Anomalies and Genetics, etc
Review
MFM– CREOG Review

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Objectives

• CREOG- 3+part slide set
• Aneuploidies
• Genetics
• Fetal infections
• Tocolytics
• NAIT
• Thrombocytopenia
• Twins
• Sickle cell disease
• Alloimmunization
Table 1. Risk of Chromosomal Abnormalities Based on Maternal Age at Term

<table>
<thead>
<tr>
<th>Age at Term</th>
<th>Risk of Trisomy 21*</th>
<th>Risk of Any Chromosome Abnormality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>15+</td>
<td>1:1,578</td>
<td>1:454</td>
</tr>
<tr>
<td>16+</td>
<td>1:1,572</td>
<td>1:475</td>
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<tr>
<td>17+</td>
<td>1:1,565</td>
<td>1:499</td>
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<td>18+</td>
<td>1:1,556</td>
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<td>19+</td>
<td>1:1,544</td>
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<td>50</td>
<td>1:25</td>
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</table>


†Risk of any chromosomal abnormality includes the risk of trisomy 21 and trisomy 18 in addition to trisomy 13, 47,XXY, 47,XYY, Turner syndrome genotype, and other clinically significant abnormalities, 47,XXX not included. Data from Hook EB. Rates of chromosome abnormalities at different maternal ages. Obstet Gynecol 1981;58:282–5.


§Data not available.
<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Gestational Age Range for Screening (Weeks)</th>
<th>Detection Rate for Down Syndrome (%)</th>
<th>Screen Positive Rate* (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Method</th>
</tr>
</thead>
</table>
| First trimester†    | 11–14†                                      | 82–87                               | 5                        | 1. Early screening  
2. Single test  
3. Analyte assessment of other adverse outcomes | Lower DR than combined tests  
NT required                        | NT+PAPP-A and hCG                |
| Triple screen       | 15–22                                       | 69                                  | 5                        | 1. Single test  
2. No specialized US required  
3. Also screens for open fetal defects  
4. Analyte assessment for other adverse outcomes | Lower DR than with first-trimester or quad screening  
Lowest accuracy of the single lab tests | hCG, AFP, uE3                    |
| Quad screen†        | 15–22                                       | 81                                  | 5                        | 1. Single test  
2. No specialized US required  
3. Also screens for open fetal defects  
4. Analyte assessment for other adverse outcomes | Lower DR than combined tests                | hCG, AFP, uE3, DIA               |
| Integrated†         | 11–14, then 15–22                           | 96                                  | 5                        | Highest DR of combined tests  
Also screens for open fetal defects | Two samples needed before results are known | NT+PAPP-A, then quad screen |
| Sequential‡  
Stepwise       | 11–14, then 15–22                           | 95                                  | 5                        | First-trimester results provided;  
Comparable performance to integrated, but FTS results provided; also screens for open fetal defects; analyte assessment for other adverse outcomes | Two samples needed | NT+hCG+ PAPP-A then quad screen |
| Contingent screening‡ | 88–94                                      | 5                                   | First-trimester test result:  
Positive: diagnostic test offered  
Negative: no further testing  
Intermediate: second-trimester test offered  
Final: risk assessment incorporates first- and second-trimester results | Possibly two samples needed | NT+hCG+ PAPP-A, then quad screen |
| Serum Integrated‡   | 11–14; then 15–22                           | 88                                  | 5                        | 1. DR compares favorably with other tests. Two samples needed;  
2. No need for NT  
no first-trimester results |                          | PAPP-A+quad                     |
### Table 2. Characteristics, Advantages, and Disadvantages of Common Screening Tests for Aneuploidy

<table>
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<tr>
<th>Screening Test</th>
<th>Gestational Age Range for Screening (Weeks)</th>
<th>Detection Rate for Down Syndrome (%)</th>
<th>Screen Positive Rate* (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Method</th>
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| Cell-free DNA           | 10 - term                                   | 99 (in patients who receive a result) | 0.5                     | 1. Highest DR for Down syndrome  
2. Can be performed at any gestational age after 10 weeks  
3. Low false-positive rate in high-risk women (or women at high risk of Down syndrome) | 1. NPV and PPV not clearly reported  
2. Higher false-positive rate in women at low risk of Down syndrome  
3. Limited information about three trisomies and fetal sex  
4. Results do not always represent a fetal DNA result | Three roughly equivalent molecular methods |
| Nuchal Translucency     | 11–14                                       | 64–70                                | 5                       | Allows individual fetus assessment in multifetal gestations  
Provides additional screening for fetal anomalies and possibly for twin–twin transfusion syndrome | 1. Poor screen in isolation  
2. Ultrasound certification necessary | US only                                  |

Abbreviations: AFP, alpha fetoprotein; DIA, dimeric inhibin-A; DR, detection rate; DS, Down syndrome; FTS, first-trimester screening; hCG, human chorionic gonadotropin; NPV, negative predictive value; NT, nuchal translucency; NTD, neural tube defect; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value; uE3, unconjugated estriol; US, ultrasonography.

*Screen positive test result includes all positive test results: the true positives and false positives.

1First-trimester combined screening: 87%, 85%, and 82% for measurements performed at 11 weeks, 12 weeks, and 13 weeks, respectively. Malone FASTER 2005.


4Because of variations in growth and conception timing, some fetuses at the lower and upper gestational age limits may fall outside the required crown–rump length range.

<table>
<thead>
<tr>
<th>Soft Marker</th>
<th>Imaging Criteria</th>
<th>Aneuploidy Association</th>
<th>Management</th>
</tr>
</thead>
</table>
| First trimester: enlarged nuchal  | Certified ultrasonography measurement ≥ 3.0 mm or above the 99th percentile for  | Aneuploidy risk increases with size of NT Also associated with Noonan syndrome,      | 1. Genetic counseling  
| translucency                      | the CRL                                                                          | multiple pterygium syndrome, skeletal dysplasias, congenital heart disease, and other  | 2. Offer cfdNA or CVS  
|                                  |                                                                                 | anomalies                                                                 | 3. Second-trimester detailed anatomic survey and fetal cardiac ultrasonography |
| First trimester: cystic hygroma   | Large single or multilocular fluid-filled cavities, in the nuchal region and can  | If septate, approximately 50% are aneuploid                                           |                                                                            |
|                                  | extend the length of the fetus                                                   |                                                                                        |                                                                            |
| Second trimester: echogenic      | Echogenic tissue in one or both ventricles of the heart seen on standard four-   | LR 1.4–1.8 for Down syndrome Seen in 15–30% of Down syndrome and 4–7% euploid fetuses  | 1. If isolated finding, aneuploidy screening should be offered if not done previously  
| intracardiac foci                 | chamber view                                                                     |                                                                                        | 2. If aneuploidy screen result is negative, no further evaluation is required. |
| Second trimester: pyelectasis    | Renal pelvis measuring ≥ 4 mm in anteroposterior diameter up to 20 weeks of     | LR 1.5–1.6 for Down syndrome                                                           | 1. If isolated finding, aneuploidy screening should be offered if not performed previously  
|                                  | gestation                                                                        |                                                                                        | 2. Repeat ultrasonography in third trimester for potential urinary tract obstruction |
| Second trimester: echogenic      | Fetal small bowel as echogenic as bone                                            | LR 5.5–6.7 for Down syndrome Associated with aneuploidy, intra-amniotic bleeding,     | 1. Further counseling  
| bowel                             |                                                                                 | cystic fibrosis, CMV                                                                    | 2. Offer CMV, CF, and aneuploidy screening or diagnostic testing |
| Second trimester: thickened       | ≥ 6 mm from outer edge of the occipital bone to outer skin in the midline        | LR 11–18.6 with 40–50% sensitivity and > 99% specificity for Down syndrome Most     | 1. Detailed anatomic survey  
| nuchal fold                      |                                                                                 | powerful second-trimester marker                                                      | 2. Further detailed genetic counseling and aneuploidy screening or diagnostic testing |

1. Genetic counseling  
2. Offer cfdNA or CVS  
3. Second-trimester detailed anatomic survey and fetal cardiac ultrasonography
LR calculation re: Down sd

- 31 yo
- a priori ~1 in 800
- NT/PAPPA/HCG- FDS risk 1 in 2000
  - Sonogram – 18wk – echogenic bowel- LR 6.7
  - Adjusted risk -1 in 298
- If no testing prior to sonogram
  - Adjusted risk – 1 in 119
<table>
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<th>Imaging Criteria</th>
<th>Aneuploidy Association</th>
<th>Management</th>
</tr>
</thead>
</table>
| Second trimester: mild ventriculomegaly | Lateral ventricular atrial measurement between 10–15 mm | Associated with aneuploidy | 1. Genetic counseling  
2. Second-trimester detailed anatomic ultrasound evaluation  
3. Consider diagnostic testing for aneuploidy and CMV  
4. Repeat ultrasound in third trimester |
| Second trimester: choroid plexus cysts | Discrete cyst(s) in one or both choroid plexus(es) | In isolation, no aneuploidy association | 1. Second-trimester detailed anatomic survey and fetal cardiac ultrasound  
2. No further follow-up if isolated  
3. Consider aneuploidy screening or diagnostic testing if other markers are present |
| Second trimester: short femur length | Measurement < 2.5 percentile for gestational age | LR 1.2–2.2 for Down syndrome. Can be associated with aneuploidy, IU, short limb dysplasia | 1. Second-trimester detailed fetal anatomic evaluation for short limb dysplasia  
2. Further detailed counseling  
3. Consider repeat ultrasonography in third trimester for fetal growth |

Abbreviations: CF, cystic fibrosis; cfDNA, cell-free DNA; CMV, cytomegalovirus; CRL, crown–rump length; CVS, chorionic villus sampling; IU, intrauterine growth restriction; LR, likelihood ratio; NT, nuchal translucency.

<table>
<thead>
<tr>
<th>Test</th>
<th>Turnaround Time</th>
<th>Conditions Detected</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional karyotype</td>
<td>7–14 days</td>
<td>Chromosomal abnormalities &gt; 5–10 Mb</td>
<td>Traditional method for diagnosis of chromosomal abnormalities</td>
</tr>
<tr>
<td>FISH — Direct preparation (interphase)</td>
<td>24–48 hours</td>
<td>Rapid assessment of major aneuploidies (chromosomes 13, 18, 21, X, and Y)</td>
<td>FISH with direct testing of cells from CVS is less accurate than with cultured cells from CVS or amniocentesis. Results should be confirmed on cultured cells or have additional clinical features before acting on results.</td>
</tr>
<tr>
<td>FISH — Cultured cells (metaphase)</td>
<td>7–14 days</td>
<td>Microdeletions and duplications</td>
<td>Can be used to test for specific abnormalities when clinically suspected</td>
</tr>
<tr>
<td>Chromosomal microarray</td>
<td>3–5 days (direct testing); 10–14 days (cultured cells)</td>
<td>Copy number variants &gt;50–200 kb</td>
<td>Whole genome screen for copy number variants. Detects major chromosomal abnormalities except balanced rearrangements and some triploidies. Detection varies with different microarray platforms.</td>
</tr>
<tr>
<td>Preimplantation genetic diagnosis</td>
<td>1–2 days</td>
<td>Genetic disorder in which familial mutation has been identified</td>
<td>Due to possibility of error, confirmation with CVS or amniocentesis is recommended</td>
</tr>
<tr>
<td>Molecular DNA testing</td>
<td>3–14 days (faster with direct testing than when cultured cells are required)</td>
<td>Genetic mutations previously demonstrated to be present in a family or suspected based on ultrasound or other findings in a fetus</td>
<td>Usually a targeted test focusing on a specific disorder (or category of disorders) suspected to be present in a fetus based on ultrasound findings or family history</td>
</tr>
<tr>
<td>AFP</td>
<td>hCG</td>
<td>uE3</td>
<td>Condition</td>
</tr>
<tr>
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<td>---------------------------------------------------------------------------</td>
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<tr>
<td>lo</td>
<td>hi</td>
<td>lo</td>
<td>Down syndrome, dates less advanced, Turner syndrome with cystic hygroma</td>
</tr>
<tr>
<td>lo</td>
<td>lo</td>
<td>lo</td>
<td>trisomy 18</td>
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<tr>
<td>hi</td>
<td>nl</td>
<td>nl</td>
<td>open spina bifida, abdominal wall defects, fetal death</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>lo</td>
<td>anencephaly</td>
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<tr>
<td>hi</td>
<td>lo</td>
<td>hi</td>
<td>dates more advanced</td>
</tr>
<tr>
<td>nl</td>
<td>nl</td>
<td>very low</td>
<td>fetal death, X-linked ichthyosis, congenital adrenal hyperplasia, Smith Lemli Opitz Syndrome</td>
</tr>
</tbody>
</table>
Typical Appearance of Different Chromosomal Aneuploidies

- Trisomy 21 – Down syndrome
- Trisomy 18 – Edwards syndrome
- Trisomy 13 – Patau syndrome
- 45, X – Turner syndrome
Trisomy 21 – Down syndrome

- Cardiovascular – A-V canal and VSD
- Central nervous system – mild ventriculomegaly
- Gastrointestinal – duodenal atresia
- Craniofacial – cystic hygroma
- Hydrops fetalis
Duodenal atresia
Case – AV canal & pleural effusion
Trisomy 18 – Edwards syndrome

- **Head** – strawberry shape, choroid plexus cysts, small cerebellum, ventriculomegaly
- **Face** – clefts, micrognathia
- **Cardiovascular** – septal and valvular defects
- **G-I** – omphalocele and diaphragmatic hernia
- **Extremities** – clenched fists, rocker bottom feet, club feet
- **Kidneys** – horseshoe kidney and hydronephrosis
7-7-09 –
1971g (35%ile)
33 0/7 at 33 3/7
Omphalocele vs Gastrochisis

12. Ventral Wall Defects

13. Typical features of omphalocele with extracorporeal placement of the liver (B)

6. Typical features of gastrochisis shown on external view (A) and on a section (B)
The contralateral lung is measured by multiplying the lung’s longest axis by the longest measurement perpendicular to the former (27 by 14 mm2).

This measurement is proportionated over the head circumference, measured in the standard biparietal view, showing two symmetrical hemispheres, the septum cavum pellucidum one-third of the way from the front to the back and the posterior horns of the lateral ventricles (bottom right).

Calculation of LHR (Deprest, 2006)
Strawberry head shape
Strawberry head shape
Cleft Lip with or without Cleft Palate
Clenched fist
Dandy-Walker malformation
Trisomy 13 – Patau syndrome

- Head – holoprosencephaly, facial clefts, single nostril, hypotelorism and cyclopia
- Neural tube defects
- Cardiac – septal defects, Tetralogy of Fallot, hypoplastic left heart
- G-I – omphalocele
- Kidneys – polycystic kidneys
- Extremities – polydactyly
Holoprosencephaly

• Holoprosencephaly - absent or incomplete cleavage of forebrain (prosencephalon) into the two cerebral hemispheres and lateral ventricles.

• Prognosis of affected infants depends on the severity of holoprosencephaly

• Associated abnormalities – trisomies, 13, 18; partial monosomies of 13q and 18q.

• Holoprosencephaly 1/16,000 LB; aneuploidy risk 40-60% (t13, t18, 18p-)
Alobar

- Alobar (most severe) - no cleavage of prosencephalon occurred
  - Instead of a ventricular system with distinct lateral and third ventricles, a monoventricle cavity is present.
  - The thalamus and corpus striatum are fused in the midline, while the midbrain, brainstem, and cerebellum may be structurally normal. Facial abnormalities associated with this type include cleft lip and palate, cyclopia, and chromosomal aberrations, usually trisomy 13, are common in the group.

- Lethal

- Smith Lemli Opitz- AR disease – abnormal cholesterol biosynthesis – elevated amniotic fluid 7-dehydrocholesterol level and the DHCR7 mutations ; -
Polydactyly
Omphalocele
45, X – Turner syndrome

- Neck – cystic hygromas
- Cardiovascular – coarctation
- General – hydrops fetalis
• Turner syndrome (45,X) →
  – Complete/partial absence of 2\textsuperscript{nd} X chromosome
  – 1 in 4-5,000 female live births; 1-2% of all conceptuses; 99% abort; make up 25% of first trimester spontaneous abortions (Moore,c10,s19)
  – Error is paternal nondisjunction (70%), maternal (30%); (Moore,c10,s77)
  – Clinically – short stature, webbed neck, gonadal dysgenesis, characteristic facies, renal/CV abnormalities (hypoplastic left heart syndrome, coarctation of the aorta); 10% with mild MR
  – Counseling - Recurrence risk – nominal -1% or age related risk
Case – 45,X

• 26 yo P0 at 13 weeks seen in consultation for cystic hygroma; - Amniocentesis at 15+ weeks – karyotype – 45,X
Genetics %

- Frequency of chromosomal abnormalities
  - Live births 0.6%
  - With congenital anomaly + MR = 23%
  - Congenital heart disease = 13%
  - Institutional individual with MR = 12%
  - Couples with multiple sab = 5%
  - Stillbirths/perinatal deaths = 6%
  - Spont ab 1st trim = 60%
Genetics %

- Chromosomal abnormalities in newborns (freq at birth)
  - Balanced translocation (1 in 500)
  - Unbalanced translocation (1 in 2000)
  - Pericentric inversion (1 in 100)
  - Tri 21 (1 in 700)
  - Tri 18 (1 in 6000)
  - Trisomy 13 (1 in 10,000)
  - 47,XXY (1 in 1000 males)
  - 47,XYY (1 in 1000 males)
  - 47,XXX (1 in 1000 females)
  - 45X (1 in 5000 females)
Genetics %

- Examples of numerical abnormalities
  - 45,x
  - 45,XY,-9 (monosomy 9)
  - 47,XX,+13 (trisomy 13)
  - 47,XXY (klinefeters sd – XXY is all you need for klinefelters sd – can have 48XXYY, 49XXXYY)
- 1st trimester spontaneous abortions – SAB
- Normal chromosomes – 40%
- Abnormal chromosomes – 60%
  - Autosomal trisomy – 50%; trisomy 16 (most common, 100% abort); trisomy 18 (98% abort); trisomy 21 (78% abort)
  - 45,X – 25% (99% abort)
- Triploid, tetraploid – 20%
- Structural abnormalities <5%
- Most chromosomal abnormalities end as prenatal lethals
Autosomal Dominant Pedigree
Autosomal Dominant

• Males and females equally affected
• Affected person has an affected parent
• Many are structural
• Many are new mutations
• Penetrance and expressivity are important
  – Penetrance – If you inherit the gene, will you show the disease
  – Expressivity – If you show the disease, how severe will you show it
• Age of onset is important
• 50% recurrence risk
Autosomal Dominant Conditions

• Marfan syndrome
• Neurofibromatosis
• Autosomal dominant polycystic kidney disease
• Huntington’s disease
• Waardenburg syndrome
• Achondroplasia
• Tuberous sclerosis
Marfan syndrome – Overview

• Definition – connective tissue disease from mutation of fibrillin 1 gene (15q21.1 – OMIM)
• Incidence – 1 in 10,000
• Pathogenesis – FBN1 encodes fibrillin 1 (ECM glycoprotein) - polymerizes to form micro-fibrils in both elastic and nonelastic tissues, such as the aortic adventitia, ciliary zonules and skin. Mutations affect fibrillin 1 synthesis, processing, secretion, polymerization, or stability.
Marfan Syndrome

Pedigree 2. An idealized pedigree demonstrating the effects of incomplete penetrance.

Slideshare.net
https://www.uic.edu/classes/bms/bms655/lesson4.html
Marfan Syndrome - Diagnosis

- Diagnosis – clinical (need following)
  - Aortic root dilation/dissection
  - Lens displaced superiorly
  - Spontaneous pneumothorax or apical blebs
  - Striae or recurrent hernia
  - 4 of 8 specific skeletal features
  - Family history of Marfan syndrome (recommend the mutation be identified regarding the FBN1 mutation or haplotype around FBN1)
  - Diagnosis must include anthropometric measurements
    - At least 10-20% of Marfan syndrome individuals have normal stature
Marfan syndrome – Genetic Principles

• Autosomal dominant; 25-35% of patients result from de novo mutations making the mutation unique to the family
• Dominant negative mutations - Studies of fibrillin 1 deposition and cell culture expression assays suggest a dominant negative pathogenesis (i.e. production of mutant fibrillin 1 inhibits formation of normal microfibrils by normal fibrillin 1 or stimulates inappropriate proteolysis of extracellular microfibrils) – (Nussbaum, p286)
• Variable expressivity (varying degrees of severity)

• Counsel the family re: the female’s risk if female fetus!!

