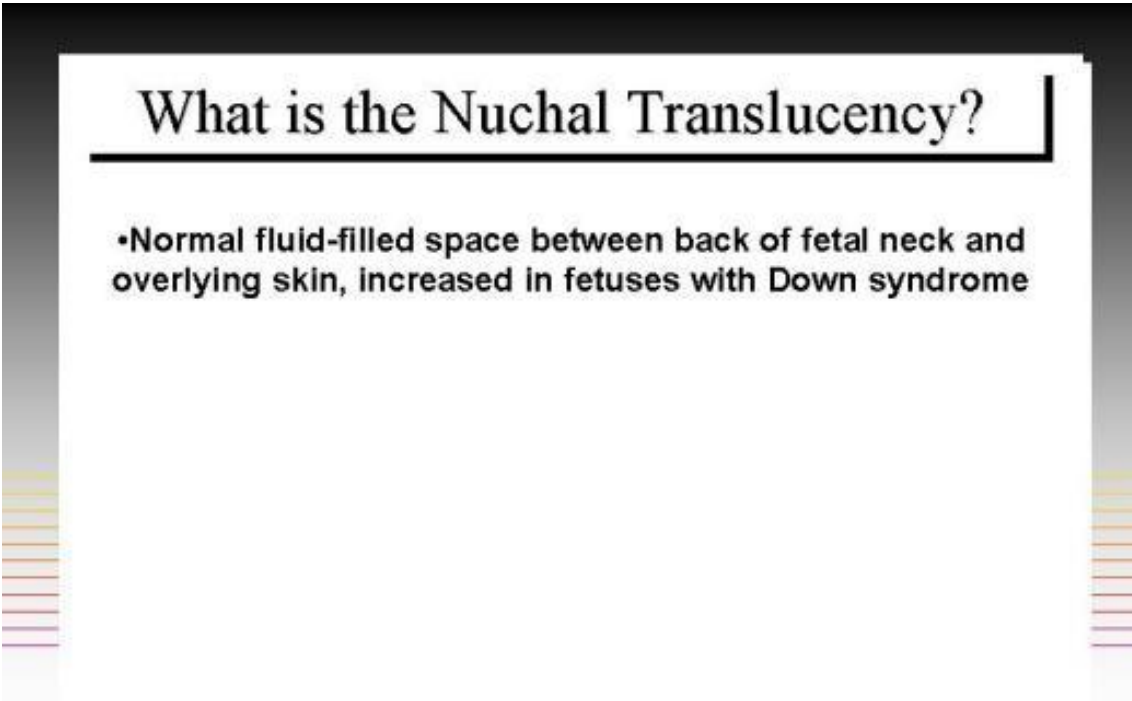
**Prenatal Sonography**

- Two-dimensional imaging of fetal anatomy via high frequency sound waves
- Can be performed at any gestational age
- Fluid-filled structures especially well seen
- Heart anomalies are difficult to diagnose

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6.

## What is the Nuchal Translucency?

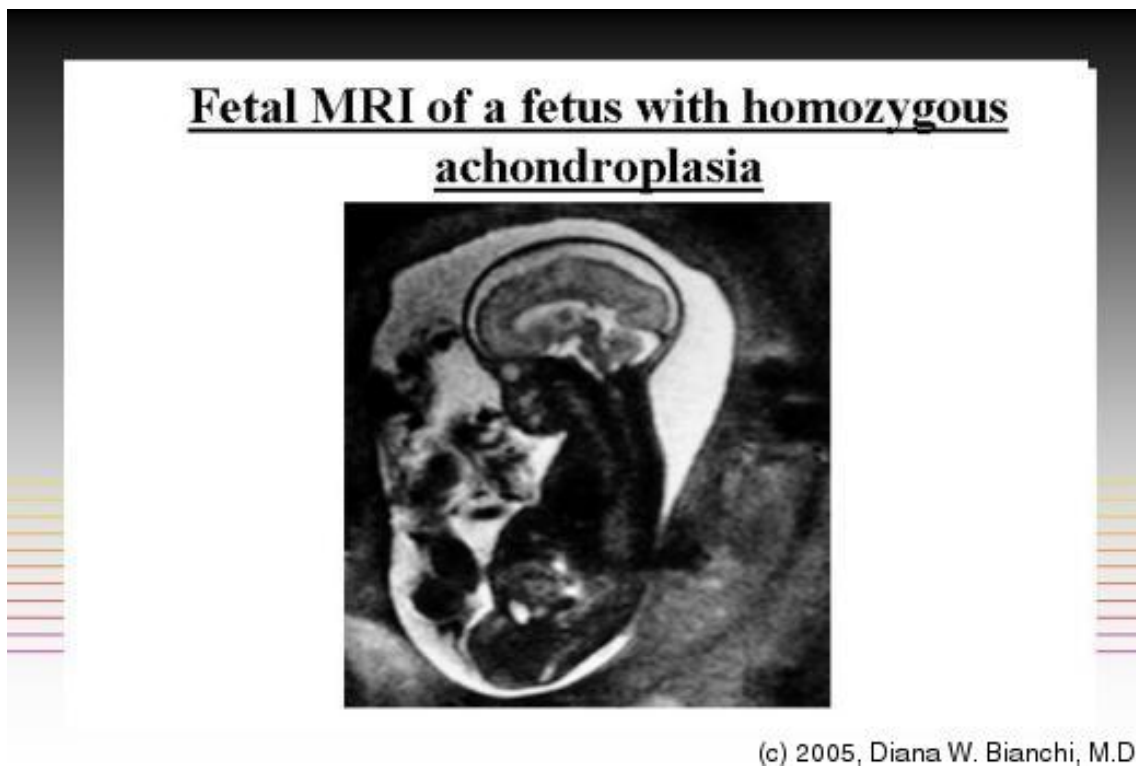


**What is the Nuchal Translucency?**

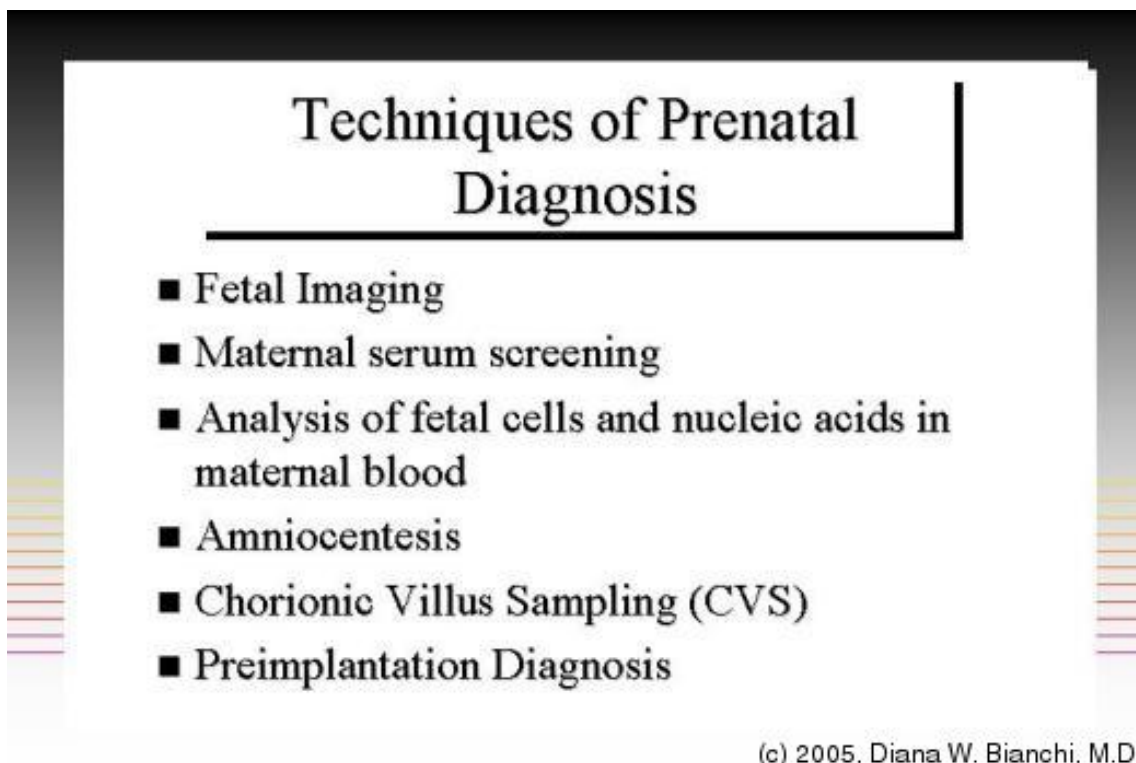
- Normal fluid-filled space between back of fetal neck and overlying skin, increased in fetuses with Down syndrome