Genetics in Medicine
Marfan Syndrome & Pregnancy

- Prenatal diagnosis – requires linkage analysis of the mutation that is unique to the family
- AD – 50% chance of affected offspring
- 1% risk of dissection in pregnancy if normal root
- Aortic root cutoff – 40mm for excess risk (Rossiter 1995) - reason is <40mm is less likely to have significant expansion during pregnancy and less likely to dissect
  - β-blockade to prevent aortic root dilation/dissection (HR <90) – propranolol 40-80mg/d, labetalol
  - Echocardiogram q4-6 weeks to screen for progressive dilation
  - L&D – labor in lateral decubitus, oxygen, assisted 2nd stage
- Risk if increased until 6-8 weeks PP

European Cardiac Society Guidelines - 2011
40 mm aortic root cutoff in pregnancy (Rossiter et al, 1995)

- N=45 pregnancies in 21 patients
- 1983-92; prospective study (Johns Hopkins)

**Fig. 1.** Aortic root diameter measurements before, during, and after pregnancy. *Least-squares linear regression lines*, each extending through measurements of aortic root diameter from last study before pregnancy, all studies during pregnancy, and early postpartum study.
Marfan Syndrome –
Progressive Aortic Dilation

- Prepregnancy surgery if root >45mm
- Beta blocker
- Surgery in pregnancy if root dilation is increasing
- Delivery by Cesarean at term if root >40mm (Simpson 2012), >45mm (ESC guidelines)

European Cardiac Society Guidelines - 2011
Autosomal Recessive Pedigree
Autosomal Recessive

- Males and females equally affected
- Carrier parents are usually normal
- Most are biochemical disorders
- Most are usually the first case in the family
- Consanguinity
- 25% recurrence risk
Autosomal recessive

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<td>aa</td>
</tr>
</tbody>
</table>

CF**
Cauc carrier rate 1/25
2/3 sibling carrier rate if affected
sibling and pt does not have disease
x 1/4 for affected child risk of
parents with this hx
x 1/2 carrier rate
1/25 * 2/3 * 1/4 = 1 in 149
Carrier risk – 1 in 75
Autosomal Recessive Conditions

- Cystic fibrosis
- Sickle cell anemia
- Spinal muscular atrophy
- Congenital adrenal hyperplasia
- Phenylketonuria
- Autosomal recessive polycystic kidney disease
- Meckel-Gruber syndrome - (polycystic kidneys, encephalocele, polydactyly, hepatic anomaly)
End part I
Perinatal infections

• Related anomalies
CMV – most common congenital infection

- Primary infection – 40% fetal infection rate
  - <20 weeks, infection rate less, more severe infection,
  - >20 weeks, esp >28 weeks, infection rate higher, less severe infection
  - 90/10 rule of primary infection
    - 90% asymptomatic at birth, 10% with symptoms at 2 yo (hearing loss, chorioretinitis
    - 10% symptomatic at birth (30% mortality rate), 90% of these will have long term complications;
- Nonprimary recurrent infection 10-15% risk of long term complications, usually not symptomatic at birth
CMV sonogram findings

- IUGR
- Microcephaly
- Intracranial calcifications
- Ventriculomegaly
- Echogenic bowel

- Complications
  - Chorioretinitis
  - Hearing loss
  - Thrombocytopenia
  - Hyperbilirubinemia
  - Hepatitis

- Therapy – CMV IVIG, Gancyclovir
Toxoplasmosis

- Protozoan that affects humans via ingestion of contaminated meat or cat feces
- 0.8/10,000 US; 10/10,000 France
- 400-4000 estimate new cases of congenital toxoplasmosis each year
- 50% of US women with evidence of prior exposure

- 40% risk of congenital infection – risk is greatest in 3\textsuperscript{rd} trimester; severity of infection is worse in first trimester
- Rate of infection at 13 wks - 6\%, at 36 weeks 72\%;
- if infection <20 weeks, 11\% of newborns had congenital infection
- If infection >20 weeks, 45\% had congenital infection
Toxoplasmosis

- Disseminated rash, hepatosplenomegaly, chorioretinitis, uveitis, seizures, MR
- Diagnosis: Serologic testing performed by standardized reference lab (send if + to lab Palo Alto California), toxoplasmosis PCR in amniotic fluid
- Sonogram findings - IUGR, ascites, ventriculomegaly, periventricular calcifications
- Treatment – Spiramycin to reduce risk and severity of congenital infection, confirmed by PCR in amniotic fluid or by reference lab
- Spiramycin to prevent infection; treatment if primary maternal infection; reduces risk of congenital infection; does not treat active infection
- If fetal infection diagnosed (sono findings, + PCR) treatment is with pyrimethamine, sulfadiazine, folinic acid
- Controversial if + maternal infection and neg PCR late in pregnancy as whether to give other medications in addition to spiramycin
Toxoplasmosis

- Which of the following is true about fetal rates of toxoplasmosis infection related to fetal age at the time of maternal infection?
  - **A** - Risk of fetal infection increases with advancing fetal age
  - **B** - Risk of fetal infection decreases with advancing fetal age
  - **C** - Severity of fetal infection is much greater in late pregnancy
  - **D** - Risk and severity of fetal infection are not dependent on gestational age

- Williams OB
Varicella

- Diagnosis – disseminated, pruritic, vesicular rash often associated with fever; varicella pneumonia (admission, IV ACV, respiratory support)
  - Anti-VZV IgM antibodies
- Congenital varicella – very rare (<1% in first trimester, <2% in second trimester)
  - Ultrasound findings – IUGR, microcephaly, ventriculomegaly, echogenic foci in liver, limb anomalies
  - Highest rate of infection at term
  - Chorioretinitis, microphthalmia, skin or bone defects
- Neonatal varicella – maternal varicella 5 days before to 2 days after delivery; disseminated mucocutaneous lesions, visceral infection, pneumonia, encephalitis
- Treatment – within 72-96 hours of exposure
  - VZIG (not in US)
  - Acyclovir 800mg po 5x/d x 7 days or valacyclovir 1000mg po TID x7 days
  - Respiratory support (oxygen, ABG, pH, CO2 in pregnancy)
  - No varicella vaccination in pregnancy
  - No evidence that tocolysis at term works
  - VariZIG - Canada
- Varicella zoster – Treatment with acyclovir
  - No increased risk of fetal infection
Varicella
Rubella

- Rubella – fetal infection rate
- 1\textsuperscript{st} trimester infection increased rate of infection – 80-90% 
- 13-20 weeks - 54% infection rate
- Late 2\textsuperscript{nd} – early 3\textsuperscript{rd} trimester – 25% infection rate, then increases late in 3\textsuperscript{rd} trim
- Most common defect – Sensorineural deafness, second is heart defects, PDA, pulmonary artery stenosis
Classic findings of fetal rubella syndrome: renal disorders, hypospadias, cryptorchidism, meningocele, glaucoma, patent ductus arteriosus, and peripheral pulmonary stenosis.
Parvovirus

The risk for congenital infection from an infected mother is between 10% to 20% and is highest in the first and second trimesters.

Pathophys - Aplastic anemia, High output cardiac failure, Myocardial damage from virus, Decreased oncotic pressure (anemia)
Listeriosis

- Gram + rod
- Risks of IUFD, PTL, fetal infection
- Early onset – sepsis, IUFD
- Late onset – meningitis, hydrocephalus, MR
- Hematogenous infection, leads to placental abscesses, fetal sepsis, IUFD
- Avoid unpasteurized cheeses, meats (uncooked hot dogs)
- Tx Ampicillin

Placental villitis is shown here with a small microabscess containing mostly neutrophils in a case of congenital infection with Listeria monocytogenes. Listeriosis is generally not life-threatening to the mother, but is potentially a cause for fetal demise. http://library.med.utah.edu/WebPath/PLACHtml/PLAC034.html
Lyme Disease

- Lyme:
- Borrelia burgdorferi
- Erythema chronicum migrans (60-80%)
- Erythema is later followed by meningitis or Bell’s palsy and peripheral radiculopathies
- 5-10% of patients will have cardiac disease—AV block
- Late infection associated with arthritis
- Associated with poor pregnancy outcome—but no pattern of teratogenesis (rash, syndactaly, IUG)
- May treat with amox 500 qid x 14-30 days
- Ceftriaxone 2gm IV daily for 14 days crosses blood brain barrier well
Syphilis

- Syphilis
- Incubate 10-90 days
- Primary lesion disappears in 2-6 weeks
- Secondary, or bacteremic stage lasts 2-6 weeks
- Early latent — may again get lesions, bacteremia up to 4 yrs
- Late latent - not infectious sexually
- Tertiary develops in 33% of patients
- Primary or secondary has 50% transmission, with 50% death rate
- Early latent 40% transmission and 20% death rate
- Late-10% transmission
- Early signs — rash, hepatosplenomegaly, snuffles, chorioretinitis
- Late-Hutchinson’s teeth, saber shins, saddle nose, cardiac
- After treatment VDRL should become negligible in 12 months. Do titers every 3 months for 1 year
- 2.4 mill units benzathine X 1 for primary and secondary or latent < 1 yr, otherwise repeat X 3
Tocolytics
Tocolysis

- Only benefit is to allow for administration of ANCS and to try to achieve transfer to a tertiary facility

- No superior tocolytic exists
Safety Announcement

[02-17-2011] The U.S. Food and Drug Administration (FDA) is warning the public that injectable terbutaline should not be used in pregnant women for prevention or prolonged treatment (beyond 48-72 hours) of preterm labor in either the hospital or outpatient setting because of the potential for serious maternal heart problems and death. The agency is requiring the addition of a Boxed Warning and Contraindication to the terbutaline injection label to warn against this use. In addition, oral terbutaline should not be used for prevention or any treatment of preterm labor because it has not been shown to be effective and has similar safety concerns. The agency is requiring the addition of a Boxed Warning and Contraindication to the terbutaline tablet label to warn against this use.
Uterine Contraction Mechanism

**A**
- CRH, β2-sympathomimetics, prostaglandin E₂
- Relaxation
- Smooth muscle cell
- Phosphatase
- Myosin LC20
- Nucleus
- Intracellular Ca²⁺ low

**B**
- Oxytocin, thrombin, prostaglandin F₂α
- Contraction
- Gα
- PLC
- DAG + IP₃
- PIP₂
- Sarcoplasmic reticulum
- Ca²⁺
- Ca²⁺-calmodulin complex
- Myosin LC20
- Phosphomyosin LC20
- Intracellular Ca²⁺ high


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Beta sympathomimetics

• Beta 2 receptor agonists-
  – Binds beta 2 adrenergic receptors >
    >increases adenyl cyclase >increases cAMP (intracellular) >activates PK (protein kinase)
    >phosphorylation of intracellular proteins
    >results in decreased Ca2+ intracellular
    >decreases MLCK activity >interferes with interaction b/n actin and myosin >less myometrial contractility
  – tachyphylaxis
## Table 1. Common Tocolytic Agents

<table>
<thead>
<tr>
<th>Agent or Class</th>
<th>Maternal Side Effects</th>
<th>Fetal or Newborn Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Calcium channel blockers</td>
<td>Dizziness, flushing, and hypotension; suppression of heart rate, contractility, and left ventricular systolic pressure when used with magnesium sulfate; and elevation of hepatic transaminases</td>
<td>No known adverse effects</td>
<td>Hypotension and preload-dependent cardiac lesions, such as aortic insufficiency</td>
</tr>
<tr>
<td>Agent or Class</td>
<td>Maternal Side Effects</td>
<td>Fetal or Newborn Adverse Effects</td>
<td>Contraindications</td>
</tr>
<tr>
<td>----------------------------------------</td>
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<td>---------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nonsteroidal anti-inflammatory drugs</td>
<td>Nausea, esophageal reflux, gastritis, and emesis; platelet dysfunction is rarely of clinical significance in patients without underlying bleeding disorder</td>
<td>In utero constriction of ductus arteriosus*, oligohydramnios*, necrotizing enterocolitis in preterm newborns, and patent ductus arteriosus in newborn†</td>
<td>Platelet dysfunction or bleeding disorder, hepatic dysfunction, gastrointestinal ulcerative disease, renal dysfunction, and asthma (in women with hypersensitivity to aspirin)</td>
</tr>
</tbody>
</table>
## Table 1. Common Tocolytic Agents

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<th>Fetal or Newborn Adverse Effects</th>
<th>Contraindications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta-adrenergic receptor agonists</td>
<td>Tachycardia, hypotension, tremor, palpitations, shortness of breath, chest discomfort, pulmonary edema, hypokalemia, and hyperglycemia</td>
<td>Fetal tachycardia</td>
<td>Tachycardia-sensitive maternal cardiac disease and poorly controlled diabetes mellitus</td>
</tr>
</tbody>
</table>
### Table 1. Common Tocolytic Agents

<table>
<thead>
<tr>
<th>Agent or Class</th>
<th>Maternal Side Effects</th>
<th>Fetal or Newborn Adverse Effects</th>
<th>CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Magnesium sulfate</td>
<td>Causes flushing, diaphoresis, nausea, loss of deep tendon reflexes, respiratory depression, and cardiac arrest; suppresses heart rate, contractility and left ventricular systolic pressure when used with calcium channel blockers; and produces neuromuscular blockade when used with calcium-channel blockers</td>
<td>Neonatal depression‡</td>
<td>Myasthenia gravis</td>
</tr>
</tbody>
</table>
Tocolytics – ACOG
Contraindications to Tocolysis

- Intrauterine fetal demise
- Lethal fetal anomaly
- Nonreassuring fetal status
- Severe preeclampsia or eclampsia
- Maternal bleeding with hemodynamic instability
- Chorioamnionitis
- Preterm premature rupture of membranes*
- Maternal contraindications to tocolysis (agent specific)

*In the absence of maternal infection, tocolytics may be considered for the purposes of maternal transport, steroid administration, or both.
Magnesium Sulfate – effect on risk of cerebral palsy

The possibility that magnesium sulfate administered to mothers delivering prematurely might prevent cerebral palsy in their infants was first shown in a case–control study\(^8\) in which children with cerebral palsy were much less likely to have been exposed to magnesium sulfate than were control subjects (odds ratio, 0.14; 95% confidence interval [CI], 0.05 to 0.51). This protective association has biologic plausibility, because magnesium may reduce vascular instability, prevent hypoxic damage, and mitigate cytokine or excitatory amino acid damage, all of which threaten the vulnerable preterm brain.\(^9\) We performed this study to test the hypothesis that the administration of magnesium sulfate to women at high risk for early preterm delivery would reduce the risk of cerebral palsy in their children.
Biologic Plausibility
MgSO4 Neuroprotection

• MgSO4 may exert a vasodilator effect in the fetal cerebral vessels mitigating hypoxia and/or ischemia induced brain damage.

• MgSO4 exerts an anti-inflammatory effect resulting in decreased production of pro-inflammatory cytokines and free radicals which ultimately decreases cerebral cell death secondary to inflammation.

• MgSO4 down regulates NMDA receptors for the neurotransmitter glutamate thereby decreasing Calcium entry into the cell and modulating a protective mitigation of excitatory action potential propagation.

http://www.slideshare.net/bjebelli/magnesium-sulfate
antenatal interventions have been identified that effectively decrease CP risk among preterm infants.

**Magnesium Sulphate for Neuroprotection**

In two studies published in the 1980s, preterm infants born to women with preeclampsia had a lower incidence of adverse CNS outcomes than gestational age-matched neonates born to mothers without preeclampsia.\textsuperscript{18,19} In 1995, a seminal case-control study\textsuperscript{20} was conducted with data derived from the California Cerebral Palsy project.\textsuperscript{21} It demonstrated an association between antenatal magnesium sulphate administration prior to preterm birth and fewer cases of CP among infants born < 1500 g.\textsuperscript{20} It has been proposed that use of magnesium sulphate for eclampsia treatment and prophylaxis may underlie the potential association between antenatal administration of magnesium sulphate and CP,\textsuperscript{20,22} but the findings of subsequent observational studies investigating the association have been inconsistent.\textsuperscript{23–25} Although the effectiveness of magnesium sulphate for prevention and treatment of maternal eclampsia is well proven, there remains a lack of understanding of how it may act as a neuroprotective agent.\textsuperscript{26,27} Magnesium acts in many intracellular processes, and its actions include cerebral vasodilation, reduction in inflammatory cytokines and/or oxygen free radicals, and/or inhibition of calcium influx into cells.\textsuperscript{28,29} Animal studies have shown a neuroprotective effect.\textsuperscript{30,31}

From 2002 to 2008, 5 randomized controlled trials (6145 babies) studied magnesium sulphate for fetal neuroprotection (Table 2). In 2009, a milestone was reached with the publication of 3 meta-analyses, all of which concluded that magnesium sulphate for fetal neuroprotection decreases the risk of childhood CP.\textsuperscript{32–34} Four trials used magnesium sulphate specifically for fetal neuroprotection among women likely to deliver within 24 hours.\textsuperscript{35–38} The fifth trial\textsuperscript{26} evaluated the effectiveness of magnesium sulphate for eclampsia prevention in women with preeclampsia. Of the 4 trials with neuroprotective intent, one also included a tocolytic arm.\textsuperscript{37} Three of these 4 trials enrolled primarily women with preterm labour (with or without PPROM),\textsuperscript{35–37} whereas the fourth focused on women with PPROM.\textsuperscript{38} Children were followed-up to the age of 2 years for CP assessment, and 3 trials undertook cognitive testing.\textsuperscript{26,35,38}

Study quality was good.\textsuperscript{32} Importantly, 4 of the 5 trials (and all neuroprotective intent trials) described an adequate
Perinatal brain lesions: a multiple hit concept

Preterm labor

Inflammation  Free radicals

Excitotoxicity

WMD

Repair

http://www.slideshare.net/bjebelli/magnesium-sulfate
Magnesium sulfate (NMDA)

- NMDA receptors blocker
- Preclinical prevention of developing WM
- Safe for neonates but potential side effects in mothers
- Demonstrated benefits (gross motor dysfunction and CP) in preterm infants... ... but NNT = 63 mothers to save one CP!
- No effect in asphyxiated term infants

Marret et al., 1995
Crowther et al., 2003
Doyle et al., 2009

http://www.slideshare.net/bjebelli/magnesium-sulfate
<table>
<thead>
<tr>
<th>Outcome</th>
<th>Magnesium Sulfate (N=1041)</th>
<th>Placebo (N=1095)</th>
<th>Relative Risk (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All pregnancies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy or death*</td>
<td>118/1041 (11.3)</td>
<td>128/1095 (11.7)</td>
<td>0.97 (0.77–1.23)</td>
<td>0.80</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy alone</td>
<td>20/1041 (1.9)</td>
<td>38/1095 (3.5)</td>
<td>0.55 (0.32–0.95)</td>
<td>0.03</td>
</tr>
<tr>
<td>Death alone</td>
<td>99/1041 (9.5)</td>
<td>93/1095 (8.5)</td>
<td>1.12 (0.85–1.47)</td>
<td>0.41</td>
</tr>
<tr>
<td><strong>Pregnancies without major congenital anomalies</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy or death*</td>
<td>100/997 (10.0)</td>
<td>117/1063 (11.0)</td>
<td>0.91 (0.71–1.17)</td>
<td>0.47</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy alone</td>
<td>18/997 (1.8)</td>
<td>34/1063 (3.2)</td>
<td>0.56 (0.32–0.99)</td>
<td>0.04</td>
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<tr>
<td>Death alone</td>
<td>83/997 (8.3)</td>
<td>86/1063 (8.1)</td>
<td>1.03 (0.77–1.37)</td>
<td>0.85</td>
</tr>
<tr>
<td><strong>Scores on the Bayley Scales of Infant Development</strong></td>
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<tr>
<td>Psychomotor Development Index &lt;70</td>
<td>134/876 (15.3)</td>
<td>144/919 (15.7)</td>
<td>0.98 (0.79–1.21)</td>
<td>0.83</td>
</tr>
<tr>
<td>Psychomotor Development Index &lt;85</td>
<td>299/876 (34.1)</td>
<td>315/919 (34.3)</td>
<td>1.00 (0.88–1.13)</td>
<td>0.95</td>
</tr>
<tr>
<td>Mental Development Index &lt;70</td>
<td>165/876 (18.8)</td>
<td>171/919 (18.6)</td>
<td>1.01 (0.83–1.23)</td>
<td>0.90</td>
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<tr>
<td>Mental Development Index &lt;85</td>
<td>406/876 (46.3)</td>
<td>427/919 (46.5)</td>
<td>1.00 (0.90–1.10)</td>
<td>0.96</td>
</tr>
</tbody>
</table>

* In one twin pregnancy in the magnesium sulfate group and in three twin pregnancies in the placebo group, one of the fetuses was stillborn or died as an infant, whereas the other survived and subsequently received a diagnosis of moderate or severe cerebral palsy. Thus, the number of pregnancies associated with death alone and the number of pregnancies associated with moderate or severe cerebral palsy alone do not add up to the number of pregnancies associated with moderate or severe cerebral palsy or death.
Table 3. Stratified Analyses of the Primary Outcome and Its Components.*

<table>
<thead>
<tr>
<th>Outcome</th>
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<th>Placebo (N=1095)</th>
<th>Relative Risk (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no./total no. (%)</td>
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<td></td>
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<tr>
<td>Primary outcome</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Weeks of gestation at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>89/442 (20.1)</td>
<td>105/496 (21.2)</td>
<td>0.95 (0.74–1.22)</td>
</tr>
<tr>
<td>≥28</td>
<td>29/599 (4.8)</td>
<td>23/599 (3.8)</td>
<td>1.26 (0.74–2.15)</td>
</tr>
<tr>
<td>Magnesium sulfate treatment before randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>27/192 (14.1)</td>
<td>26/210 (12.4)</td>
<td>1.14 (0.69–1.88)</td>
</tr>
<tr>
<td>No</td>
<td>91/849 (10.7)</td>
<td>102/885 (11.5)</td>
<td>0.93 (0.71–1.21)</td>
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<tr>
<td>Singleton or twin pregnancy</td>
<td></td>
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<tr>
<td>Singleton</td>
<td>97/950 (10.2)</td>
<td>103/985 (10.5)</td>
<td>0.98 (0.75–1.27)</td>
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<tr>
<td>Twin</td>
<td>21/91 (23.1)</td>
<td>25/110 (22.7)</td>
<td>1.02 (0.61–1.69)</td>
</tr>
<tr>
<td>Moderate or severe cerebral palsy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Weeks of gestation at randomization</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;28</td>
<td>12/442 (2.7)</td>
<td>30/496 (6.0)</td>
<td>0.45 (0.23–0.87)</td>
</tr>
<tr>
<td>≥28</td>
<td>8/599 (1.3)</td>
<td>8/599 (1.3)</td>
<td>1.00 (0.38–2.65)</td>
</tr>
</tbody>
</table>
NAIT
Neonatal thrombocytopenia