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7. Prenatal Diagnosis 2005: Slide 7



8. Techniques of Prenatal Diagnosis



9. Maternal Serum Screening

## Maternal Serum Screening

- Measurement of proteins produced by fetus or placenta
- Results calculated relative to population standards (MoMs) 50%=1.0 MoM
- Accurate gestational age must be known
- First trimester measures PAPP-A,  $\beta$  hCG
- Second trimester measures AFP, hCG, uE3 +/- inhibin

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10. Serum Screening Markers (MoMs in Down Syndrome Pregnancies)...

## Serum Screening Markers (MoMs in Down Syndrome Pregnancies)

<u>Marker</u>	<u>1<sup>st</sup> Trimester</u>	<u>2<sup>nd</sup> Trimester</u>
PAPP-A	0.38	0.97
Free $\beta$ hCG	1.83	2.20
AFP	0.78	0.75
U E3	0.71	0.72
Inhibin A		1.92

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11. Screening for Fetal Down Syndrome: Current USA Standard of Ca...

**Screening for Fetal Down Syndrome:  
Current USA Standard of Care**

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In women who are 35 or older at time of delivery:

- Offer amniocentesis or CVS for fetal karyotype

In women who are under age 35 at delivery:

- 2nd trimester serum screen
- Offer invasive test for risk greater than 1 in 270
- Detects 60-70% of cases with 5% screen positive rate

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12. Screening for Fetal Down Syndrome: Results of the FASTER tria...

**Screening for Fetal Down Syndrome:  
Results of the FASTER trial**  
(N Engl J Med 2005;353:2001-2011)

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First trimester serum screen

- Maternal age, PAPP-A, free  $\beta$  hCG, nuchal translucency
- Detects 87% of cases of Down syndrome
- If results abnormal, can have CVS

“Stepwise” sequential screen

- Combine first trimester results with 2<sup>nd</sup> trimester screen
- Detects 95% of cases of Down syndrome

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13. Techniques of Prenatal Diagnosis

## Techniques of Prenatal Diagnosis

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14. Fetal Cells in Maternal Blood for Aneuploidy Diagnosis

## Fetal Cells in Maternal Blood for Aneuploidy Diagnosis



Fetal cell with 3  
copies of  
chromosome  
21

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15. Fetal Cells and DNA Are In Maternal Blood

## Fetal Cells and DNA Are In Maternal Blood

- Fetal nucleated cells can be isolated from maternal blood and used as a template for FISH analysis that counts copies of chromosome 21
- Surprisingly high amounts of fetal DNA circulate in the pregnant woman. This DNA can be used for diagnosis of gene sequences that are uniquely inherited from the father

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16. Techniques of Prenatal Diagnosis