**Differential Diagnosis**

- Infection/sepsis
  - TORCH – Toxoplasma gondii, hepatitis B, syphilis, Varicella-Zoster, HIV, parvovirus B19, Rubella, CMV, HSV
  - Perinatal infection with *E. coli*, *H. influenza*, Group B streptococcus
- Disseminated intravascular coagulation
- Neonatal alloimmune thrombocytopenia
Neonatal thrombocytopenia

• **Differential Diagnosis**
  - Maternal autoimmune thrombocytopenia with transplacental passage of antibodies
    • Immune thrombocytopenic purpura – ITP
    • Lupus
  - Maternal exposure to antiplatelet medications
    • Heparin, Enoxaparin
  - Bone marrow disorders (aplastic anemia), inherited thrombocytopenias
Neonatal Alloimmune Thrombocytopenia (NAIT)

- **Definition**
  - Maternal alloimmunization against platelet antigens inherited from the father
  - Or against platelet antigens that are seen as foreign to the mother
NAIT - Epidemiology

• Epidemiology
  – Most common cause of severe thrombocytopenia (<50,000/µL) in the newborn in the first few days of life
  – 1 in 1-5,000 births
  – Can occur as early as 18-20 weeks gestation
  – No gender preference
  – 50% of cases occur during a first pregnancy

• Risk factors
  – Previous child with NAIT or family history of NAIT
  – Recurrence risk ~100%, if homozygous FOB
NAIT - Pathophysiology

• Pathophysiology
  – Maternal alloimmunization against fetal platelet antigens inherited from the father - severity depends on antigen
  – Most commonly occurs in women lacking human platelet antigen (HPA) -1a - mother is HPA 1b/1b, with anti HPA 1a and a father that is HPA 1a/1a or HPA 1a/1b
    • 80-90% of cases occur in HPA-1a negative mothers
    • 98% of the US population is HPA-1a (+)
      • 2% of US population is HPA -1a negative or HPA 1b homozygotes
    • HPA-1a incompatibility causes the most severe form of the disease
      – HPA -3a causes the next most severe form
    • HPA-1a and -5b are the most commonly involved HPAs
    • Asian population – HPA -4 system is the most frequent cause of NAIT
  – HLA antigens not commonly involved or thought to result in alloimmunization
<table>
<thead>
<tr>
<th>Table</th>
<th>Platelet-specific alloantigens that are associated with AIT</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>HPA system name</td>
</tr>
<tr>
<td></td>
<td>Polymorphisms of glycoprotein IIIa</td>
</tr>
<tr>
<td>HPA-1</td>
<td>HPA-1a</td>
</tr>
<tr>
<td>HPA-1</td>
<td>HPA-1b</td>
</tr>
<tr>
<td>HPA-4</td>
<td>HPA-4a</td>
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<tr>
<td>HPA-4</td>
<td>HPA-4b</td>
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<tr>
<td>HPA-12</td>
<td>HPA-12bw</td>
</tr>
<tr>
<td></td>
<td>Other probable platelet alloantigen specificities</td>
</tr>
<tr>
<td>HPA-15</td>
<td>HPA-15a</td>
</tr>
<tr>
<td>HPA-15</td>
<td>HPA-15b</td>
</tr>
</tbody>
</table>

NAIT - Clinical presentation

• Clinical presentation
  – Health newborn with widespread petechiae or purpura
  – Visceral hemorrhage – GI or bladder
  – Intracranial hemorrhage – may occur in utero or intrapartum or in the neonatal period
    – Occurs in 7-20% of cases of NAIT – 75% of these cases occur in the antenatal period – as early as mid 2nd trimester
  • Fatal in 1/3 of patients
  • 20-30% have neurologic impairment
  – High recurrence rate in subsequent pregnancies
    • Usually more severe
NAIT - Diagnosis

- Diagnosis is made in thrombocytopenic infants when maternal and paternal platelet typing reveals the father has a platelet antigen that the mother lacks and the mother has detectable antibodies to this antigen.
- A combination of test results are used to determine the likelihood of NAIT.
Pregnancies at risk for NAIT - History

- Previous pregnancy affected by NATP or previous baby affected – severity, ICH present or not
- Fetal death due to intracranial hemorrhage
- Neonatal thrombocytopenia of undetermined etiology
  - All cases of neonatal thrombocytopenia <50k, regardless of etiology
- Family history (esp in sisters of the patient)
Pregnancies at risk for NAIT

• After an index case, over 85% of the couple’s subsequent fetuses will carry the offending platelet antigen and be at risk for NATP
  – Ex – affected proband – likely HPA 1b/1b
    • Father
      – 25% HPA 1a/1b – 50% of progeny will be 1a/1b and at risk
      – 75% are HPA 1a/1a – 100% of progeny will be 1a/1b and at risk
NAIT - lab

- Universal screening not cost effective
- Personal or family history suggestive of NAIT
  - Maternal HPA antibodies
  - Maternal and paternal platelet antigen testing usually performed simultaneously looking for incompatibility for the HPA – 1a/1b antigen system
  - Maternal serum antibody screening is for HLA antibodies and RBC antigens (HLA not thought to be a significant cause of NATP, but if it is, then it’s probably class I
  - If initial antibody screen is negative, then testing each trimester if there is HPA incompatibility since the HPA antibodies can occur later in the pregnancy
NAIT - lab

- Fetal platelet typing
  - Fetal DNA from amniocytes
    - Amniocentesis is preferred as CVS potential risk for sensitization is greater
    - If FOB is heterozygous, fetal antigen typing is recommended to avoid unnecessary treatment in fetuses not at risk
  - Uses PCR to determine fetal HPA status by typing fetal DNA for platelet antigens
Platelet Alloimmunization

Paternal zygosity result for involved platelet antigen

Homozygous

Heterozygous

PCR testing of amniotic fluid for fetal genotype

Antigen + fetus

Antigen - fetus

No further therapy required

Previous infant with only thrombocytopenia

Previous fetus/child w/IVH @ 36 weeks' gestation to neonatal life (HIGH RISK)

Previous fetus w/IVH @ 28 - 36 weeks' gestation (VERY HIGH RISK)

Previous fetus w/IVH @ < 28 weeks' gestation (EXTREMELY HIGH RISK)

20 weeks EGA
Begin 1 gr/kg/wk IVIG & 0.5 mg/kg/day prednisone OR 2 gr/kg/wk IVIG

12 weeks EGA
Begin 1 gr/kg/wk IVIG

12 weeks EGA
Begin 1 gr/kg/wk IVIG

24 weeks EGA
↑ IVIG to 2 gr/kg/wk OR add prednisone 0.5 mg/kg/day

20 weeks EGA
Add prednisone 1 mg/kg/day

28 weeks EGA
↑ IVIG to 2 gr/kg/wk

20 weeks EGA
Add prednisone 1 mg/kg/day
NAIT - Management

- **Management**
  - Expectant
  - In-utero platelet transfusions
  - Medical
    - IVIG
    - Corticosteroids
  - Neonatal platelet transfusion (antigen negative)
Natural history

- Bussel 1997 – review of 3 trials – N=107
  - Pre-treatment
    - 53 pt with plt <20k (50%), only 4 had normal platelet counts (>100k)
    - Majority HPA 1a incompatibility
    - 41/107 infants sampled at 25 weeks had platelet counts lower than previous affected siblings
    - If >50,000 and did not get treated – platelet count decreased by 10,000/mL³ per week
  - Most significant predictor for more severe disease in subsequent pregnancy was antenatal hemorrhage in the affected sibling

- Starting with IVIG, avoid initial FBS
NAIT - Management

- Management
  - Expectant – in absence of intervention, thrombocytopenia in the second affected child is always as or more severe than in the previous affected infant
  - Intracranial hemorrhage is the reason for the majority of morbidity and mortality and prevention of this is the goal of treatment

- Up to 75% of ICH occurs antenatally
Fetal blood sampling

• Management
  – In-utero platelet transfusions
  – Invasive
    • Any fetal blood sampling procedure – 1% risk of fetal loss
    • Risk is higher in an affected NAIT pregnancy – up to 8% due to exsanguination at puncture site of cord
  – In utero transfusion of platelets concentrated (maternal) should be performed at the time of FBS if platelet count is determined to be <50k before the needle is removed to avoid exsanguination
NAIT

- Management – medical
  - IVIG
  - Corticosteroids
NAIT - IVIG

• *Has been shown to reduce the risk of intracranial hemorrhage when compared to prior untreated pregnancies (bussel 1998, lynch 1992)

• Most common to start IVIG –
  – 1gm/kg/week in pregnancies at 20 weeks of gestation
  – High risk pregnancy –
    • Hx of antenatal ICH,
    • Hx of peripartum ICH
    • Platelet count <20k obtained via cordocentesis
    • If above is present – may need to do 2gm/kg/week or add 1mg/kg/day of prednisone
When to add steroids

- Bussel 1996 – 54 patients
  - All got IVIG +/- dexamethasone
  - Rescue therapy for nonresponders – prednisone 60mg /day increased the platelet counts
  - Dexamethasone did not help improve platelet counts
Antenatal therapy – a protocol

• Standard risk – previous affected child with thrombocytopenia without ICH
  – IVIG 1gm/kg/week or prednisone 0.5mg/kg/day starting at 20 weeks

• High risk – previous affected child with thrombocytopenia and ICH in peripartum period
  – IVIG 1gm/kg/week + prednisone 1mg/kg/day starting at 20 weeks
Antenatal therapy – a protocol

- Very high risk – previously affected child with antenatal ICH
  - IVIG – 2gm/kg/week started at 12 weeks
  - FBS at 20 weeks, if plt <50k, prednisone 1mg/kg/day is started
  - Weekly in utero platelet transfusions or delivery are the remaining options when medical therapy is not adequate

- Cesarean delivery – (vaginal delivery possible option if fetal platelets >50k prior to delivery)

Paidis - uptodate
When to add steroids

• Bussel 1996 – 54 patients
  – All got IVIG +/- dexamethasone
  – Rescue therapy for nonresponders – prednisone 60mg /day increased the platelet counts
  – Dexamethasone did not help improve platelet counts
In-utero intracranial hemorrhage
Conclusions

- Thrombocytopenia
  - Exclude clumping first
  - Remember differential diagnosis
- For ITP adding steroids at platelet counts of 50-70k is controversial, most recommend starting steroids when <50k
- Differentiate maternal from neonatal thrombocytopenia
Thrombocytopenia
Definition

- **Mild** – 100,000 – 150,000
- **Moderate** - 50,000 – 100,000
- **Severe** - <50,000

- Spontaneous bleeding at <20k
- Serious bleeding complications are rare, even in those with severe thrombocytopenia
- Bleeding with trauma/surgery if <50k

ACOG Bulletin
Epidemiology

- 7-8% of all pregnancies
- 3/1000 will have clumping of platelets in EDTA and are NOT at risk for bleeding and do not require further evaluation/surveillance unless indicated for other conditions such as hypertension, etc
- ITP occurs in 3/1000 pregnancies
Platelet clumping
Etiologies and Differential Diagnosis

• Major
  – Gestational thrombocytopenia
  – Severe preeclampsia
  – HELLP syndrome
  – Disseminated intravascular coagulation
  – Platelet clumping
  – Medications – Heparin/enoxaparin, quinine derivatives
Etiologies and Differential Diagnosis

- Uncommon
  - Immune thrombocytopenia purpura
  - Human immunodeficiency virus
  - Lupus
  - APLS
Etiologies and Differential Diagnosis

• Rare causes
  – Thrombotic thrombocytopenic purpura
  – Hemolytic Uremic syndrome
  – Type IIB von Willebrand’s disease
  – Hematologic malignancies
  – Folate deficiency
  – Congenital disorders – May-Hegglin Anomaly and Gray Platelet syndrome
**Immune Thrombocytopenic Purpura**

- **Platelet count > 20,000/mm³**
  - Check platelet count at regular intervals and watch for signs of clinical bleeding

- **Platelet count ≤ 20,000/mm³ or clinical bleeding**
  - IV methylprednisolone 1.0–1.5 mg/kg/day administered in 2 or 3 divided doses

  - **Fails to respond**
    - Intravenous immunoglobulin 0.4–1.0 g/kg/day for 3–5 days
      - **Fails to respond**
        - Splenectomy
      - **Platelet count rises**
        - Repeat as necessary
        - Consider other immunosuppressive medications
          - **Follow platelet counts for the remainder of pregnancy and be aware that neonate may still have severe thrombocytopenia**

  - **Platelet count rises**
    - Change to oral prednisone, 1 mg/kg/day, then taper to keep platelets approximately 100,000/mm³

*FIG. 4-3: Management of the pregnant woman with immune thrombocytopenic purpura.*

Foley OB ICU Care Manual
Thrombotic Thrombocytopenic Purpura

- Rare, life threatening, medical emergency
- Platelets aggregate, producing platelet thrombi, occluding arterioles and capillaries, leads to ischemia, infarction
  - Can affect any organ system
  - Esp brain, kidneys
Microangiopathic Hemolytic Anemia

A schistocyte count greater than 1% appears to be diagnostic of TTP in the appropriate clinical setting (Burns 2004)
TTP – Clinical Diagnosis

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Neurologic abnormalities
  - Confusion, HA, paresis, visual hallucinations, seizures
- Fever
- Renal dysfunction
- *Top 3 in 75% of TTP patients, pentad seen in 40%
- Differentiation from other microangiopathic hemolytic anemias of pregnancy (severe preeclampsia/HELLP)
TTP – Management

• Medical

• Plasmapharesis/plasma exchange
  – FFP to temporize and transfer to facility capable of plasmapharesis

• IV steroids

• Dialysis if renal failure is present

• Refractory cases
  – Vincristine
  – Cryoprecipitate
  – Splenectomy
  – Azathioprine
Management of the gravida with TTP. Before adopting this approach, the treating physician must be certain of the diagnosis. TTP is a clinical diagnosis and can mimic severe preeclampsia. The criteria for diagnosing TTP are listed in Table 4-6.
Alloimmunization

• At present slides not developed

• Calculations, examples
• Tests for MFN hemorrhage

• See ACOG bulletin, UTD, Creasey – for reference;
• Call /text Dr. Farley for info/problem cases and to schedule time to review if desired;
Twins

• See ACOG bulletin, UTD, Creasey – for reference;

• Call /text Dr. Farley for info/problem cases and to schedule time to review if desired;

• See previous slide sets for details, available on website/on request
• No financial interests to disclose.
Multiples

• Maternal physiology
• Risks
• Twins
  – Specific risks
• Triplets
• Delivery timing
• Questions
Case 1

- 30 yo P1001
- Monochorionic/diamniotic twins
  - Risks?
  - Surveillance?
  - Delivery timing?
Case 2

- 22 yo P0
- Monoamniotic twins
  - Risks?
  - Surveillance?
  - Delivery timing?
Cardiovascular Changes of Pregnancy

- Cardiac Output Increased by 30-50%
- Twin Pregnancy: Add another 15%
- Starts Early and Peaks at 20 Weeks
- Increase in Stroke Volume
- Increase in Heart Rate
Cardiac Output Across Gestation

Cardiac Output Increased by 30-50%
Twin Pregnancy: Add another 15%
Starts Early and Peaks at 20 Weeks

Adapted from Uptodate - Citation Bonica 1994 Obstetrical Anesthesia
Epidemiology

- **Of all twins…without ART**
  - Dizygotic twins (~70%)
    - Ethnic variation in incidence of DZ twinning
  - Monozygotic twins (~30%)
    - Incidence of MZ twins is relatively stable worldwide at 3 to 5 per 1000 births
    - 70% MCDA, 30% DCDA

- **Triplets+…193.5/100,000 (1980s-90s)**
  - 153.4/100,000 (2009)
Twinning

• Determine early in gestation
  – Location, fetal sex, insertion sites, thickness of membranes

• Why do we care about placentation?
  – Predicting risk…
    • Monochorionic, diamniotic
      – Risk of sharing a placenta; shunting, anastomosis
      – unequal blood distribution - TTTS
      – 15% occurrence rate
    • Monoamniotic (cord entanglement)
      – 1/10,000 of all pregnancies
      » 1-5% of monozygotic twins
2 placentas
2 amnions
2 chorions
(dizygotic twins or monozygotic twins with cleavage of zygote during first 3 days after fertilization)
Lambda sign/twin peak

1 placenta
2 amnions
1 chorion
(monozygotic twins with cleavage of zygote days 4-8 post-fertilization)
T sign

1 placenta
1 amnion
1 chorion
(monozygotic twins with cleavage of zygote days 8-12 post-fertilization)

*if split occurs after 12 days post-fertilization, conjoined twins result

YS #
UTD
Placentation

- Multiple gestations – (e.g. twins)
- Dependent on when zygote splits post-fertilization in monozygotic pregnancy
  - the earlier the split the more tissue each pregnancy gets to itself
    - <3 dichorionic
    - 3-8 diamniotic
    - 8-12 monoamniotic
    - >12 conjoined
  - Dichorionic placentation (two placentas, in all dizygotic and some monozygotic twins)
  - Monochorionic placentation
    - monozygotic twins develop with only one placenta
    - higher risk of complications during pregnancy
    - preeclampsia
    - shunting of blood from 1 twin to the other (TTTS)
  - Monoamniotic placentation
Dichorionic twin pregnancy (lambda sign)
Thick interdividing membrane of dichorionic twin pregnancy
Thin intertwin membrane characteristic of monochorionic diamniotic twin pregnancy
Risks during the pregnancy

- Preterm birth
- Anomalies
- GDM
- Preeclampsia
Nutrition

• NUTRITION — Women carrying multiple gestations should increase their daily dietary intake by about 300 kcal above that for a singleton pregnancy, or 600 kcal over that of a nonpregnant woman
• Institute of Medicine recommendations for weight gain
  • BMI <18.5 kg/m² (underweight) — no recommendation due to insufficient data
  • BMI 18.5 to 24.9 kg/m² (normal weight) — weight gain 37 to 54 lbs (16.8 to 24.5 kg)
  • BMI 25.0 to 29.9 kg/m² (overweight) — weight gain 31 to 50 lbs (14.1 to 22.7 kg)
  • BMI ≥30.0 kg/m² (obese) — weight gain 25 to 42 lbs (11.4 to 19.1 kg)
• These thresholds represent the 25th through 75th percentile weight gains in women who gave birth to twins weighing at least 2500 g and appear to be associated with a decreased risk of preterm birth and higher birth weights
• Dietary or vitamin/mineral supplementation - folate, etc
Society of Maternal-Fetal Medicine recommendations for nutrition in twin pregnancy are shown in the table.
Twinning Complications
• TRAP sequence
• Occurs only in monochorionic twins
• 1 in 35,000 pregnancies
• Acardiac twin pregnancy
• Due to arterioarterial anastomoses resulting in a pump twin and a perfused twin
• Perfused twin – Abnl
• Pump twin -NL
• Perfused twin –
  - Reversed Doppler flow in umbilical cord present, this blood is low in oxygen and nutrients
  - Usually acardiac or has a rudimentary heart and its head and upper limbs are usually absent
  - Trunk and lower limbs may be well-developed, most internal organs are absent or malformed. It can be significantly larger than the pump twin due to hydrops fetalis

• Pump twin –
  - Not malformed, but is at high risk of perinatal morbidity/mortality from high output cardiac failure or preterm birth due to uterine overdistention related to the twin mass or polyhydramnios.

• Treatment - Separation of the two circulations is therapeutic for the pump twin and can be accomplished by fetoscopic laser coagulation of the placental vascular anastomoses or radiofrequency ablation of the umbilical cord of the acardiac twin
Monoamniotic twins

- No membrane
- Exclude conjoined
- 1 yolk sac - 1\textsuperscript{st} trim
- Risk is cord entanglement
- Surveillance at viability, ANCS/NP mag
- Delivery at 32-34wk
Conjoined Twins

- Only in monochorionic twins
- 1 in 50,000 pregnancies
- Conjoined twins are classified according to the site of union (eg, chest, head) with the suffix "pagus" (meaning fixed, eg thoracopagus)
- Sonogram - MA sac, contiguous skin, twins that stay in the same orientation to one another, fetal scoliosis, unusual limb positioning, and more than three vessels in the cord
- Associated congenital defects unrelated to the area of fusion are common
- Increased IUFD rate
- Anatomy sonogram, FE, MRI – used to determine extent of deformity and counsel the parents about prognosis
- Delivery of potentially viable infants is always by cesarean.
Case 3

• 24 yo P1001

• Triplets
  – Counseling on multifetal pregnancy reduction?