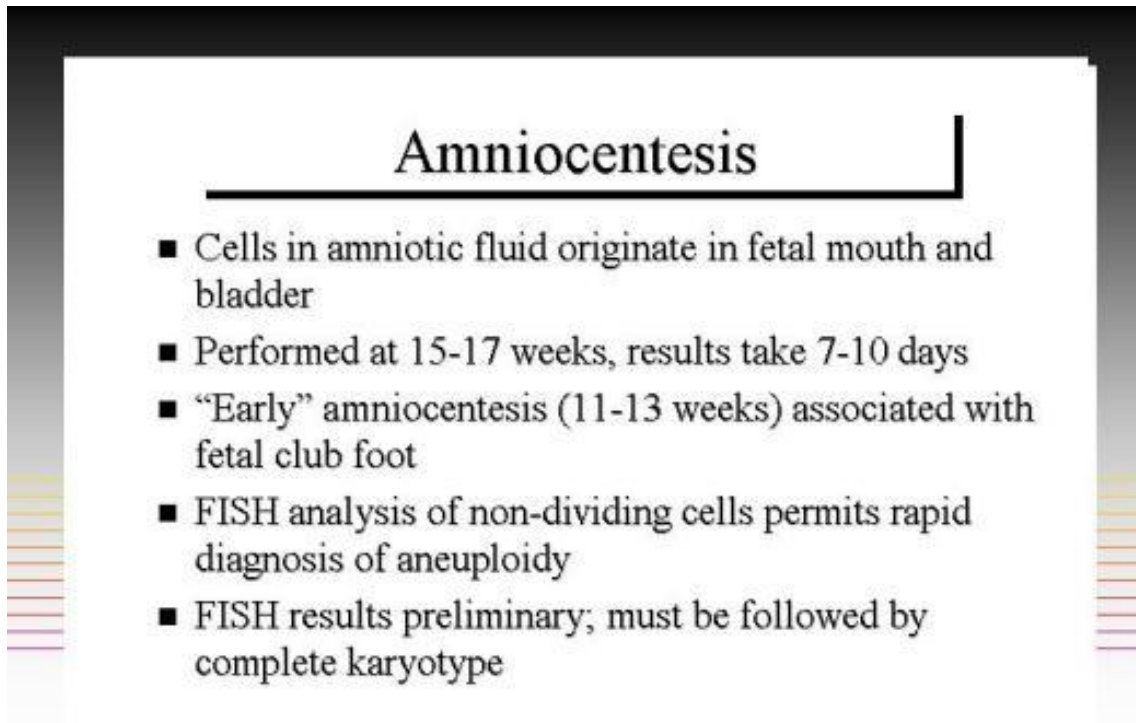
## Techniques of Prenatal Diagnosis

- Ultrasonographic examination
- Maternal serum screening
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17.