• Quadruplets
  – Counseling on multifetal pregnancy reduction?
Case 4

- 28 yo P2002
- Monochorionic /diamniotic twins
  - 1 twin normal
  - 1 twin anencephaly

  - Management?
Multifetal pregnancy reduction and selective termination

- MFPR, selective termination
- 5-8% of pregnancy loss <24 weeks
- Selective fetal reduction —
  - Reduction of anomalous fetus to improve outcome of other fetuses
  - Anencephaly – risk of polyhydramnios and PTB increases risk to cotwin survival in MC/DA and DC/DA twin pregnancies
- MFPR
  - Triplets → Twins – Risks of morbidity/mortality <8% from prematurity as triplets average GA at delivery is 31 weeks (ACOG)
  - Quadruplets (and +) → triplets, twins
    - Risks of morbidity/mortality ≥8% from prematurity as quadruplets average GA at delivery is 29 weeks (ACOG) and infant mortality rate is high (>50%)
- Method – Medical (KCl, digoxin)
  - Laser photocoagulation, Radiofrequency ablation
TTTS
TWIN-TWIN TRANSFUSION SYNDROME

Diagnosis –

MCDA twins

Polyhydramnios/oligohydramnios

Due to uncompensated vascular anastomoses in the placenta

Intertwin differences in growth may present as early as the first trimester

Prognosis for untreated severe cases is poor: perinatal mortality is 70 to 100 percent, survivors are at high risk of neurologic, cardiac, and renal impairment
TTTS

- **Incidence**
- 5-15% in monochorionic-diamniotic twin pregnancies
  - 6% of monoamniotic twin pregnancies
- **Possible in monoamniotic or dichorionic diamniotic twins, but rare**

**Diagnosis**
- **Suspicion of monochorionic-diamniotic twin pregnancy**
- Polyhydramnios (>8cm) - recipient; oligohydramnios (<2cm) - donor
Etiology

- **TYPE OF ANASTOMOSIS**
  - A-V anastomosis: unidirectional flow; intravillous (placental surface single unpaired artery carrying blood from donor twin to placental cotyledon together with single unpaired vein carrying blood from that cotyledon back to the recipient twin)
  - A-A, V-V anastomosis: superficially located on chorionic plate, allow bidirectional flow, ‘saving type’ of anastomosis
  - Less A-A and V-V anastomoses increases probability of A-V anastomoses leading to TTTS
  - Discordant placental size or sharing of placenta
Classification

- Classification (no good system for prediction of progression or prognosis)
- Quintero staging system (?good for monitoring disease progression, not predicting outcomes or determining which pregnancies will progress)
- Stage I — + Poly/oligo (POS); +bladder in donor
- Stage II — +POS; NO bladder seen in donor; normal Dopplers
- Stage III — +POS; NO bladder seen in donor; abnormal Doppler (absent, REDV in donor umbilical artery; reversed ductus venous flow; pulsatile umbilical vein venous flow in recipient)
- Stage IV — + POS, hydrops in either twin
- Stage V — Fetal demise of either or both twins
- Staging system based on presence of A-A anastamoses (Jain et al)
  - antenatal identification of A-A anastomosis, which is "protective" against TTTS
FIGURE 5
Algorithm for screening for TTTS

MCDA pregnancy

First trimester:
- Confirm monochorionic, diamniotic placentaion
- NT screening

~ 16 weeks
Start ultrasound surveillance with MVP in each sac, and fetal bladder in each fetus, every 2 weeks, until delivery

MVP >2cm and <8cm in each sac

Yes
Continue ultrasound surveillance every 2 weeks

No
MVP <2cm in 1 sac and MVP >8 cm in other sac: Diagnosis = TTTS

See Figure 10

MCDA, monochorionic diamniotic; MVP, maximum vertical pocket; NT, nuchal translucency; TTTS, twin-twin transfusion syndrome.
Treatment

- Expectant management
- Amnioreduction
- Septostomy
- Selective feticide
- Fetoscopic laser ablation of vascular anastomoses (16-26 weeks)
Treatment

- Treatment (prolonged neural outcomes not known in treatments, limits counseling patients)
- Amnioreduction (decrease pressure leading to less uterine distension, allows better placental blood flow, may help with maternal symptoms)
- Survival based on serial amnioreductions (2001 registry); (223 sets of twins; TTTS <28 wks) follow-up data until 4 weeks old; major findings included:
  - 78% born alive
  - 60% alive 4 weeks after birth
  - Abnormal neonatal cranial scan in ~25% recipients and donors
  - Better survival related to older gestational age, no Doppler abnormalities or hydrops, removal of less fluid, higher birthwt
  - Amnioreduction - may be appropriate if significant fluid discordance; more widely available; lower complication rate
Endoscopic Laser Surgery versus Serial Amnioreduction for Severe Twin-to-Twin Transfusion Syndrome

Marie-Victorie Senat, M.D., Jan Deprest, M.D., Ph.D., Michel Boulvain, M.D., Ph.D., Alain Paupe, M.D., Norbert Winer, M.D., and Yves Ville, M.D.

ABSTRACT

BACKGROUND
Monochorionic twin pregnancies complicated by severe twin-to-twin transfusion syndrome at midgestation can be treated by either serial amnioreduction (removal of large volumes of amniotic fluid) or selective fetoscopic laser coagulation of the communicating vessels on the chorionic plate. We conducted a randomized trial to compare the efficacy and safety of these two treatments.

METHODS
Pregnant women with severe twin-to-twin transfusion syndrome before 26 weeks of gestation were randomly assigned to laser therapy or amnioreduction. We assessed perinatal survival of at least one twin (a prespecified primary outcome), survival of at least one twin at six months of age, and survival without neurologic complications at six months of age on the basis of the number of pregnancies or the number of fetuses or infants, as appropriate.

RESULTS
The study was concluded early, after 72 women had been assigned to the laser group and 70 to the amnioreduction group, because a planned interim analysis demonstrated a significant benefit in the laser group. As compared with the amnioreduction group, the laser group had a higher likelihood of the survival of at least one twin to 28 days of age (76 percent vs. 56 percent; relative risk of the death of both fetuses, 0.63; 95 percent confidence interval, 0.25 to 0.93; \( P = 0.009 \)) and 6 months of age (\( P = 0.002 \)). Infants in the laser group also had a lower incidence of cystic periventricular leukomalacia (6 percent vs. 14 percent, \( P = 0.02 \)) and were more likely to be free of neurologic complications at six months of age (52 percent vs. 31 percent, \( P = 0.003 \)).

CONCLUSIONS
Endoscopic laser coagulation of anastomoses is a more effective first-line treatment than serial amnioreduction for severe twin-to-twin transfusion syndrome diagnosed before 26 weeks of gestation.
### TABLE 5
Randomized trial of laser photocoagulation vs amnioreduction (Eurofetus)\(^65,77\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser, n = 72 pregnancies/ n = 144 twins</th>
<th>Amnioreduction, n = 70 pregnancies/ n = 140 twins(^a)</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median gestational age at delivery, wk</td>
<td>33.3</td>
<td>29.0(^a)</td>
<td>.004</td>
</tr>
<tr>
<td>Survival of at least 1 twin at 6 mo of age</td>
<td>76% (55/72)</td>
<td>56% (36/70)</td>
<td>.009</td>
</tr>
<tr>
<td>All perinatal deaths up to 6 mo of age</td>
<td>44% (63/144)</td>
<td>61% (86/140)</td>
<td>.01</td>
</tr>
<tr>
<td>Cystic periventricular leukomalacia at 6 mo</td>
<td>6% (8/144)</td>
<td>14% (20/140)</td>
<td>.02</td>
</tr>
<tr>
<td>Alive and free of neurologic complications at 6 mo</td>
<td>52% (75/144)</td>
<td>31% (44/140)</td>
<td>.003</td>
</tr>
<tr>
<td>Normal neurologic development at 6 y(^b)</td>
<td>82% (60/73)</td>
<td>70% (33/47)</td>
<td>.12</td>
</tr>
</tbody>
</table>

\(^a\) Of women in amnioreduction group, 11 (16%) had voluntary termination of pregnancy between 21-25 wk; \(^b\) Includes only children delivered in France and still alive at 6 mo of age.

---

### TABLE 6
Randomized trial of laser photocoagulation vs amnioreduction (NICHD-sponsored)\(^67\)

<table>
<thead>
<tr>
<th>Variable</th>
<th>Laser, n = 20 pregnancies/ n = 40 twins</th>
<th>Amnioreduction, n = 20 pregnancies/ n = 40 twins</th>
<th>(P) value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean gestational age at delivery, wk</td>
<td>30.5</td>
<td>30.2</td>
<td>NS</td>
</tr>
<tr>
<td>Survival of at least 1 twin at 30 d of age</td>
<td>65% (13/20)</td>
<td>75% (15/20)</td>
<td>.73</td>
</tr>
<tr>
<td>All perinatal deaths up to 30 d of age</td>
<td>55% (22/40)</td>
<td>40% (16/40)</td>
<td>.18</td>
</tr>
<tr>
<td>Recipient twin fetal mortality</td>
<td>70% (14/20)</td>
<td>35% (7/20)</td>
<td>.03</td>
</tr>
</tbody>
</table>

\(NICHD, Eunice Kennedy Shriver National Institute of Child Health and Human Development; NS, nonsignificant.\)

Laser Coagulation

- Laser coagulation (obliterate visible A-V anastomoses); amnioreduction done at end of surgery to buffer increases until the coagulation can take effect
- Appears to be an appropriate therapy in cases of significant discordance or when there is fetal myocardial dysfunction
- Eurofetus RCT (laser vs serial amnioreduction); interim analysis halted study as it showed better outcomes in the laser arm

- Overall perinatal survival (57 versus 41 percent)
- Survival of at least one twin to age 28 days (76 versus 56 percent)
- Survival without major neurologic morbidity at six months (52 versus 31 percent of the initial cohorts)
TTTS – Laser Photocoagulation - Complications

• Perioperative complications
  – PPROM – 7-17% (1-3 weeks post laser)
  – Amniotic fluid leakage into the maternal peritoneal cavity (7 percent),
  – Vaginal bleeding (4 percent),
  – Abruption (2 percent), and
  – Chorioamnionitis (2 percent).
  – Amniotic band-like syndrome has also been reported
• Amnioreduction – similar to above, lower rate of PPROM
TTTS - Other previously studied treatments

- Septostomy of amniotic membrane (does not address underlying pathophysiology); only big study limited by crossover of septostomy patients to amnioreduction arm

- Selective termination (difficult to tell which twin would be ultimately more severely affected)

- Medical – digoxin, prostaglandin synthase inhibitors (limited use)
TTTS

- Morbidity/Mortality
- Profound anemia, placental insufficiency of donor
- Heart failure from circulatory overload in recipient
- PTL (hydramnios) complications of prematurity
- Lethal congenital anomalies associated with monozygosity
- Survival depends on gestational age and severity at time of diagnosis (before 1990, 80-100% mortality)
- Death of one twin corresponds to 30-50% risk of mortality/neurologic damage to survivor
- Survival based on laser coagulation of A-V anastomoses
Neurodevelopmental outcome at 2 years in children born preterm treated by amnioreduction or fetoscopic laser surgery for twin-to-twin transfusion syndrome: comparison with dichorionic twins

Richard Lencen, MD; Giuseppina Ciarlo, MD; Alain Paupe, MD; Laurence Bussieres, MD; Yves Ville, MD

OBJECTIVE: We sought to assess long-term neurodevelopment of children born prematurely treated for twin-to-twin transfusion syndrome and dichorionic (DC) twins.

STUDY DESIGN: In all, 21 and 88 children treated with amnioreduction (AR) and fetoscopic laser surgery (FLS), respectively, and 222 DC twins matched for gestational age at delivery were assessed with Ages and Stages Questionnaire and standardized examination at 2 years of age.

RESULTS: Normal development was noted in 81% in the AR group, 88.6% in the FLS group, and 93.1% in the DC twins. Minor and major neurologic impairment was found in 9.5% and 9.5% following AR, in 6.8% and 4.6% of FLS children, and in 3.4% and 3.4% in DC twins, respectively. Ages and Stages Questionnaire assessment was similar in FLS and DC children but scores were lower ($P = .01$) and domains were more often abnormal (60% vs 27%; $P = .005$) following AR.

CONCLUSION: Neurodevelopmental outcome is similar in twin-to-twin transfusion syndrome survivors treated by FLS and in DC control subjects; but survivors treated with AR have an increased risk of neurodevelopmental delay at 2 years of age.

Key words: dichorionicity, laser surgery, monochorionicity, neurodevelopmental, outcome, twin-to-twin transfusion syndrome

Algorithm for management of TTTS

MCDA pregnancy with MVP < 2 cm in 1 sac and MVP < 8 cm in other sac: Diagnosis = TTTS

Do staging (Table 1): check fetal bladder, UA Doppler

Stage I
- Counseling. Consider expectant management, with fetal bladder, UA Doppler, and hydrops ultrasonographic checks at least once per week

Stage II, III, IV
- Counseling. Consider referral to fetal center for laser treatment at 16-25 6/7 weeks; if unable or outside eligibility criteria, consider amnioreduction

Stage V.
- Counsel regarding co-twin 10% risk of death and 10-30% risk of neurologic complications. Consider expectant management.

MCDA, monochorionic diamniotic; MVP, maximum vertical pocket; TTTS, twin-twin transfusion syndrome; UA, umbilical artery.

Normal MC placenta (gestational age at delivery: 28 weeks) showing several AV and VA anastomoses (green and white stars, respectively) and 2 AA anastomoses (blue stars).
TAPS

- Twin Anemia/Polycythemia sequence
- Atypical chronic form of TTTS
- Large intertwin Hb discordance, without polyhydramnios/oligohydramnios

**Incidence** –
  - Spontaneous - 3-6% of previously uncomplicated MC/DA twins, diagnosed in 3rd trimester
  - Following SFLP – 2-13% incidence

Uptodate
Fig. 5 – Spontaneous TAPS placenta (gestational age at delivery: 33 weeks) showing 3 small AV anastomoses (green stars) and 1 small AA anastomosis (blue star). Note the difference in color between the plethoric placental share of the recipient and the pale placental share of the donor.
TAPS

- **Twin Anemia/Polycythememia sequence**
- **Diagnosis** –
  - MCA Doppler >1.5MOMs in donor twin
  - MCA Doppler <0.8MOMs in recipient twin
  - Postnatal diagnosis – Hb difference of >8.0g/dL with intertwin reticulocyte ratio of >1.7 (Donor retic/Recipient retic) and a placental injection examination with small AV anastomoses
  - In post-laser TAPS, small arteriovenous anastomoses between the recipient and donor allow slow passage of red cells in a reverse manner so that the recipient twin becomes anemic and the donor twin becomes plethoric
- **Management** –
  - Laser Photocoagulation
  - IUT
  - Delivery

Uptodate
Risk of IUFD

- General rate of IUFD – 6/1000
- Twins - 12/1000 (OR 2.8)
- Triplets – 34/1000 (OR 2.8-3.7)
- GDM – treated – 6-35/1000 (OR 1.7-7)
- CHTN – 6-25/1000 (2.7)
- Lupus – 40-150/1000 (OR 6-20)

ACOG IUFD bulletin
Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice.
AU Kahn B; Lumey LH; Zybert PA; Lorenz JM; Cleary-Goldman J; D'Alton ME; Robinson JN SO.

Table 3. Fetal Death Rate and Prospective Risk of Fetal Death for Singletons

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Deliveries</th>
<th>Fetuses at risk*</th>
<th>Fetal deaths</th>
<th>Fetal death rate (per 1000 deliveries) (95% CI)</th>
<th>Prospective risk of fetal death (per 1000 fetuses at risk) (95% CI)</th>
<th>Neonatal death rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>10,906</td>
<td>11,061,599</td>
<td>3101</td>
<td>284.34 (275.90, 292.93)</td>
<td>0.28 (0.27, 0.29)</td>
<td>414.86 (403.91, 425.90)</td>
</tr>
<tr>
<td>25</td>
<td>11,692</td>
<td>11,050,693</td>
<td>2544</td>
<td>217.58 (210.16, 225.20)</td>
<td>0.23 (0.22, 0.24)</td>
<td>248.47 (239.67, 257.48)</td>
</tr>
<tr>
<td>26</td>
<td>13,285</td>
<td>11,039,001</td>
<td>2288</td>
<td>172.22 (165.86, 178.78)</td>
<td>0.21 (0.20, 0.22)</td>
<td>167.77 (160.86, 174.92)</td>
</tr>
<tr>
<td>27</td>
<td>13,756</td>
<td>11,025,716</td>
<td>2008</td>
<td>145.97 (140.14, 152.01)</td>
<td>0.18 (0.17, 0.19)</td>
<td>110.32 (104.74, 116.15)</td>
</tr>
<tr>
<td>28</td>
<td>15,569</td>
<td>11,011,960</td>
<td>2015</td>
<td>129.42 (124.21, 134.82)</td>
<td>0.18 (0.18, 0.19)</td>
<td>84.11 (79.52, 88.94)</td>
</tr>
<tr>
<td>29</td>
<td>17,431</td>
<td>10,996,391</td>
<td>1804</td>
<td>103.49 (99.03, 108.13)</td>
<td>0.16 (0.16, 0.17)</td>
<td>59.06 (55.44, 62.90)</td>
</tr>
<tr>
<td>30</td>
<td>23,078</td>
<td>10,978,960</td>
<td>1936</td>
<td>83.89 (80.36, 87.56)</td>
<td>0.18 (0.17, 0.18)</td>
<td>42.38 (39.72, 45.20)</td>
</tr>
<tr>
<td>31</td>
<td>27,728</td>
<td>10,955,882</td>
<td>1792</td>
<td>64.63 (61.78, 67.60)</td>
<td>0.18 (0.17, 0.19)</td>
<td>30.54 (28.49, 32.72)</td>
</tr>
<tr>
<td>32</td>
<td>39,551</td>
<td>10,928,154</td>
<td>1972</td>
<td>49.86 (47.75, 52.06)</td>
<td>0.18 (0.17, 0.19)</td>
<td>19.61 (18.25, 21.08)</td>
</tr>
<tr>
<td>33</td>
<td>61,653</td>
<td>10,888,603</td>
<td>1972</td>
<td>31.99 (30.62, 33.41)</td>
<td>0.18 (0.17, 0.19)</td>
<td>13.35 (12.46, 14.32)</td>
</tr>
<tr>
<td>34</td>
<td>125,999</td>
<td>10,826,950</td>
<td>2340</td>
<td>18.57 (17.84, 19.34)</td>
<td>0.22 (0.21, 0.23)</td>
<td>8.39 (7.90, 8.92)</td>
</tr>
<tr>
<td>35</td>
<td>231,475</td>
<td>10,700,951</td>
<td>2462</td>
<td>10.64 (10.22, 11.06)</td>
<td>0.23 (0.22, 0.24)</td>
<td>5.02 (4.73, 5.32)</td>
</tr>
<tr>
<td>36</td>
<td>418,129</td>
<td>10,469,476</td>
<td>2709</td>
<td>6.48 (6.24, 6.73)</td>
<td>0.26 (0.25, 0.27)</td>
<td>3.39 (3.22, 3.57)</td>
</tr>
<tr>
<td>37</td>
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<td>2856</td>
<td>3.49 (3.36, 3.62)</td>
<td>0.28 (0.27, 0.29)</td>
<td>2.08 (1.98, 2.18)</td>
</tr>
<tr>
<td>38</td>
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<td>9,232,114</td>
<td>3247</td>
<td>1.93 (1.86, 1.99)</td>
<td>0.35 (0.34, 0.36)</td>
<td>1.26 (1.21, 1.31)</td>
</tr>
<tr>
<td>39</td>
<td>2,654,221</td>
<td>7,545,992</td>
<td>2986</td>
<td>1.13 (1.09, 1.17)</td>
<td>0.40 (0.38, 0.41)</td>
<td>0.92 (0.89, 0.96)</td>
</tr>
<tr>
<td>40</td>
<td>2,590,504</td>
<td>4,891,771</td>
<td>2795</td>
<td>1.08 (1.04, 1.12)</td>
<td>0.57 (0.55, 0.59)</td>
<td>0.85 (0.82, 0.89)</td>
</tr>
<tr>
<td>41</td>
<td>1,438,442</td>
<td>2,301,267</td>
<td>1480</td>
<td>1.03 (0.98, 1.08)</td>
<td>0.64 (0.61, 0.68)</td>
<td>0.93 (0.88, 0.98)</td>
</tr>
<tr>
<td>42</td>
<td>493,493</td>
<td>862,825</td>
<td>647</td>
<td>1.31 (1.21, 1.42)</td>
<td>0.75 (0.69, 0.81)</td>
<td>1.15 (1.06, 1.25)</td>
</tr>
<tr>
<td>43+</td>
<td>369,332</td>
<td>369,332</td>
<td>453</td>
<td>1.23 (1.12, 1.35)</td>
<td>1.23 (1.12, 1.35)</td>
<td>1.12 (1.01, 1.23)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
* Calculated for births of 24 weeks gestation or more.
Table 4. Fetal Death Rate and Prospective Risk of Fetal Death for Twins

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Deliveries</th>
<th>Fetuses at risk*</th>
<th>Fetal deaths</th>
<th>Fetal death rate (per 1000 deliveries) (95% CI)</th>
<th>Prospective risk of fetal death (per 1000 fetuses at risk) (95% CI)</th>
<th>Neonatal death rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>2097</td>
<td>297,622</td>
<td>274</td>
<td>130.66 (116.68, 146.02)</td>
<td>0.92 (0.82, 1.04)</td>
<td>461.88 (438.82, 495.09)</td>
</tr>
<tr>
<td>25</td>
<td>2358</td>
<td>295,525</td>
<td>282</td>
<td>119.59 (106.91, 133.53)</td>
<td>0.95 (0.85, 1.07)</td>
<td>284.20 (264.98, 304.23)</td>
</tr>
<tr>
<td>26</td>
<td>2757</td>
<td>293,167</td>
<td>206</td>
<td>74.72 (63.31, 85.33)</td>
<td>0.70 (0.61, 0.81)</td>
<td>172.48 (158.13, 187.83)</td>
</tr>
<tr>
<td>27</td>
<td>3117</td>
<td>290,410</td>
<td>175</td>
<td>56.14 (48.45, 64.96)</td>
<td>0.60 (0.52, 0.70)</td>
<td>109.11 (98.19, 121.07)</td>
</tr>
<tr>
<td>28</td>
<td>3547</td>
<td>287,293</td>
<td>193</td>
<td>54.41 (47.29, 62.52)</td>
<td>0.67 (0.58, 0.78)</td>
<td>72.45 (64.02, 81.88)</td>
</tr>
<tr>
<td>29</td>
<td>4220</td>
<td>283,746</td>
<td>199</td>
<td>47.16 (41.05, 54.10)</td>
<td>0.70 (0.61, 0.81)</td>
<td>47.75 (41.46, 54.92)</td>
</tr>
<tr>
<td>30</td>
<td>5565</td>
<td>279,526</td>
<td>162</td>
<td>29.11 (24.92, 33.96)</td>
<td>0.58 (0.50, 0.68)</td>
<td>33.50 (28.94, 38.74)</td>
</tr>
<tr>
<td>31</td>
<td>7664</td>
<td>273,961</td>
<td>182</td>
<td>23.75 (20.51, 27.47)</td>
<td>0.66 (0.57, 0.77)</td>
<td>19.85 (16.06, 22.40)</td>
</tr>
<tr>
<td>32</td>
<td>10,619</td>
<td>266,297</td>
<td>187</td>
<td>17.61 (15.23, 20.34)</td>
<td>0.70 (0.61, 0.81)</td>
<td>13.13 (11.08, 15.56)</td>
</tr>
<tr>
<td>33</td>
<td>14,849</td>
<td>255,678</td>
<td>201</td>
<td>13.54 (11.77, 15.56)</td>
<td>0.79 (0.68, 0.90)</td>
<td>8.33 (6.95, 9.97)</td>
</tr>
<tr>
<td>34</td>
<td>23,262</td>
<td>240,829</td>
<td>220</td>
<td>9.46 (8.27, 10.81)</td>
<td>0.91 (0.80, 1.04)</td>
<td>5.82 (4.89, 6.91)</td>
</tr>
<tr>
<td>35</td>
<td>33,287</td>
<td>217,567</td>
<td>212</td>
<td>6.37 (5.56, 7.30)</td>
<td>0.97 (0.85, 1.12)</td>
<td>3.30 (2.72, 3.99)</td>
</tr>
<tr>
<td>36</td>
<td>45,405</td>
<td>184,280</td>
<td>205</td>
<td>4.51 (3.93, 5.19)</td>
<td>1.11 (0.97, 1.28)</td>
<td>2.88 (2.41, 3.43)</td>
</tr>
<tr>
<td>37</td>
<td>49,436</td>
<td>138,875</td>
<td>197</td>
<td>3.98 (3.46, 4.59)</td>
<td>* 1.42 (1.23, 1.63)</td>
<td>2.29 (1.90, 2.77)</td>
</tr>
<tr>
<td>38</td>
<td>41,859</td>
<td>89,439</td>
<td>136</td>
<td>3.25 (2.74, 3.85)</td>
<td>1.52 (1.28, 1.80)</td>
<td>2.06 (1.66, 2.56)</td>
</tr>
<tr>
<td>39</td>
<td>24,957</td>
<td>47,580</td>
<td>114</td>
<td>4.57 (3.79, 5.51)</td>
<td>2.40 (1.99, 2.89)</td>
<td>2.05 (1.54, 2.72)</td>
</tr>
<tr>
<td>40</td>
<td>11,895</td>
<td>22,623</td>
<td>70</td>
<td>5.88 (4.62, 7.47)</td>
<td>3.09 (2.43, 3.93)</td>
<td>3.30 (2.38, 4.55)</td>
</tr>
<tr>
<td>41+</td>
<td>10,728</td>
<td>10,728</td>
<td>54</td>
<td>5.03 (3.82, 6.61)</td>
<td>5.03 (3.82, 6.61)</td>
<td>4.22 (3.11, 5.69)</td>
</tr>
</tbody>
</table>

CI = confidence interval.
* Calculated for births of 24 weeks gestation or more.

greater than for twins. In our data set, the prospective risk of fetal death for twins equaled the prospective risk of fetal death for postterm singletons by approximately 36 to 37 weeks' gestation. The upswing in fetal death risk accompanies decreases in the third trimester for twins and even more so for triplets.

We think it is more useful clinically to compare gestation-specific prospective risk of fetal death with gestation-

Prospective risk of fetal death in singleton, twin, and triplet gestations: implications for practice. AU Kahn B; Lumey LH; Zybert PA; Lorenz JM; Cleary-Goldman J; D'Alton ME; Robinson JN. SO Obstet Gynecol 2003 Oct;102(4):685-92.

**Table 5. Fetal Death Rate and Prospective Risk of Fetal Death for Triplets**

<table>
<thead>
<tr>
<th>Gestational age (wk)</th>
<th>Deliveries</th>
<th>Fetuses at risk*</th>
<th>Fetal deaths</th>
<th>Fetal death rate (per 1000 deliveries) (95% CI)</th>
<th>Prospective risk of fetal death (per 1000 fetuses at risk) (95% CI)</th>
<th>Neonatal death rate (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>24</td>
<td>236</td>
<td>15,375</td>
<td>20</td>
<td>84.75 (53.83, 129.73)</td>
<td>1.30 (0.82, 2.05)</td>
<td>509.26 (440.73, 577.45)</td>
</tr>
<tr>
<td>25</td>
<td>280</td>
<td>15,139</td>
<td>13</td>
<td>46.43 (26.00, 79.99)</td>
<td>0.86 (0.48, 1.51)</td>
<td>247.19 (197.56, 304.25)</td>
</tr>
<tr>
<td>26</td>
<td>327</td>
<td>14,859</td>
<td>13</td>
<td>39.76 (22.24, 68.70)</td>
<td>0.87 (0.49, 1.54)</td>
<td>130.57 (96.34, 174.11)</td>
</tr>
<tr>
<td>27</td>
<td>485</td>
<td>14,532</td>
<td>15</td>
<td>30.93 (18.05, 51.66)</td>
<td>1.03 (0.60, 1.75)</td>
<td>104.26 (78.83, 136.34)</td>
</tr>
<tr>
<td>28</td>
<td>697</td>
<td>14,047</td>
<td>17</td>
<td>24.39 (14.73, 39.58)</td>
<td>1.21 (0.73, 1.98)</td>
<td>39.71 (26.83, 58.01)</td>
</tr>
<tr>
<td>29</td>
<td>648</td>
<td>13,350</td>
<td>13</td>
<td>20.06 (11.19, 34.98)</td>
<td>0.97 (0.54, 1.71)</td>
<td>26.77 (16.17, 43.41)</td>
</tr>
<tr>
<td>30</td>
<td>970</td>
<td>12,702</td>
<td>11</td>
<td>11.34 (5.97, 20.85)</td>
<td>0.87 (0.46, 1.60)</td>
<td>14.60 (8.33, 25.0)</td>
</tr>
<tr>
<td>31</td>
<td>1345</td>
<td>11,732</td>
<td>22</td>
<td>16.36 (10.53, 25.09)</td>
<td>1.88 (1.20, 2.89)</td>
<td>9.83 (5.47, 17.21)</td>
</tr>
<tr>
<td>32</td>
<td>1602</td>
<td>10,387</td>
<td>17</td>
<td>10.61 (6.40, 17.31)</td>
<td>1.64 (0.99, 2.68)</td>
<td>5.68 (2.77, 11.17)</td>
</tr>
<tr>
<td>33</td>
<td>2022</td>
<td>8785</td>
<td>9</td>
<td>4.45 (2.17, 8.76)</td>
<td>1.02 (0.50, 2.02)</td>
<td>5.96 (3.23, 10.71)</td>
</tr>
<tr>
<td>34</td>
<td>2342</td>
<td>6763</td>
<td>13</td>
<td>5.55 (3.09, 9.74)</td>
<td>1.92 (1.07, 3.38)</td>
<td>4.29 (2.18, 8.16)</td>
</tr>
<tr>
<td>35</td>
<td>1987</td>
<td>4421</td>
<td>18</td>
<td>9.06 (5.54, 14.58)</td>
<td><strong>4.07 (2.49, 6.57)</strong></td>
<td>4.57 (2.23, 9.00)</td>
</tr>
<tr>
<td>36</td>
<td>1249</td>
<td>2434</td>
<td>12</td>
<td>9.61 (5.21, 17.22)</td>
<td>4.93 (2.67, 8.86)</td>
<td>1.62 (0.28, 6.50)</td>
</tr>
<tr>
<td>37</td>
<td>502</td>
<td>1185</td>
<td>9</td>
<td>17.93 (8.77, 35.00)</td>
<td>7.59 (3.71, 14.92)</td>
<td>4.06 (0.70, 16.22)</td>
</tr>
<tr>
<td>38+</td>
<td>683</td>
<td>683</td>
<td>9</td>
<td>13.18 (6.44, 25.80)</td>
<td>13.18 (6.44, 25.80)</td>
<td>2.97 (0.51, 11.89)</td>
</tr>
</tbody>
</table>

CI = confidence interval.

* Calculated for births of 24 weeks gestation or more.
Delivery timing

- Di/di twins – 38 weeks
- MC/DA twins – 34-37 6/7 weeks
- Monoamnionitic twins – 32-34 weeks
- Triplets – 35-36 weeks
- Quadruplets – 34 weeks
ANCS and NP magnesium

- If patient is at risk of delivering at <34 weeks, then ANCS are recommended
- If <32 weeks, then NP magnesium is recommended
- Late preterm (34 0/7-36 6/7 weeks) and rescue ANCS – Data is lacking
ACMG POLICY STATEMENT

all chromosomes; this is due, at least in part, to differing content of cytosine and guanine nucleotide pairs. False-positive screening results do occur. Furthermore, the sequences derived from NIPS are derived from the placenta and therefore, like chorionic villus sampling, may not reflect the true fetal karyotype. Therefore, invasive testing is recommended for confirmation of a positive screening test and should remain an option for patients seeking a definitive diagnosis. This document addresses some of the challenges of incorporating NIPS for fetal aneuploidy into obstetrical practice.

WHERE DOES NIPS FIT INTO THE ANEUPLOIDY SCREENING PARADIGM?

NIPS in vivo, as the acronym implies, a screening test to identify pregnancies at risk for common autosomal aneuploidies (e.g., trisomy 21, 18, and 13). Some laboratories also offer screening for sex chromosome aneuploidies.

For women seeking a definitive diagnosis, invasive procedures for diagnostic testing, such as amniocentesis or chorionic villus sampling, should be offered.

WHAT ARE THE CURRENT LIMITATIONS OF NIPS?

1. Risk assessment is limited to specific fetal aneuploidies (trisomy 13, 18, and 21) at this time. Some platforms also screen for sex chromosome abnormalities. Approximately 50% of cytogenetic abnormalities routinely identified by amniocenteses will not be detected when trisomy 21, 18, and 13 are the only aneuploidies being screened. When patients <35 years or ≥35 years are considered separately, 75% and 43% of chromosomal abnormalities will be missed, respectively. 12

2. Chromosomal abnormalities such as unbalanced translocations, deletions, and duplications will not be detected by NIPS. Therefore, when fetal abnormalities are detected, invasive diagnostic testing and cytogenomic microarray analysis are more likely to detect chromosomal imbalances than NIPS and may be a better testing option. 13

3. NIPS is not able to distinguish specific forms of aneuploidy.

For example, NIPS cannot determine if Down syndrome is due to the presence of an extra chromosome (trisomy 21), a Robertsonian translocation involving chromosome 21 or high-level mosaicism. Identification of the mechanism of aneuploidy is important for recurrence risk counseling and emphasizes the importance of diagnostic testing following NIPS.

4. NIPS does not screen for single-gene mutations.

5. Uninformative test results due to insufficient isolation of cell-free fetal DNA could lead to a delay in diagnosis or eliminate the availability of information for risk assessment. Biologic factors associated with reduced available cell-free fetal DNA include a high body mass index and early gestational age (<10 weeks gestation). 14

6. Currently, it takes longer for NIPS test results to be returned than for test results on maternal serum analyte. Providers should keep this in mind when offering patients NIPS if timing is important for reproductive decision making. In most cases, NIPS is offered between 10 and 20 weeks gestation, which allows time for follow-up of positive test results. It is reasonable to offer NIPS after 20 weeks if an expectant woman desires information regarding risk, reassurance, or knowledge in order to inform obstetrical management and/or preparation for birth.

7. NIPS does not screen for open neural tube defects. Maternal serum a-fetoprotein testing should still be offered at 15-20 weeks gestation to screen for open neural tube defects even when NIPS is performed. 3

8. NIPS does not replace the utility of first-trimester ultrasound examination, which has been proven to be useful for accurate gestational dating, assessment of the nuchal translucency region to identify a fetus at increased risk for a chromosomal abnormality, identification of twins and higher-order pregnancies, pleural abnormalities, and genitourinary anomalies. 15

9. Limited data are currently available on the use of NIPS in twins and higher-order pregnancies. Utilization of these clinical settings may depend on specific laboratory platforms, proprietary bioinformatics, and clinical validation studies.

10. NIPS has no role in predicting late-pregnancy complications.

SHOULD PRETEST OR POSTTEST GENETIC COUNSELING ABOUT ANEUPLOIDY SCREENING BE PERFORMED?

Pretest information should be provided by a prenatal care provider, a trained designer, or a genetic counselor to ensure patients make informed decisions. Aneuploidy screening is not a routine prenatal test; it is acceptable for patients to decline screening.

Pretest information should include:

1. A brief explanation of the purpose of NIPS.

2. Advantages of NIPS as compared with maternal serum analyte screening.

• On the basis of available data, detection rates appear to be higher.

• There is a higher negative predictive value for Down syndrome. This may be important for patients seeking to avoid the risks (e.g., fetal loss) inherent with invasive testing.

• NIPS has a lower false-positive rate, meaning fewer women will receive a “positive” screen, necessitating fewer invasive procedures.

• Risk assessment is less dependent on gestational age.

3. Considerations for follow-up invasive testing if NIPS indicates an increased risk for aneuploidy.

4. Limitations of NIPS.

Posttest counseling is recommended when NIPS indicates that a patient is at high risk or has a “screen-positive” result. When a “screen-negative” result is encountered, residual
5K & Memorial Walk
Old Cowtown Museum
REGISTER AT KIDSKS.ORG
APRIL 21, 2018
End
Sickle cell disease

• See ACOG bulletin, UTD, Creasey – for reference;
• Call /text Dr. Farley for info/problem cases and to schedule time to review if desired;
• See previous slide sets for details, available on website/on request
Hematologic Disease in Pregnancy & Hemoglobinopathies

Darren Farley, MD
Clinical Assistant Professor
Division of Maternal-Fetal Medicine
Dept. of Obstetrics and Gynecology
University of Kansas School of Medicine – Wichita
Objectives

- Case reviews
- High yield facts
- Complete study guide questions-turn in to Jennifer
Case –
19 yo – 29wk – anemia with Hb 8g/dL – peripheral smear shows microcytic hypochromic red cells - lab findings – decreased serum ferritin level (most sensitive test); <10-15mcg/L – confirms iron deficiency anemia – other definition is 1g/dL increase after iron tx; high total iron binding capacity is present if checked;
Normal TIBC – 216-400mcg/dL – if increased – then iron deficient;
Normal serum ferritin in pregnancy is >10mcg/dL
Plasma iron level – normal – 40-1756mcg/dL
Transferrin saturation – 16-60% is normal;
Free erythrocyte protoporphyrin level is <3mcg/g; this is normal;
Usual diet – 15mg/day of elemental iron; recommend amount of daily allowance of ferrous iron is 27mg/day;
• Case –
• -36 yo P2002 – 18 weeks – sx – fatigue – Hb 7.5g/dL; RBC MCV is elevated markedly at 124fL; peripheral blood smear – macrocytic red cells – dx is most likely folate deficiency;
• Rec folate tx –;
• Check folate and B12 levels;

Megaloblastic anemia – hypersegmented neutrophils
https://step2.medbullets.com/heme/120228/folic-acid-deficiency
High yield facts
Physiologic changes in pregnancy

- Anemia in pregnancy
  - First/third trimester – Hb <11g/dL
  - Second trim – Hb <10.5g/dL

- Iron requirements in pregnancy
  - Total 1000mg
    - 300mg (fetus/placenta)
    - 500mg (expansion of maternal Hb mass)
    - 200mg (shed through gut, urine, skin)
Pregnancy associated changes in coagulation

- Increased concentration of all clotting factors except for XI, XIII and Protein S free levels which decrease
  - Fibrinogen, II, V, VII, VIII, IX, X, XII, PAI-1, 2
    - 200% increase
  - Von Willebrand factor increases 100-150%
- Decrease – XI, XIII, protein S
- Unchanged - Protein C, Antithrombin (ATIII)
- Levels of thrombin-ATIII complex increase, suggesting coagulation activation is consistent with elevated fibrinopeptides
Coagulation changes

- Fibrinogen level (increased concentration with increased plasma volume)
  - Avg nonpregnancy 300mg/dL (200-400)
  - Avg pregnancy increase is 50%; 450mg/dL late in pregnancy (300-600)
    - End product of coagulation cascade is fibrin formation
- Prothrombin time – no change
- Partial thromboplastin time – no change
Figure 18. Diagnostic assessment of anemia in pregnancy. Abbreviation: Hb indicates hemoglobin.
Case 1

- 25 yo P0000
- Sickle cell disease (hx of multiple transfusions/admissions for pain crisis)
- Presents at 28 weeks – pain crisis, Hb 6.5g/dL
Severe anemia

- Severe anemia with maternal Hb <6g/dL has been associated with abnormal fetal oxygenation resulting in NR FHR patterns, oligohydramnios, fetal cerebral vasodilatation and fetal death. Thus maternal transfusion should be considered for fetal indications. 

ACOG
Case 2 - Sickle cell disease

- 25 yo P0000- 12 weeks pregnant, hx of sickle cell disease –
- FOB – unknown if carrier – ethnicity – African American
- Inheritance pattern ?
- Carrier rate in general population?
- Chance fetus – is carrier ? Is affected with sickle cell disease?
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>HB SS</th>
<th>Hb AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1/700</td>
<td>1/14</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>0/1600</td>
<td>1/700</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/46,000</td>
<td>1/180</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0/22,000</td>
<td>1/360</td>
</tr>
<tr>
<td>Native American</td>
<td>1/17,000</td>
<td>1/180</td>
</tr>
<tr>
<td>White</td>
<td>1/160,000</td>
<td>1/600</td>
</tr>
<tr>
<td>Asian</td>
<td>0/200,000</td>
<td>1/1300</td>
</tr>
</tbody>
</table>
Hardy-Weinberg Principle & Assumptions

(T/T Genetics in Medicine)

• 2 components

• 1 – Under certain ideal conditions a simple relationship exists between allele frequencies and genotype frequencies in a population
  – The HW Law states that the frequency of the three genotypes AA, Aa, and aa is given by the terms of the binominal expansion of \((p+q)^2 = p^2 + 2pq + q^2\)

• 2 – If allele frequencies do not change from generation to generation, the relative proportion of the genotypes will not change either; that is the population genotype frequencies from generation to generation will remain constant, at equilibrium, if the allele frequencies \(p\) and \(q\) remain constant. More specifically, when there is random mating in a population that is at equilibrium and genotypes AA, Aa, and aa are present in the proportions \(p^2 : 2pq : q^2\), then genotype frequencies in the next generation will remain in the same relative proportions, \(p^2 : 2pq : q^2\)
HW Assumptions

(T/T Genetics in Medicine)

• The population is large and matings are random with respect to the locus in question

• Allele frequencies remain constant over time because:
  – There is no appreciable rate of mutation
  – Individuals with all genotypes are equally capable of mating and passing on their genes, that is, there is no selection against any particular genotype
  – There has been no significant immigration of individuals from a population with allele frequencies very different from the endogenous population
Hardy-Weinberg example

• Williams quest – What is approximate incidence of sickle cell anemia in African Americans if carrier rate is 1/12?

• 1 = p + q
• 1 = p^2 + 2pq + q^2
• p = dominant allele
• q = recessive allele
• q = 1/12; q^2 x ¼ (chance that 2 carriers would have affected child)
• 1/12 x 1/12 x ¼ = 1 in 576
What is the approximate incidence of sickle cell anemia—an autosomal recessive disease—in African Americans if the carrier rate is 1/12?