## Amniocentesis



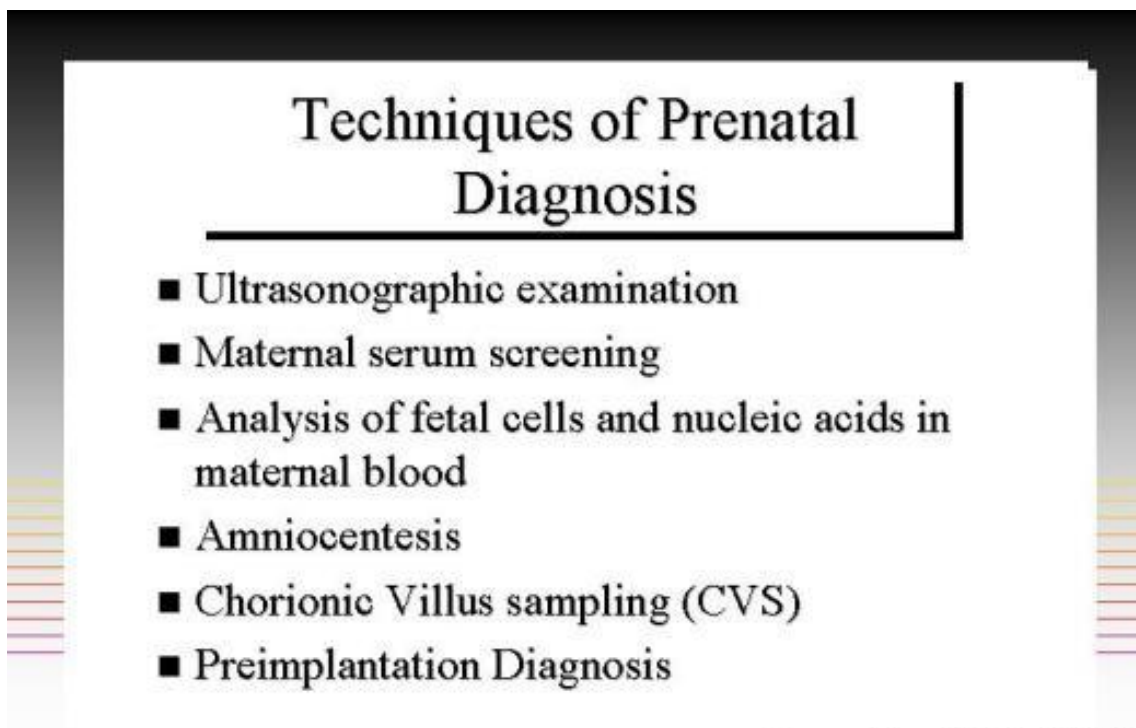
**Amniocentesis**

- Cells in amniotic fluid originate in fetal mouth and bladder
- Performed at 15-17 weeks, results take 7-10 days
- “Early” amniocentesis (11-13 weeks) associated with fetal club foot
- FISH analysis of non-dividing cells permits rapid diagnosis of aneuploidy
- FISH results preliminary; must be followed by complete karyotype

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18.

## Techniques of Prenatal Diagnosis



**Techniques of Prenatal Diagnosis**

- Ultrasonographic examination
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19. Advantages of CVS over Amniocentesis

### Advantages of CVS over Amniocentesis

- Performed at 11 weeks' gestation
- Restores privacy to reproductive decisions
- Mitotically active cells = rapid karyotype
- Tissue obtained is preferable for DNA analysis
- Mosaic trisomy detected; identifies fetuses at risk for uniparental disomy (UPD)
- Preferable for diagnosing certain conditions

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20. Disadvantages of CVS

### Disadvantages of CVS

- Elevated risk of fetal loss (0.5-1.0%)
- Slightly elevated risk of maternal infection
- Limb malformation syndrome?
- Confined placental mosaicism in 1% of cases
- Amniotic fluid alphafetoprotein not assayed

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21. CDC Recommendations for CVS Counseling 7/95

**CDC Recommendations for  
CVS Counseling 7/95**

- Risk of miscarriage with amnio=1/200-400  
Risk of miscarriage with CVS= 1/100-200
- Risk of limb deficiency with CVS=  
1/1000-1/3000
- Risk and severity of limb deficiency  
associated with timing of CVS:  
<10 wks (0.20%) >10 wks (0.07%)

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22. Techniques of Prenatal Diagnosis

**Techniques of Prenatal  
Diagnosis**

- Ultrasonographic examination
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maternal blood
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23. What is Preimplantation Genetic Diagnosis (PGD)?

**What is Preimplantation Genetic Diagnosis (PGD)?**

- The process of screening embryos for genetic abnormalities prior to transferring to the uterus
- **Requires:** *in vitro fertilization (IVF)*
- +/- intracytoplasmic sperm injection (ICSI)
- Embryo biopsy on third day
- FISH or PCR analysis of single blastomere

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24. Preimplantation Genetic Diagnosis

**Preimplantation Genetic Diagnosis**

- 1989 Handyside reported gender determination of embryos by PCR
- PGD originally developed for use in fertile patients to avoid birth of (or termination of pregnancy for) an affected child with single gene disorder
- Now most common use is in subfertile patients to improve chance of successful pregnancy

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25. Preimplantation Genetic Diagnosis