- a. 1/25
- b. 1/150
- c. 1/300
- d. 1/600***
HW – PKU example

- PKU
- Frequency of affected homozygotes in the population can be determined accurately through newborn screening programs
- Heterozygotes – asymptomatic silent carriers, population incidence is impossible to measure directly from phenotype
- HW law allows estimate of heterozygote frequency to be made and used subsequently for counseling
- Frequency of PKU 1 in 4500 – 1/4500 in Ireland
  - Frequency of affected individuals = 1/4500 = q², q =0.015, and 2pq = 0.029 or approx ~3%
  - Carrier frequency in the Irish population ~3%
- If pt is a known carrier – Partner is Irish (3% heterozygote rate)
  - Chance of affected offspring – 0.5 x 0.03 x 0.25 = 1 in 267
  - Chance of carrier offspring - 0.5 x 0.03 x 0.5 = 1 in 133
- If pt is known carrier – Partner is from Finland (PKU frequency 1/200,000)
  - Frequency of affected individuals = 1/200,000 = q², q =0.002, and 2pq = 0.004 = 0.4% = carrier rate
  - Chance of affected offspring = 0.5 x 0.004 x 0.25 = 1 in 2000
  - Chance of carrier offspring = 0.5 x 0.004 x 0.5 = 1 in 1000
Case 3

- 21 yo P0000 - 28 weeks
- Hx of sickle cell disease
- Presents with fever, cough, dyspnea
- CXR – bilateral infiltrates
- DDX?
- Diagnosis?
- Management?
Sickle crisis – Pulmonary crisis

- Acute chest syndrome – potentially fatal
- Fever, pleuritic cp, tachypnea, pulmonary infiltrates
- DDX – PE, fat embolism, AFE
- Tx – oxygenation, hydration, treatment of infection, pain control
- Transfusion to increase HbA >40%, Hct <30%, HBS<60%
Pathophysiologic Implications

• Mom is able to hold her breath less
  – 1 vs 2 lung example

• Decreased FRC
  – Closing capacity – amount of volume that has to be behind to keep small airways open
    - diminished

• Develop hypoxemia quicker than when not pregnant (at greater risk of hypoxemia)

• Pulmonary insults are tolerated less well
## ABG Changes in Pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>Nonpregnant</th>
<th>Pregnant</th>
</tr>
</thead>
<tbody>
<tr>
<td>pH</td>
<td>7.35-7.43</td>
<td>7.4-7.47</td>
</tr>
<tr>
<td>pCO2 (mmHg)*</td>
<td>37-40</td>
<td>27-31</td>
</tr>
<tr>
<td>pO2 (mmHg)**</td>
<td>103</td>
<td>101-104</td>
</tr>
<tr>
<td>P(A-a)O2 (mmHg)***</td>
<td>14</td>
<td>20</td>
</tr>
<tr>
<td>HCO3- (mEq/L)</td>
<td>22-26</td>
<td>18-22</td>
</tr>
<tr>
<td>Base deficit (mEq/L)</td>
<td>1</td>
<td>3</td>
</tr>
</tbody>
</table>

- *compensatory increase in renal bicarbonate excretion*
- **decreased in supine position and 3\textsuperscript{rd} trimester**
- ***increased by 6 in supine position and 3\textsuperscript{rd} trimester***
ACS

- Diagnostic criteria for ACS — ACS is defined as radiographic evidence of consolidation: a new segmental (involving at least one complete segment) radiographic pulmonary infiltrate [3], AND at least one of the following:
  - Temperature ≥38.5°C
  - >2 percent decrease in SpO₂ (O₂ saturation) from a documented steady-state value on room air (FiO₂ = 0.21)
  - PaO₂ <60 mmHg
  - Tachypnea (per age-adjusted normal)
  - Intercostal retractions, nasal flaring, or use of accessory muscles of respiration
  - Chest pain
  - Cough
  - Wheezing
  - Râles
- Of importance, the presence of pneumonia can formally be considered as meeting the criteria for ACS, since the two cannot be reliably distinguished from one another.
ACS severity index — Severity of ACS is considered mild, moderate, severe, or very severe,

- **Mild ACS** — Meets the diagnostic criteria for ACS plus ALL of the following:
  - Transcutaneous oxygen saturation >90 percent on room air (FiO$_2$ = 0.21)
  - Segmental or lobar infiltrates that involve no more than one lobe by chest radiography
  - Responsive to simple transfusion of no more than 2 units of red blood cells (or 15 mL/kg of packed RBCs)

- **Moderate ACS** — Meets the diagnostic criteria for ACS plus ALL of the following:
  - Transcutaneous oxygen saturation ≥85 percent on room air (FiO$_2$ = 0.21)
  - Segmental or lobar infiltrates that involve no more than two lobes by chest radiography
  - Responsive to transfusion of ≥3 units of red cells (or >20 mL/kg packed RBCs)
ACS severity index — Severity of ACS is considered mild, moderate, severe, or very severe,

- **Severe ACS** — Meets the diagnostic criteria for ACS plus one or more of the following:
  - Respiratory failure present (PaO$_2$ <60 mmHg or PCO$_2$ >50 mmHg)
  - Mechanical ventilatory support required
  - Transcutaneous oxygen saturation <85 percent on room air or ≤90 percent despite maximal supplemental O$_2$
  - Segmental or lobar infiltrates that involve three or more lobes by chest radiography
  - Requiring transfusion or exchange transfusion of RBCs to achieve hemoglobin A levels ≥70 percent

- **Very severe ACS** — Acute respiratory distress syndrome (ARDS) present or sudden, life-threatening lung failure. ARDS is defined by the following three criteria of the American-European Consensus Conference and includes:
  - Acute onset of bilateral infiltrates on chest radiography
  - Pulmonary artery wedge pressure <19 mmHg or the absence of clinical evidence of left atrial hypertension
  - PaO$_2$/FiO$_2$ ≤200 regardless of positive end expiratory pressure (PEEP) level
Hepatic crisis

- Vaso-occlusion of hepatic vasculature
- Fever, RUQ pain, leukocytosis, elevated LFTs, bilirubin
- DDX – cholecystitis, HELLP sd
- Management – hydration, pain control, antibiotics, serial labs
Exchange transfusion

- Prophylactic partial exchange transfusions prior to onset of vaso-occlusive crisis
- Decreased incidence of pain crisis, less maternal anemia, no consistent improvement in perinatal outcome
- Transfusion to increase HbA >40%, Hct <30%, HBS<60%
  - Standard exchange of 6 units of washed packed RBCs, increases HbA to 70%
  - Tables used to calculate required volume of transfusion given % of Hb A, Hct of transfused blood, patient weight (kg)
- Alloimmunization is main risk, thus prophylactic transfusions are not recommended
Simple transfusion

- Hb/Hct <6-7g/dL, 18-21%
- Goal of HCT <30% so as to avoid increased viscosity of blood which can precipitate a crisis

- Improved blood counts, risks of alloimmunization, etc, does not improve time of pain crisis or symptoms of pain crisis acutely
Case 4

- P0000 – 12 weeks – platelet count normal;
- 28 weeks – platelets – 30k
- DDX?
- Management?
Immune Thrombocytopenic Purpura (ITP)

- Autoimmune disease
- Increased platelet destruction by reticuloendothelial system
- 3 per 1000 pregnancies
Immune Thrombocytopenic Purpura (ITP)

• Childhood
  – Adolescents, follows infection
  – Rapid remission, rare relapses

• Adult
  – Chronic, frequent exacerbations, remissions
  – Usually requires long-term steroids or immune globulin therapy
ITP

• Diagnosis
  – H&P and degree of thrombocytopenia
  – Platelet antibody testing
    • Sensitivity/specificity varies with lab
    • Traditional antibody testing cannot distinguish ITP from gestational thrombocytopenia
    • Direct – platelet bound
    • Indirect – Free, indirect, serum
      – Have been associated with neonatal thrombocytopenia in women with ITP
        » 13-24% of women with true ITP will give birth to neonates with platelets <50k
      – Antiplatelet antibodies lack high PPV, but the NPV is high, again will vary among labs
ITP – Management issues

• Corticosteroids
  – To maintain platelets >30k during pregnancy
  – To maintain platelets >50k at delivery
  – Most panels (ACOG, Am Society of Hematology, Creasy) recommend starting steroids when platelets <50k

  • Creasy suggests ‘More aggressive treatment is often pursued close to the estimated due date, in anticipation of potential bleeding, surgery, or need for regional anesthesia. Some anesthesiologists may require a platelet count greater than 80,000/μL before deeming the woman's condition safe for placement of an epidural catheter.’
ITP - Management

• Refractory cases
  – IVIG
  – Platelet transfusion
  – Splenectomy
  – Immunosuppressive medications – azathioprine, vincristine
  – Rh immune globulin has been reported
Management of the pregnant woman with immune thrombocytopenic purpura.

**Immune Thrombocytopenic Purpura**

1. **Platelet count > 20,000/mm³**
   - Check platelet count at regular intervals and watch for signs of clinical bleeding

2. **Platelet count ≤ 20,000/mm³ or clinical bleeding**
   - IV methylprednisolone 1.0–1.5 mg/kg/day administered in 2 or 3 divided doses
     - Fails to respond
       - Intravenous immunoglobulin 0.4–1.0 g/kg/day for 3–5 days
         - Fails to respond
           - Splenectomy
         - Platelet count rises
           - Repeat as necessary

     - Platelet count rises
       - Change to oral prednisone, 1 mg/kg/day, then taper to keep platelets approximately 100,000/mm³
         - Follow platelet counts for the remainder of pregnancy and be aware that neonate may still have severe thrombocytopenia

**FIG. 4-3** Management of the pregnant woman with immune thrombocytopenic purpura.
ITP – Mode of delivery

• Hemorrhagic complications appear to be unrelated to mode of delivery
• Most hemorrhagic complications occur in neonatal period
• Maternal treatment (steroids, IVIG) does not affect rate of hemorrhagic complications

Burrows 1988; Cook 1991; Burrows 1993; Payne 1997; Laros 1994; Burrows 1993; Silver 1998
ITP – Mode of delivery

• Series of 474 neonates (born to mothers with ITP) – 29% (vaginal) vs 30% (cesarean) suffered clinical bleeding (Cook 1991, 1993) – with 3% rate of ICH unrelated to mode of delivery

• Per Creasy - A careful analysis of the literature also suggests that no case of ICH has been directly attributable to intrapartum events

• ICH infrequency – No cases of ICH in series of 16,000 pregnancies, 48 maternal ITP cases (Burrows 1993)
  – 3 infants had ICH but were due to alloimmune, not autoimmune thrombocytopenia, 1 IUFD due to ICH
  – The proportion of infants with platelet counts lower than 50,000/μL is about 15%, and this may be an overestimate of the risk because of publication bias.
ITP – Mode of delivery

• Reserve cesarean for obstetrical indications

• Stress dose steroids if on chronic steroids at delivery
Case 5

- P0102 – s/p CD at 35 weeks for presumed severe preeclampsia/HELLP sd;
- POD #3- platelets 20k; Hb 7; LDH 2000 (peak- 10000); LFTs increased/stable

- Diagnosis?
- Management?
Thrombotic Thrombocytopenic Purpura

- Rare, life threatening, medical emergency
- Platelets aggregate, producing platelet thrombi, occluding arterioles and capillaries, leads to ischemia, infarction
  - Can affect any organ system
  - Esp brain, kidneys
Microangiopathic Hemolytic Anemia

A schistocyte count greater than 1% appears to be diagnostic of TTP in the appropriate clinical setting (Burns 2004)
TTP – Clinical Diagnosis

- Microangiopathic hemolytic anemia
- Thrombocytopenia
- Neurologic abnormalities
  - Confusion, HA, paresis, visual hallucinations, seizures
- Fever
- Renal dysfunction
- *Top 3 in 75% of TTP patients, pentad seen in 40%
- Differentiation from other microangiopathic hemolytic anemias of pregnancy (severe preeclampsia/HELLLP)
TTP – Management

• Medical
• Plasmapharesis/plasma exchange
  – FFP to temporize and transfer to facility capable of plasmapharesis
• IV steroids
• Dialysis if renal failure is present
• Refractory cases
  – Vincristine
  – Cryoprecipitate
  – Splenectomy
  – Azathioprine
Management of the gravida with TTP. Before adopting this approach, the treating physician must be certain of the diagnosis. TTP is a clinical diagnosis and can mimic severe preeclampsia. The criteria for diagnosing TTP are listed in Table 4-6.
HELLP syndrome

- Delivery
- Seizure prophylaxis
- Hypertensive control
- +/- Steroids
HELP Syndrome Management

- Delivery regardless of GA
- Seizure prophylaxis
- +/- corticosteroids
  - Increase the chance for a regional anesthetic?
  - Data on improved outcomes otherwise are lacking
HELPP syndrome

For women with HELLP syndrome from the gestational age of fetal viability to 33 6/7 weeks of gestation, it is suggested that delivery be delayed for 24–48 hours if maternal and fetal condition remains stable to complete a course of corticosteroids for fetal benefit.*

Quality of evidence: Low
Strength of recommendation: Qualified

*Corticosteroids have been used in randomized controlled trials to attempt to improve maternal and fetal condition. In these studies, there was no evidence of benefit to improve overall maternal and fetal outcome (although this has been suggested in observational studies). There is evidence in the randomized trials of improvement of platelet counts with corticosteroid treatment. In clinical settings in which an improvement in platelet count is considered useful, corticosteroids may be justified.
Case 7

- 30 yo P0000
- Asian
- 28 weeks
- Diagnosis?
- DDX?
- Test?

Chest wall edema, pleural effusion

https://iame.com/online/hydrops/content.php
Thalassemias
Hemoglobinopathies

• Definition –
  – qualitative (sickle cell – Beta globin gene mutation)
  – quantitative (thalassemia, unbalance of alpha or beta globin chains) abnormality in the hemoglobin molecule

• Incidence – allele frequency depends on ethnicity;
  – worldwide > 270 million heterozygous carriers;
  – > 300,000 affected homozygotes or compound heterozygotes born each year (ACOG 2007)
Thalassemia (α/β) – overview

• Definition – quantitative abnormality of the globin chains
• Incidence – α-thal trait - 0.01% in nonmalarial exposed populations Iceland, UK, Japan; 49% in southwest Pacific islanders
  – Hb H disease, hydrops fetalis – restricted to Mediterranean and SE Asia
  – β-thal trait – 1-2% Africans and African Americans; 30% in Sardinia
• Pathogenesis - deficient synthesis of α-globin or β-globin chain that forms the hemoglobin molecule, unbalanced accumulation of alpha/beta subunits (Gelehrter, p96); childhood onset, hypochromic microcytic anemia, HSM, extramedullary hematopoiesis
  – ~80% untreated pts die within 5 years;
  – Transfusion therapy alone – death <30yo (due to infection, hemochromatosis)
  – Iron chelation therapy can reduce chance of hemochromatosis and cardiac, hepatic complications - from repeated transfusions
Thalassemia – genetic principles

• Heterozygote advantage – carriers of trait display resistance to malaria; prevalence in an ethnic group reflects past and present exposure of a population to malaria
  – Ethnic variation in allele frequencies

• Gene dosage – amount of gene present affects degree of symptoms
Thalassemia & Pregnancy

- Thalassemia trait not increased risk
- Autosomal recessive implications, Screening at risk ethnic groups (Asians, Mediterranean, Blacks)
- Thalassemia major (little to no $\beta$ chain production)- pregnancy is recommended if normal cardiac function, Hb > 10g/dL after hypertransfusion and iron chelation therapy (ACOG 2007)
  - During pregnancy Hb goal >10 g/dL ; Deferoxamine stopped
  - Fetal testing (serial growth scans, weekly testing); CD for obstetric indications
  - Echocardiogram prepregnancy
- $\beta$-thalassemia minor – mild anemia; only ppx iron; fetal testing (ACOG 2007)
- Supportive therapy – Hct >21% (Hb >6g/dL); ideal Hct > 30%
Thalassemias –
Beta globin gene -- chromosome 11
Alpha globin gene -- chromosome 16

Life span
Of RBC 120d
51-22. A 25-year-old Asian primigravida undergoes sonographic examination at 28 weeks’ gestation. This image of the fetal abdomen is obtained. Amniocentesis is performed and sent for analysis of the Alpha-globin gene. What is the expected genotype of this fetus?

- a. aa/-a
- b. a/-a
- c. —/-a
- d. —/— ***
<table>
<thead>
<tr>
<th>Number of functional Globin Genes (ratio of $\alpha/\beta$ globin)</th>
<th>Genotype</th>
<th>Description</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (1)</td>
<td>$\alpha\alpha/\alpha\alpha$</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3 (0.8)</td>
<td>$\alpha-/\alpha\alpha$</td>
<td>Heterozygous $\alpha$-thal trait (silent carrier)</td>
<td>Asymptomatic (silent carrier)</td>
</tr>
<tr>
<td>2 (0.6)</td>
<td>$\alpha-/\alpha-\alpha\alpha/-$</td>
<td>“$\alpha$-thal trait” affected</td>
<td>Mild anemia</td>
</tr>
<tr>
<td>1 (0.3)</td>
<td>$\alpha-/--\ 1^\alpha, \text{rest } \beta$</td>
<td>Hb H disease ($\beta$4 tetramers detected)</td>
<td>Hb H – marked hemolytic anemia at birth (MCV &lt;50mm$^3$)</td>
</tr>
<tr>
<td>0 (0)</td>
<td>--/-- All 4 $\gamma$</td>
<td>Hb Bart’s – no alpha globin</td>
<td>Hb Bart's (hydrops fetalis)</td>
</tr>
</tbody>
</table>

$\alpha$ thalassemia – diagnosed by DNA based testing (S. blot, PCR, ASO)

$\beta$thalassemia - $\beta$ chain deficiency (Hb electrophoresis - $>0.5\%$ F, $>3.5\%\%$ A2)
α-thalassemia

- Autosomal recessive; Classification table
- Chromosome 16 – 2 functioning α genes
  - Heterozygous α thal 2 (α-/αα) – silent carrier
  - ‘α thal trait’ – α thal 1 (2 of 4 α globin genes deleted)
    - Southeast Asians – (αα/--) heterozygous for α 1, 2
    - Blacks – (α-/α-) – homozygous for α thal 2 chromosome
    - MCV slightly reduced, asymptomatic
  - Hb H → α-/-- essentially all 4 Beta chains, severe anemia
  - Hb Barts – hydrops (--/--) all gamma chains
- Most common abnormality – leads to loss of 1 α-globin gene on a chromosome – unequal crossing over of α-globin cluster on chromosome 16
  - High degree of homology of nucleotide sequences around α1 and α2 genes
**β thalassemia**

- Autosomal recessive; β-globin gene Chromosome 11
- Large number of mutations that can result in decreased or absent function of β-globin gene
- Due to 1 β-globin gene per chromosome 11, chance for unequal crossing over is much reduced (vs α thal)
- Classes
  - Minor – 1 normal β-gene, 1 nonfunctional gene
  - Intermedia – abnormality of both β-globin chains, anemic, symptomatic, but not transfusion dependent
  - Major – No β-globin made (both genes mutated), no Hb A made, severe anemia, transfusion dependent
End

- Following are slides/notes/
Complete quiz. Williams Q

- Grade own quiz
- Turn into Jennifer-to tabulate
Anomalies - Definitions

- Epidemiology: 2-3% general population anomaly rate. CHD most common.
• Malformation – programmed deformity; develops incorrectly; example – TGA, conotruncal defects in CHD – programmed to develop abnormally and thus intrinsically, genetically abnormal
Deformation

- Recognizable pattern of dysmorphic features caused by extrinsic factors that affect the fetus in utero
- Genetically normal structure develops abnormally because of mechanical forces
- Abnormal development due to a mechanical problem
  - Ex – normal limb that develops contractures because of prolonged oligohydramnios from PPROM – Potter deformation sequence (from preivable PPROM or renal anomaly)
Disruption

- **Destruction of tissue from**
  - a) vascular occlusion ;
  - b) teratogen (alcohol, thalidomide, CMV, toxo, rubella)
  - c) rupture of amniotic sac with entrapment

- **Genetically normal, development programmed normal until event then becomes abnormal**

- **Defect from external or internal disruption of a previously normal part (destructive – breakdown of normal tissue)**
  - More severe than deformation
• One event leads to another (order is known)
• Genetically normal structure develops abnormally because of mechanical forces
• One defect dependent on one prior defect
• All abnormalities developed sequentially as the result of one initial insult
• Potter deformation sequence (from previable PPROM or renal anomaly)

• CHAOS (congenital high airway obstruction sequence) CHAOS is a syndrome in which there is blockage of the upper airway of the fetus during pregnancy. The human airway has several components that start with the mouth, windpipe (trachea), and voice box (larynx). During development, portions of the amniotic fluid are produced and exhaled by the lungs. If there is a blockage of the airway at any level, fluid from the lungs can back up. Longstanding and severe cases of CHAOS can cause heart failure and can lead to fetal demise. Although most infants will make it to birth without problems, there is great concern that the infant will not be able to breathe at time of delivery. This will require special considerations and treatments, such as an EXIT (Ex Utero Intrapartum Treatment) procedure at birth.

• Potter deformation sequence – oligohydramnios leads to contractures, lung hypoplasia, facial deformities
Association

- Association – statistical clustering of defects; group of anomalies occurring more common than would be expected by chance or at random
- Next step is syndrome when single cause is known to cause all the defects
- VACTERL association – Vertebral defects, Anal atresia, Coloboma, TE fistula, Radial /renal anomalies/agenesis, Limb defects
- CHARGE (now syndrome, used to be association) because gene is known – Coloboma (hole in one of structures of eye), Heart defect, Atresia of nasal choanae, R (MR, IUGR), GU – genitourinary; Ear (deafness)
VACTERL association

- VACTERL association –
- Vertebral defects,
- Anal atresia,
- Coloboma,
- TE fistula,
- Radial /renal anomalies/agenesis,
- Limb defects
Syndrome

- Syndrome – all abnormalities from one cause; condition of a single known cause; ex – trisomy 21, 18, 13
- Order is not known, thus not sequence
- ABS example – cephalocele, amputated right arm and arm bands secondary to amniotic band
- Fetal alcohol syndrome – 1%, 10/1000
  - IUGR, microcephaly, CNS defects, VSD, facies (smooth philtrum, thin vermilion/upper lip thins, small palpebral fissures/eye width decreases), MR, renal dysplasia, skeletal defects
CHARGE

- CHARGE (now syndrome, used to be association) because gene is known – CHD7 gene leads to the production of an abnormally short, nonfunctional CHD7 protein, which presumably disrupts chromatin remodeling and the regulation of gene expression
- Coloboma (hole in one of structures of eye),
- Heart defect,
- Atresia of nasal choanae,
- R (MR, IUGR),
- GU – genitourinary;
- Ear (deafness)
Radiation
Radiation exposure

• Diagnostic radiographic procedures have very low exposure and should not be delayed if they would directly affect therapy

• Therapeutic – significant fetal exposure – depends on tissue being treated, dose and field size
  – a/e – cell death, carcinogenesis, genetic affects on future generations
  – Exposure of < 5 cGy (5 rad) – negligible risk of major malformations

• Likely that 15-20 cGy is the threshold for radiation effects
Therapeutic radiation exposure

- Most susceptible period – organogenesis
- Characteristic fetal effects – microcephaly and mental retardation
  - Late exposure can cause growth restriction and brain damage
  - Possible that termination from radiation is part of treatment plan
- Abdominal shielding
- Radiation from breast cancer – significant shatter doses can accrue to the fetus
# Diagnostic imaging in preg - ACOG

## Table 1. Some Measures of Ionizing Radiation

<table>
<thead>
<tr>
<th>Measure</th>
<th>Definition</th>
<th>Unit</th>
<th>Unit</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exposure</td>
<td>Number of ions produced by X-rays per kilogram of air</td>
<td>Roentgen (R)</td>
<td>Roentgen (R)</td>
</tr>
<tr>
<td>Dose</td>
<td>Amount of energy deposited per kilogram of tissue</td>
<td>Rad (rad)*</td>
<td>Gray (Gy)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>1 Gy = 100 rad</td>
<td></td>
</tr>
<tr>
<td>Relative effective</td>
<td>Amount of energy deposited per kilogram of tissue normalized for biological</td>
<td>Roentgen</td>
<td>Sievert (Sv)</td>
</tr>
<tr>
<td>dose</td>
<td>effectiveness</td>
<td>equivalents</td>
<td>1 Sv = 100 rem</td>
</tr>
<tr>
<td></td>
<td></td>
<td>man (rem)*</td>
<td></td>
</tr>
</tbody>
</table>

*For diagnostic X-rays, 1 rad = 1 rem

# Diagnostic imaging in pregnancy - ACOG

## Table 2. Estimated Fetal Exposure From Some Common Radiologic Procedures

<table>
<thead>
<tr>
<th>Procedure</th>
<th>Fetal Exposure</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chest X-ray (2 views)</td>
<td>0.02–0.07 mrad</td>
</tr>
<tr>
<td>Abdominal film (single view)</td>
<td>100 mrad</td>
</tr>
<tr>
<td>Intravenous pyelography</td>
<td>≥1 rad*</td>
</tr>
<tr>
<td>Hip film (single view)</td>
<td>200 mrad</td>
</tr>
<tr>
<td>Mammography</td>
<td>7–20 mrad</td>
</tr>
<tr>
<td>Barium enema or small bowel series</td>
<td>2–4 rad</td>
</tr>
<tr>
<td>CT† scan of head or chest</td>
<td>&lt;1 rad</td>
</tr>
<tr>
<td>CT scan of abdomen and lumbar spine</td>
<td>3.5 rad</td>
</tr>
<tr>
<td>CT pelvimetry</td>
<td>250 mrad</td>
</tr>
</tbody>
</table>

*Exposure depends on the number of films

†Abbreviation: CT, computed tomography

Autosomal Dominant Pedigree
Autosomal Dominant

- Males and females equally affected
- Affected person has an affected parent
- Many are structural
- Many are new mutations
- Penetrance and expressivity are important
  - Penetrance – If you inherit the gene, will you show the disease
  - Expressivity – If you show the disease, how severe will you show it
- Age of onset is important
- 50% recurrence risk
Autosomal Dominant Conditions

- Marfan syndrome
- Neurofibromatosis
- Autosomal dominant polycystic kidney disease
- Huntington’s disease
- Waardenburg syndrome
- Achondroplasia
- Tuberous sclerosis
Marfan syndrome – Overview

- Definition – connective tissue disease from mutation of fibrillin 1 gene (15q21.1 – OMIM)
- Incidence – 1 in 10,000
- Pathogenesis – FBN1 encodes fibrillin 1 (ECM glycoprotein) - polymerizes to form micro-fibrils in both elastic and nonelastic tissues, such as the aortic adventitia, ciliary zonules and skin. Mutations affect fibrillin 1 synthesis, processing, secretion, polymerization, or stability.
Marfan Syndrome

Pedigree 2. An idealized pedigree demonstrating the effects of incomplete penetrance.

Slideshare.net
https://www.uic.edu/classes/bms/bms655/lesson4.html
Marfan Syndrome - Diagnosis

• Diagnosis – clinical (need following)
  – Aortic root dilation/dissection
  – Lens displaced superiorly
  – Spontaneous pneumothorax or apical blebs
  – Striae or recurrent hernia
  – 4 of 8 specific skeletal features
  – Family history of Marfan syndrome (recommend the mutation be identified regarding the FBN1 mutation or haplotype around FBN1)
  – Diagnosis must include anthropometric measurements
    • At least 10–20% of Marfan syndrome individuals have normal stature

OMIM, GHR
Marfan syndrome – Genetic Principles

• Autosomal dominant; 25-35% of patients result from de novo mutations making the mutation unique to the family

• Dominant negative mutations - Studies of fibrillin 1 deposition and cell culture expression assays suggest a dominant negative pathogenesis (i.e. production of mutant fibrillin 1 inhibits formation of normal microfibrils by normal fibrillin 1 or stimulates inappropriate proteolysis of extracellular microfibrils) – (Nussbaum, p286)

• Variable expressivity (varying degrees of severity)

• Counsel the family re: the female’s risk if female fetus!!

Genetics in Medicine
Marfan Syndrome & Pregnancy

- Prenatal diagnosis – requires linkage analysis of the mutation that is unique to the family
- AD – 50% chance of affected offspring
- 1% risk of dissection in pregnancy if normal root
- Aortic root cutoff – 40mm for excess risk (Rossiter 1995) - reason is <40mm is less likely to have significant expansion during pregnancy and less likely to dissect
  - β-blockade to prevent aortic root dilation/dissection (HR <90) – propranolol 40-80mg/d, labetalol
  - Echocardiogram q4-6 weeks to screen for progressive dilation
  - L&D – labor in lateral decubitus, oxygen, assisted 2nd stage
  - Risk if increased until 6-8 weeks PP

European Cardiac Society Guidelines - 2011
40 mm aortic root cutoff in pregnancy (Rossiter et al, 1995)

- N=45 pregnancies in 21 patients
- 1983-92; prospective study (Johns Hopkins)

**Fig. 1.** Aortic root diameter measurements before, during, and after pregnancy. *Least-squares linear regression lines*, each extending through measurements of aortic root diameter from last study before pregnancy, all studies during pregnancy, and first study after pregnancy.
Marfan Syndrome – Progressive Aortic Dilation

- Prepregnancy surgery if root >45mm
- Beta blocker
- Surgery in pregnancy if root dilation is increasing
- Delivery by Cesarean at term if root >40mm (Simpson 2012), >45mm (ESC guidelines)

European Cardiac Society Guidelines - 2011
Autosomal Recessive Pedigree
Autosomal Recessive

- Males and females equally affected
- Carrier parents are usually normal
- Most are biochemical disorders
- Most are usually the first case in the family
- Consanguinity
- 25% recurrence risk
Autosomal recessive

<table>
<thead>
<tr>
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<td>A</td>
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<td>a</td>
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<td>aa</td>
</tr>
</tbody>
</table>

CF**
Cauc carrier rate 1/25
2/3 sibling carrier rate if affected sibling and pt does not have disease
x1/4 for affected child risk of parents with this hx
x½ carrier rate
1/25 * 2/3 * ¼ = 1 in 149
Carrier risk – 1 in 75
Autosomal Recessive Conditions

- Cystic fibrosis
- Sickle cell anemia
- Spinal muscular atrophy
- Congenital adrenal hyperplasia
- Phenylketonuria
- Autosomal recessive polycystic kidney disease
- Meckel-Gruber syndrome- (polycystic kidneys, encephalocele, polydactyly, hepatic anomaly)
Spinal Muscular Atrophy (SMA)
Spinal Muscular Atrophy

- Spinal muscular atrophy (SMA) - autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness.

- Caused by a mutation in the gene known as the survival motor neuron gene (SMN1), which is responsible for the production of a protein essential to motor neurons.

- Chromosome 5q13.2

- Incidence – 1 in 6000- 10,000

- Leading genetic cause of infant death

- Carrier rates – 1 in 40 –60
  – CF 1 in 25, Tay Sachs 1 in 31
Spinal Muscular Atrophy

- Complex genetics, limitations in molecular diagnostic assays available, accurate prediction of the phenotype in affected fetuses may be not be possible.

- Incidence - 1 in 10,000 live births

- Leading genetic cause of infant death

- Carrier frequencies are estimated at 1 in 40-60

- No effective treatment

- Types 1-3
  - Type I – most severe; (Wernig–Hoffman), has symptomatic onset of the disease before 6 months of age and death from respiratory failure within the first 2 years of life.
  - Type II, most common form of SMA disease; intermediate severity; onset <2 yr old; Affected children are able to sit but few are able to stand or walk unaided. Respiratory insufficiency is a frequent cause of death during adolescence; life expectancy is 2 years to 20s;
  - Type III (Kugelberg–Welander), ; mild form; onset >18months old; variable sx profile; most reach major motor milestones, but function ranges from requiring wheelchair assistance in childhood to completely unaided ambulation into adulthood with minor muscular weakness. Many patients have normal life expectancies. There are other forms of SMA-like disorders with similar symptoms as those described previously, but they are linked to genes other than SMN1.

OMIM, GHR
Pedigrees of spinal muscular atrophy (SMA) families with biallelic absence of the SMN1 gene in unaffected subjects.

(a) family 1,
(b) family 2,
(c) family 3; circles represent females, squares represent males, black symbols represent biallelic SMN1 absence, dots represent heterozygous SMA carriers, arrows represent asymptomatic carriers of biallelic SMN1 absence.

Unaffected patients with a homozygous absence of the SMN1 gene
Spinal Muscular Atrophy

- **Molecular Genetics**
- 2 genes - nearly identical - SMN1, SMN2 present in humans
- SMN1 is considered the active gene for survival motor neuron protein production and more than 98% of patients with SMA have an abnormality in both SMN1 genes, which can be caused by a deletion (95%), or other mutation.
- SMN1 – 1 or 2 copies, usually 1 per chromosome
- SMN2 – 0-3 copies per chromosome
- SMN2 gene produces little of functional survival motor neuron protein
- SMN2 – primary genetic feature – determines severity of SMA – number of gene copies of SMN2; a higher number of SMN2 copies correlates with generally milder clinical phenotype
- Predictor of clinical severity due to variable copy numbers of SMN2 is the result of a small amount of full-length SMN transcripts and the protein generated by SMN2
- This protein product can partially compensate for the complete absence of protein from the SMN1 alleles.
- Accurate prediction of SMA phenotype based on SMN2 copy number is not possible; Most of the population has 1-3 copies of SMN2; approx 15% of NORMAL individuals have no copies of SMN2 gene.

OMIM, GHR
DNA Assay

For diagnosis of SMA, it is sufficient to simply detect the classic SMN1 deletion using DNA analysis in both SMN1 alleles.

- 95% sensitive (100% specific) for pt with SMA symptoms
- Not sufficient for ID of heterozygotes/carriers for SMN1 deletion
- Carrier testing requires a quantitative PCR assay that provides a measure of SMN1 copy number. Detection of a single normal copy of SMN1 would indicate the carrier state.

- Limitations of this assay to determine carrier status
  - ~3-4% of the general population, having two SMN1 copies on one chromosome and no copies on the other, will be incorrectly identified as being negative, or not carriers of SMA.
  - These individuals are carriers because one of their chromosomes is missing the SMN1 allele.
  - Another 2% of the general population has SMN1 mutations that are not detectable by the polymerase chain reaction method of SMN1 dosage analysis.

- Therefore, the counseling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from SMA affected families.

OMIM, GHR
Spinal Muscular Atrophy

- **Carrier Screening**
- **In current practice** – Pt with FHX of SMA are being offered carrier screening for the SMN1 deletion mutations.
- **ACMG** - Proponents of testing (American College of Medical Genetics) of carrier screening in general population because of severity of the disease and relatively high carrier frequency, as well as the advent of improved DNA diagnostic assays for mutations in the disease causing gene (SMN1).
- **ACMG** - Recommends offering carrier testing to all couples regardless of race or ethnicity.

**Limitations**
- Lack of studies in US to determine best practices for pretest and posttest education and counseling with specific regard to SMA screening.
- Lack of studies to determine patient preferences and utility measures that would allow the completion of an analysis of the cost-effectiveness of widespread carrier screening for SMA.
Spinal Muscular Atrophy – Who to screen?

• …American College of Obstetricians and Gynecologists’ Committee on Genetics states that preconception and prenatal screening for SMA is not recommended in the general population at this time…

• ACGM – Carrier screening should be offered to all patients
Residual Risk

- **CF** –
  - White patient – carrier rate 1 in 25, with negative carrier screening, rate is decreased to 1 in 200
  - <1% de novo mutation rate

- **SMA** –
  - 2% denovo mutation rate, thus residual risk is higher, unknown %
  - 2 copies of SMN1 mutation on same chromosome
Kansas Newborn Screening
http://www.kdheks.gov/newborn_screening/disorder_listing.htm

- **Amino Acid Disorders** - Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Homocystinuria (HCY), Tyrosinemia Type I (TYR I), Argininosuccinic acidemia (ASA), Citrullinemia (CIT)

- **Fatty Acid Disorders** - Medium chain Acyl-CoA dehydrogenase deficiency (MCAD), Very Long chain Acyl-CoA dehydrogenase deficiency (VLCAD), Long Chain Hydroxy Acyl-CoA dehydrogenase deficiency (LCHAD), Trifunctional protein deficiency (TFP), Carnitine uptake defect (CUD),

- **Organic Acid Disorders** - Isovaleric Acidemia (IVA), Glutaric Aciduria Type I (GA-I), 3-hydroxy-3-methylglutaryl CoA lyase deficiency (HMG), Multiple carboxylase deficiency(MCD), Methylmalonic Acidemia/Methylmalonyl-CoA mutase (MUT), Methylmalonic Acidemia/Vitamin B12 Disorders (Cbl A,B), 3-methylcrotonyl-CoA carboxylase deficiency (3MCC), Propionic Acidemia (PROP), Beta ketothiolase deficiency (BKT),

- **Hemoglobinopathies** - Sickle Cell Anemia (SCA), Sickle C Disease (HB S/C), Sickle Beta Thalassemia (HB S/Th)

- **Other Disorders** - Hypothyroidism (HYPOTH), Biotinidase deficiency (BIO), Congenital Adrenal Hyperplasia (CAH), Transferase Deficient Galactosemia (GALT), Cystic Fibrosis (CF), Hearing (HEAR)
Perinatal infections

- Related anomalies
CMV – most common congenital infection

- Primary infection – 40% fetal infection rate
  - <20 weeks, infection rate less, more severe infection,
  - >20 weeks, esp >28 weeks, infection rate higher, less severe infection
  - 90/10 rule of primary infection
    - 90% asymptomatic at birth, 10% with symptoms at 2 yo (hearing loss, chorioretinitis
    - 10% symptomatic at birth (30% mortality rate), 90% of these will have long term complications;
- Nonprimary recurrent infection 10-15% risk of long term complications, usually not symptomatic at birth
CMV sonogram findings

- IUGR
- Microcephaly
- Intracranial calcifications
- Ventriculomegaly
- Echogenic bowel

- Complications
  - Chorioretinitis
  - Hearing loss
  - Thrombocytopenia
  - Hyperbilirubinemia
  - Hepatitis

- Therapy – CMV IVIG, Gancyclovir
Toxoplasmosis

- Protozoan that affects humans via ingestion of contaminated meat or cat feces
- 0.8/10,000 US; 10/10,000 France
- 400-4000 estimate new cases of congenital toxoplasmosis each year
- 50% of US women with evidence of prior exposure

- 40% risk of congenital infection – risk is greatest in 3\textsuperscript{rd} trimester; severity of infection is worse in first trimester
- Rate of infection at 13 wks - 6%, at 36 weeks 72%;
- If infection <20 weeks, 11% of newborns had congenital infection
- If infection >20 weeks, 45% had congenital infection
Toxoplasmosis

- Disseminated rash, hepatosplenomegaly, chorioretinitis, uveitis, seizures, MR
- Diagnosis: Serologic testing performed by standardized reference lab (send if + to lab Palo Alto California), toxoplasmosis PCR in amniotic fluid
- Sonogram findings: IUGR, ascites, ventriculomegaly, periventricular calcifications
- Treatment: Spiramycin to reduce risk and severity of congenital infection, confirmed by PCR in amniotic fluid or by reference lab
- Spiramycin to prevent infection; treatment if primary maternal infection; reduces risk of congenital infection; does not treat active infection
- If fetal infection diagnosed (sono findings, + PCR) treatment is with pyrimethamine, sulfadiazine, folinic acid
- Controversial if + maternal infection and neg PCR late in pregnancy as whether to give other medications in addition to spiramycin
Toxoplasmosis

- Which of the following is true about fetal rates of toxoplasmosis infection related to fetal age at the time of maternal infection?
  - *A- Risk of fetal infection increases with advancing fetal age
  - B- Risk of fetal infection decreases with advancing fetal age
  - C- Severity of fetal infection is much greater in late pregnancy
  - D-Risk and severity of fetal infection are not dependent on gestational age
- Williams OB
Varicella

- Diagnosis – disseminated, pruritic, vesicular rash often associated with fever; varicella pneumonia (admission, IV ACV, respiratory support)
  - Anti-VZV IgM antibodies
- Congenital varicella – very rare (<1% in first trimester, <2% in second trimester)
  - Ultrasound findings – IUGR, microcephaly, ventriculomegaly, echogenic foci in liver, limb anomalies
  - Highest rate of infection at term
  - Chorioretinitis, microophthalmia, skin or bone defects
- Neonatal varicella – maternal varicella 5 days before to 2 days after delivery; disseminated mucocutaneous lesions, visceral infection, pneumonia, encephalitis
- Treatment – within 72-96 hours of exposure
  - VZIG (not in US)
  - Acyclovir 800mg po 5x/d x 7 days or valacyclovir 1000mg po TID x7 days
  - Respiratory support (oxygen, ABG, pH, CO2 in pregnancy)
  - No varicella vaccination in pregnancy
  - No evidence that tocolysis at term works
  - VariZIG - Canada
- Varicella zoster – Treatment with acyclovir
  - No increased risk of fetal infection
Varicella
Rubella

- Rubella – fetal infection rate
- 1st trimester infection increased rate of infection – 80-90%
- 13-20 weeks - 54% infection rate
- Late 2nd – early 3rd trimester – 25% infection rate, then increases late in 3rd trim
- Most common defect – Sensorineural deafness, second is heart defects, PDA, pulmonary artery stenosis
Classic findings of fetal rubella syndrome: renal disorders, hypospadias, cryptorchidism, meningocele, glaucoma, patent ductus arteriosus, and peripheral pulmonary stenosis.
Parvovirus

The risk for congenital infection from an infected mother is between 10% to 20% and is highest in the first and second trimesters.