**Preimplantation Genetic Diagnosis**

- Approximately 5000 cycles performed
- Over 1000 babies born
- 24% pregnancy rate
- compare to success rate for naturally conceived pregnancies of 25% per cycle
- cost of PGD is \$12,000-\$18,000 per cycle
- No increase in birth defects

Kuliev, Curr Opin Ob Gyn (15), 2003  
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26. Uses of PGD

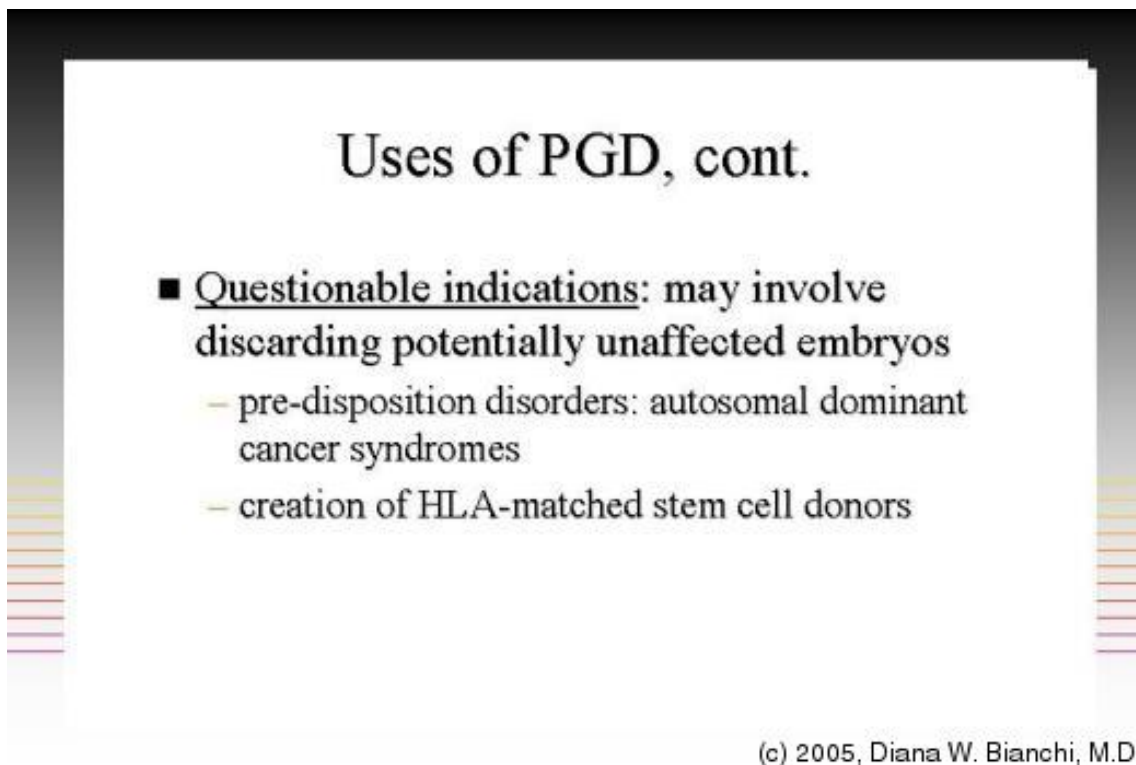
**Uses of PGD**

- Commonly accepted:
  - Aneuploidy screening by FISH: AMA, recurrent SAB, repeated IVF failure
  - Familial chromosome rearrangement by FISH: reciprocal or Robertsonian translocation, inversion
  - Embryo gender testing for X-linked conditions by FISH
  - Single gene diagnosis by PCR: autosomal, X-linked (usually untreatable or lethal) conditions

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27.

Uses of PGD, cont.



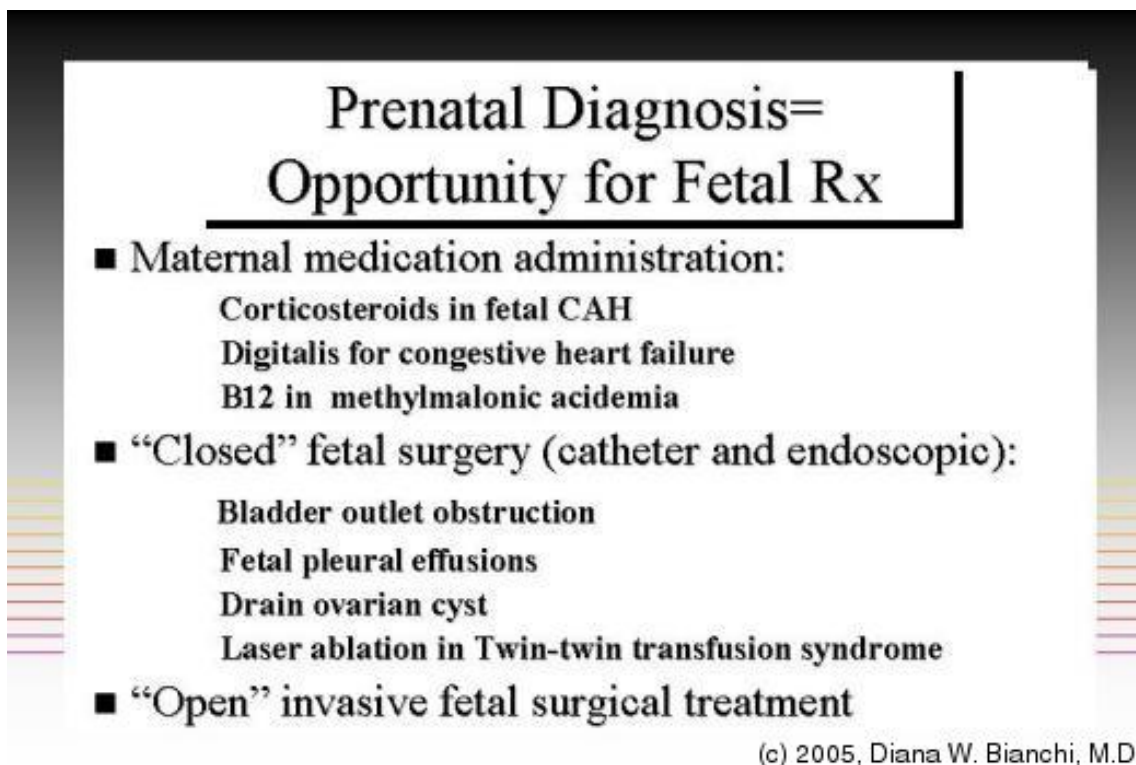
**Uses of PGD, cont.**

- **Questionable indications:** may involve discarding potentially unaffected embryos
  - pre-disposition disorders: autosomal dominant cancer syndromes
  - creation of HLA-matched stem cell donors

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28.

Prenatal Diagnosis=Opportunity for Fetal Rx



**Prenatal Diagnosis=  
Opportunity for Fetal Rx**

- **Maternal medication administration:**
  - Corticosteroids in fetal CAH
  - Digitalis for congestive heart failure
  - B12 in methylmalonic acidemia
- **“Closed” fetal surgery (catheter and endoscopic):**
  - Bladder outlet obstruction
  - Fetal pleural effusions
  - Drain ovarian cyst
  - Laser ablation in Twin-twin transfusion syndrome
- **“Open” invasive fetal surgical treatment**

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29. Patients Used to Go Directly to the Web

**Patients Used to Go Directly to the Web**

**MOMs Trial**

- NIH sponsored randomized clinical trial comparing in utero surgery to conventional postnatal treatment

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30. The Future

**The Future**

- Primary prevention of birth defects
- Take 0.4 mg folic acid per day
- 3-D ultrasound imaging
- The molecular cytogenetic karyotype/DNA microarrays
- Stem cell and gene therapy

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