Pathophys - Aplastic anemia, High output cardiac failure, Myocardial damage from virus, Decreased oncotic pressure (anemia)
Listeriosis

- Gram + rod
- Risks of IUFD, PTL, fetal infection
- Early onset – sepsis, IUFD
- Late onset – meningitis, hydrocephalus, MR
- Hematogenous infection, leads to placental abscesses, fetal sepsis, IUFD
- Avoid unpasteurized cheeses, meats (uncooked hot dogs)
- Tx Ampicillin

Placental villitis is shown here with a small microabscess containing mostly neutrophils in a case of congenital infection with Listeria monocytogenes. Listeriosis is generally not life-threatening to the mother, but is potentially a cause for fetal demise. 

http://library.med.utah.edu/WebPath/PLACHTML/PLAC034.html
Lyme Disease

- Lyme:
- Borrelia burgdoferi
- Erythema chronicum migrans (60-80%)
- Erythema is later followed by meningitis or Bell’s palsy and peripheral radiculopathies
- 5-10% of patients will have cardiac disease-AV block
- late infection associated with arthritis
- associated with poor pregnancy outcome—but no pattern of teratogenesis (rash, syndactaly, IUG)
- may treat with amox 500 qid x 14-30 days
- ceftriaxone 2gm IV daily for 14 days crosses blood brain barrier well
Syphilis

- *Syphilis*
- Incubate 10-90 days
- Primary lesion disappears in 2-6 weeks
- Secondary, or bacteremic stage lasts 2-6 weeks
- Early latent—may again get lesions, bacteremia up to 4 yrs
- Late latent—not infectious sexually
- Tertiary develops in 33% of patients
- Primary or secondary has 50% transmission, with 50% death rate
- Early latent 40% transmission and 20% death rate
- Late-10% tranmission
- Early signs—rash, hepatosplenomegaly, snuffles, chorioretinitis
- Late-Hutchinson’s teeth, saber shins, saddle nose, cardiac
- After treatment VDRL should become neglibile in 12 months. Do titers every 3 months for 1 year
- 2.4 mill units benzathine X 1 for primary and seconday or latent < 1 yr, other wise repeat X 3
X-linked Pedigree
X-linked

• Males affected
• Some carrier females mildly affected
• Affected males related through carrier females
• No male to male transmission
• 50% recurrence risk in males
X-linked Conditions

- Duchenne muscular dystrophy
- Hemophilia
- Fragile X- anticipation
Fragile X Syndrome

• Most common cause of inherited MR
• Males – 1 in 2,500 -4,000
• Females – 1 in 6-8,000
• Accounts for 3-6% of MR among boys with a +FHX of MR and no birth defects

• Carrier frequency (premutation 61-200 repeats)
  – 1 in 350 females, 1 in 1000 males

ACMG 2005
Fragile X – major phenotypic features

- Age at onset – childhood
- Mental deficiency
- Dysmorphic facies
- Male postpubertal macroorchidism

- Fragile site at Xq27.3 – located in 5’ untranslated region of the first exon of a gene called FMR1 (fragile X mental retardation 1)
Figure 2-37 • Location of genes on the X chromosome responsible for genetic diseases. (http://www.ncbi.nlm.nih.gov/disease/)
Fragile X Syndrome

• FMR1 gene product is FMRP (expressed in many cell types – mostly in neurons); may chaperone a subclass of mRNAs from the nucleus to the translational machinery

• More than 99% of FMR1 mutations are expansions of a (CGG)n repeat sequence in the 5’ untranslated region of the gene; > 200 repeats results in hypermethylation of the CGG repeat sequence and the adjacent FMR1 promoter; this inactivates the FMR1 promoter, causing a loss of FMRP expression
Fragile X Syndrome

- Expansion of repeated trinucleotide segment of DNA (cytosine–guanine–guanine, CGG) that leads to altered transcription of the fragile X mental retardation 1 (FMR1) gene.
- # of repeats varies – 4 groups - unaffected, intermediate, premutation, full mutation
  - 61–200 repeats - phenotypically normal, premutation
  - This condition occurs because the large number of repeats causes the FMR1 gene to become methylated and inactivated in these patients.
  - The number of repeats and the status of gene methylation are determined by use of DNA-based molecular tests (eg, Southern blot analysis and polymerase chain reaction).
  - DNA methylation is a process that controls tissue specific gene expression. Methylation "turns off" the regulatory region of a gene, thereby preventing DNA transcription. Rarely, the size of the triplet repeat and the methylation status do not correlate, making prediction of the clinical phenotype difficult.
# Fragile X syndrome

<table>
<thead>
<tr>
<th>Status of Individual</th>
<th>Number of Triplet Repeats (Cytosine–Guanine–Guanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Less than 45</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45-54</td>
</tr>
<tr>
<td>(also called &quot;grey zone&quot;)</td>
<td></td>
</tr>
<tr>
<td>Premutation</td>
<td>55–200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>More than 200</td>
</tr>
</tbody>
</table>

ACOG committee opinion 2010
AGG analysis (Nolin 2013)

- AGG interruption analysis (within the FMR1 repeat) – for patients that have 45-69 CGG repeats
  - Maternal alleles with NO interruptions- had greatest risk of unstable transmission
  - Magnitude of repeat expansion was larger for alleles lacking AGG interruptions
## Full Mutation Expansion from Maternal Premutation Allele

<table>
<thead>
<tr>
<th>Maternal Repeat Size</th>
<th>Full Mutation Expansion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>4</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
</tr>
<tr>
<td>70-79</td>
<td>31</td>
</tr>
<tr>
<td>80-89</td>
<td>58</td>
</tr>
<tr>
<td>90-99</td>
<td>80</td>
</tr>
<tr>
<td>100-200</td>
<td>98</td>
</tr>
</tbody>
</table>

ACOG CO – 2010

**ACOG committee opinion 2010**
X-linked Inheritance

- ½ of offspring of carrier mothers will receive the mutation and all the daughters but none of the sons of carrier fathers receive the mutation
- Risk of expansion of the CGG repeats in a premutation allele to a full mutation overlays the transmission pattern of FXS
  - Expansion of the premutation to the full mutation during transmission through a carrier woman is positively correlated with size of the woman’s repeat.
  - Smallest repeat to expand to a full mutation in one generation is 59 repeats
  - Risk of expansion to the full mutation from carrier men to their daughters is rare but has occurred
  - Premutation males pass on the premutation to their daughters typically with only small expansions or contractions
- Males affected
- Some carrier females mildly affected
- Affected males related through carrier females
- No male to male transmission
- 50% recurrence risk in males
X-linked Pedigree
Typical pedigree of fragile X syndrome. Note the presence of a transmitting male and anticipation with more affected individuals in later generations.

Ignatia B. Van den Veyver, MD Division of Maternal-Fetal Medicine and Reproductive Genetics, Department of Obstetrics and Gynecology and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (Vol, Chap 74)
Committee on Genetics recs re: testing for fragile X:

- DNA-based molecular test (Southern blot, PCR)
  - In rare cases where there is discordancy between the triplet repeat number and the methylation status, the patient should be referred to a genetic specialist.

- + FHx, or hx of fragile X MR – genetic counseling, offered genetic testing to assess risk for having an affected child.

- Prenatal testing for fragile X syndrome by amniocentesis or CVS should be offered to known carriers of the fragile X premutation or mutation. Although it is reliable for determining the number of triplet repeats, CVS may not adequately determine the methylation status of the FMR1 gene.

- Testing for fragile X syndrome should be considered in any child with developmental delay of uncertain etiology, autism, or autistic like behavior or any individual with mental retardation of uncertain etiology.

- If a woman has ovarian failure or an elevated follicle-stimulating hormone level before the age 40 years without a known cause, fragile X carrier screening should be considered to determine whether she has a premutation.
CVS pitfall

- Chorionic villus sampling (CVS) - reliable for determining the number of triplet repeats, may not be reliable for diagnosis because of gestational age differences in ultimate methylation patterns in the trophoblast and may not adequately determine the methylation status of the FMR1 gene.
Limitations of Testing

- **PCR** – Accurate for # of repeats and detection of premutation carriers
  - Cannot assess methylation status
- **Southern blot** – Crude estimate of size of repeats, also accurate assessment of methylation status
Genetic screening
<table>
<thead>
<tr>
<th>Age at Term</th>
<th>Risk of Trisomy 21*</th>
<th>Risk of Any Chromosome Abnormality†</th>
</tr>
</thead>
<tbody>
<tr>
<td>15†</td>
<td>1:1,578</td>
<td>1:454</td>
</tr>
<tr>
<td>16†</td>
<td>1:1,572</td>
<td>1:475</td>
</tr>
<tr>
<td>17†</td>
<td>1:1,565</td>
<td>1:499</td>
</tr>
<tr>
<td>18†</td>
<td>1:1,556</td>
<td>1:525</td>
</tr>
<tr>
<td>19†</td>
<td>1:1,544</td>
<td>1:555</td>
</tr>
<tr>
<td>20</td>
<td>1:1,480</td>
<td>1:525</td>
</tr>
<tr>
<td>21</td>
<td>1:1,460</td>
<td>1:525</td>
</tr>
<tr>
<td>22</td>
<td>1:1,440</td>
<td>1:499</td>
</tr>
<tr>
<td>23</td>
<td>1:1,420</td>
<td>1:499</td>
</tr>
<tr>
<td>24</td>
<td>1:1,380</td>
<td>1:475</td>
</tr>
<tr>
<td>25</td>
<td>1:1,340</td>
<td>1:475</td>
</tr>
<tr>
<td>26</td>
<td>1:1,290</td>
<td>1:475</td>
</tr>
<tr>
<td>27</td>
<td>1:1,220</td>
<td>1:454</td>
</tr>
<tr>
<td>28</td>
<td>1:1,140</td>
<td>1:434</td>
</tr>
<tr>
<td>29</td>
<td>1:1,050</td>
<td>1:416</td>
</tr>
<tr>
<td>30</td>
<td>1:940</td>
<td>1:384</td>
</tr>
<tr>
<td>31</td>
<td>1:820</td>
<td>1:384</td>
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<tr>
<td>32</td>
<td>1:700</td>
<td>1:322</td>
</tr>
<tr>
<td>33</td>
<td>1:570</td>
<td>1:285</td>
</tr>
<tr>
<td>34</td>
<td>1:456</td>
<td>1:243</td>
</tr>
<tr>
<td>35</td>
<td>1:353</td>
<td>1:178</td>
</tr>
<tr>
<td>36</td>
<td>1:267</td>
<td>1:148</td>
</tr>
<tr>
<td>37</td>
<td>1:199</td>
<td>1:122</td>
</tr>
<tr>
<td>38</td>
<td>1:148</td>
<td>1:104</td>
</tr>
<tr>
<td>39</td>
<td>1:111</td>
<td>1:80</td>
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<tr>
<td>40</td>
<td>1:85</td>
<td>1:62</td>
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<tr>
<td>41</td>
<td>1:67</td>
<td>1:48</td>
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<tr>
<td>42</td>
<td></td>
<td>1:38</td>
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<tr>
<td>43</td>
<td></td>
<td>1:30</td>
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<tr>
<td>44</td>
<td></td>
<td>1:23</td>
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<tr>
<td>45</td>
<td></td>
<td>1:18</td>
</tr>
<tr>
<td>46</td>
<td></td>
<td>1:14</td>
</tr>
<tr>
<td>47</td>
<td></td>
<td>1:10</td>
</tr>
<tr>
<td>48</td>
<td></td>
<td>1:8</td>
</tr>
<tr>
<td>49</td>
<td></td>
<td>1:6</td>
</tr>
<tr>
<td>50</td>
<td></td>
<td>1:25</td>
</tr>
</tbody>
</table>


†Risk of any chromosomal abnormality includes the risk of trisomy 21 and trisomy 18 in addition to trisomy 13, 47,XXY, 47,XYY, Turner syndrome genotype, and other clinically significant abnormalities, 47,XXX not included. Data from Hook EB. Rates of chromosome abnormalities at different maternal ages. Obstet Gynecol 1981;58:282–5.


§Data not available.
<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Gestational Age Range for Screening (Weeks)</th>
<th>Detection Rate for Down Syndrome (%)</th>
<th>Screen Positive Rate* (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Method</th>
</tr>
</thead>
</table>
| First trimester†      | 11–14†                                      | 82–87                                | 5                         | 1. Early screening  
2. Single test  
3. Analyte assessment of other adverse outcome | Lower DR than combined tests  
NT required                                                                          | NT+PAPP-A and hCG            |
| Triple screen         | 15–22                                       | 69                                   | 5                         | 1. Single test  
2. No specialized US required  
3. Also screens for open fetal defects  
4. Analyte assessment for other adverse outcomes | Lower DR than with first-trimester or quad screening  
Lowest accuracy of the single lab tests                                    | hCG, AFP, uE3                |
| Quad screen†          | 15–22                                       | 81                                   | 5                         | 1. Single test  
2. No specialized US required  
3. Also screens for open fetal defects  
4. Analyte assessment for other adverse outcomes | Lower DR than combined tests                                              | hCG, AFP, uE3, DIA            |
| Integrated†           | 11–14, then 15–22                           | 96                                   | 5                         | Highest DR of combined tests  
Also screens for open fetal defects                                               | Two samples needed before results are known                             | NT+PAPP-A, then quad screen        |
| Sequential‡ Stepwise  | 11–14, then 15–22                           | 95                                   | 5                         | First-trimester results provided;  
Comparable performance to integrated, but FTS results provided; also screens for open fetal defects; analyte assessment for other adverse outcomes. | Two samples needed                                                        | NT+hCG+PAPP-A then quad screen        |
| Contingent screening‡ | 88–94                                       | 88                                   | 5                         | First-trimester test result:  
Positive: diagnostic test offered  
Negative: no further testing  
Intermediate: second-trimester test offered  
Final: risk assessment incorporates first-and second-trimester results.       | Possibly two samples needed                                               | NT+hCG+PAPP-A, then quad screen        |
| Serum Integrated†     | 11–14; then 15–22                           | 88                                   | 5                         | 1. DR compares favorably with other tests. Two samples needed;  
2. No need for NT                                                            | No first-trimester results                                               | PAPP-A+quad                  |
<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Gestational Age Range for Screening (Weeks)</th>
<th>Detection Rate for Down Syndrome (%)</th>
<th>Screen Positive Rate* (%)</th>
<th>Advantages</th>
<th>Disadvantages</th>
<th>Method</th>
</tr>
</thead>
</table>
| Cell-free DNA*         | 10 - term                                   | 99 (in patients who receive a result) | 0.5                       | 1. Highest DR for Down syndrome  
2. Can be performed at any gestational age after 10 weeks  
3. Low false-positive rate in high-risk women (or women at high risk of Down syndrome) | 1. NPV and PPV not clearly reported  
2. Higher false-positive rate in women at low risk of Down syndrome  
3. Limited information about three trisomies and fetal sex  
4. Results do not always represent a fetal DNA result | Three roughly equivalent molecular methods |
| Nuchal Translucency†  | 11-14‡                                      | 64-70                               | 5                         | Allows individual fetus assessment in multifetal gestations  
Provides additional screening for fetal anomalies and possibly for twin-twin transfusion syndrome | 1. Poor screen in isolation  
2. Ultrasound certification necessary | US only only |

Abbreviations: AFP, alpha fetoprotein; DIA, dimeric inhibin-A; DR, detection rate; DS, Down syndrome; FTS, first-trimester screening; hCG, human chorionic gonadotropin; NPV, negative predictive value; NT, nuchal translucency; NTD, neural tube defect; PAPP-A, pregnancy-associated plasma protein A; PPV, positive predictive value; uE3, unconjugated estriol; US, ultrasonography.

*A screen positive test result includes all positive test results: the true positives and false positives.

†First-trimester combined screening: 87%, 85%, and 82% for measurements performed at 11 weeks, 12 weeks, and 13 weeks, respectively. Malone FASTER 2005.


∥Because of variations in growth and conception timing, some fetuses at the lower and upper gestational age limits may fall outside the required crown-rump length range.

<table>
<thead>
<tr>
<th>Soft Marker</th>
<th>Imaging Criteria</th>
<th>Aneuploidy Association</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>First trimester: enlarged nuchal translucency</td>
<td>Certified ultrasonography measurement ≥ 3.0 mm or above the 99th percentile for the CRL</td>
<td>Aneuploidy risk increases with size of NT Also associated with Noonan syndrome, multiple pterygium syndrome, skeletal dysplasias, congenital heart disease, and other anomalies</td>
<td>1. Genetic counseling 2. Offer cfDNA or CVS 3. Second-trimester detailed anatomic survey and fetal cardiac ultrasonography</td>
</tr>
<tr>
<td>First trimester: cystic hygroma</td>
<td>Large single or multilocular fluid-filled cavities, in the nuchal region and can extend the length of the fetus</td>
<td>If septate, approximately 50% are aneuploid</td>
<td>1. Genetic counseling 2. Offer CVS 3. Second-trimester detailed fetal anatomic survey and fetal cardiac ultrasonography</td>
</tr>
<tr>
<td>Second trimester: echogenic intracardiac foci</td>
<td>Echogenic tissue in one or both ventricles of the heart seen on standard four-chamber view</td>
<td>LR 1.4–1.8 for Down syndrome Seen in 15–30% of Down syndrome and 4–7% euploid fetuses</td>
<td>1. If isolated finding, aneuploidy screening should be offered if not done previously 2. If aneuploidy screen result is negative, no further evaluation is required.</td>
</tr>
<tr>
<td>Second trimester: pyelectasis</td>
<td>Renal pelvis measuring ≥ 4 mm in anteroposterior diameter up to 20 weeks of gestation</td>
<td>LR 1.5–1.6 for Down syndrome</td>
<td>1. If isolated finding, aneuploidy screening should be offered if not performed previously 2. Repeat ultrasonography in third trimester for potential urinary tract obstruction</td>
</tr>
<tr>
<td>Second trimester: echogenic bowel</td>
<td>Fetal small bowel as echogenic as bone</td>
<td>LR 5.5–6.7 for Down syndrome Associated with aneuploidy, intra-amniotic bleeding, cystic fibrosis, CMV</td>
<td>1. Further counseling 2. Offer CMV, CF, and aneuploidy screening or diagnostic testing</td>
</tr>
<tr>
<td>Second trimester: thickened nuchal fold</td>
<td>≥ 6 mm from outer edge of the occipital bone to outer skin in the midline</td>
<td>LR 11–18.6 with 40–50% sensitivity and &gt; 99% specificity for Down syndrome Most powerful second-trimester marker</td>
<td>1. Detailed anatomic survey 2. Further detailed genetic counseling and aneuploidy screening or diagnostic testing</td>
</tr>
</tbody>
</table>
LR calculation re: Down sd

- 31 yo
- a priori ~1 in 800
- NT/PAPPA/HCG- FDS risk 1 in 2000
  - Sonogram – 18wk – echogenic bowel- LR 6.7
  - Adjusted risk -1 in 298
- If no testing prior to sonogram
  - Adjusted risk – 1 in 119
<table>
<thead>
<tr>
<th>Soft Marker</th>
<th>Imaging Criteria</th>
<th>Aneuploidy Association</th>
<th>Management</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second trimester: mild ventriculomegaly</td>
<td>Lateral ventricular atrial measurement between 10–15 mm</td>
<td>Associated with aneuploidy</td>
<td>1. Genetic counseling</td>
</tr>
<tr>
<td></td>
<td>LR 25 for Down syndrome</td>
<td></td>
<td>2. Second-trimester detailed anatomic ultrasound evaluation</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Consider diagnostic testing for aneuploidy and CMV</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>4. Repeat ultrasound in third trimester</td>
</tr>
<tr>
<td>Second trimester: choroid plexus cysts</td>
<td>Discrete cyst(s) in one or both choroid plexus(es)</td>
<td>In isolation, no aneuploidy association</td>
<td>1. Second-trimester detailed anatomic survey and fetal cardiac ultrasound</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. No further follow-up if isolated</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Consider aneuploidy screening or diagnostic testing if other markers are present</td>
</tr>
<tr>
<td>Second trimester: short femur length</td>
<td>Measurement &lt; 2.5 percentile for gestational age</td>
<td>LR 1.2–2.2 for Down syndrome. Can be associated with aneuploidy, IUGR, short limb dysplasia</td>
<td>1. Second-trimester detailed fetal anatomic evaluation for short limb dysplasia</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>2. Further detailed counseling</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>3. Consider repeat ultrasonography in third trimester for fetal growth</td>
</tr>
</tbody>
</table>

Abbreviations: CF, cystic fibrosis; cfDNA, cell-free DNA; CMV, cytomegalovirus; CRL, crown–rump length; CVS, chorionic villus sampling; IUGR, intrauterine growth restriction; LR, likelihood ratio; NT, nuchal translucency.

<table>
<thead>
<tr>
<th>Test</th>
<th>Turnaround Time</th>
<th>Conditions Detected</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Conventional karyotype</td>
<td>7–14 days</td>
<td>Chromosomal abnormalities &gt; 5–10 Mb</td>
<td>Traditional method for diagnosis of chromosomal abnormalities</td>
</tr>
<tr>
<td>FISH — Direct preparation (interphase)</td>
<td>24–48 hours</td>
<td>Rapid assessment of major aneuploidies (chromosomes 13, 18, 21, X, and Y)</td>
<td>FISH with direct testing of cells from CVS is less accurate than with cultured cells from CVS or amniocentesis. Results should be confirmed on cultured cells or have additional clinical features before acting on results.</td>
</tr>
<tr>
<td>FISH — Cultured cells (metaphase)</td>
<td>7–14 days</td>
<td>Microdeletions and duplications</td>
<td>Can be used to test for specific abnormalities when clinically suspected</td>
</tr>
<tr>
<td>Chromosomal microarray</td>
<td>3–5 days (direct testing); 10–14 days (cultured cells)</td>
<td>Copy number variants &gt;50–200 kb</td>
<td>Whole genome screen for copy number variants. Detects major chromosomal abnormalities except balanced rearrangements and some triploidies. Detection varies with different microarray platforms.</td>
</tr>
<tr>
<td>Preimplantation genetic diagnosis</td>
<td>1–2 days</td>
<td>Genetic disorder in which familial mutation has been identified</td>
<td>Due to possibility of error, confirmation with CVS or amniocentesis is recommended</td>
</tr>
<tr>
<td>Molecular DNA testing</td>
<td>3–14 days (faster with direct testing than when cultured cells are required)</td>
<td>Genetic mutations previously demonstrated to be present in a family or suspected based on ultrasound or other findings in a fetus</td>
<td>Usually a targeted test focusing on a specific disorder (or category of disorders) suspected to be present in a fetus based on ultrasound findings or family history</td>
</tr>
</tbody>
</table>

Abbreviations: CVS, chorionic villus sampling; FISH, fluorescence in situ hybridization; IVF, in vitro fertilization.
<table>
<thead>
<tr>
<th>AFP</th>
<th>hCG</th>
<th>uE3</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>lo</td>
<td>hi</td>
<td>lo</td>
<td>Down syndrome, dates less advanced, Turner syndrome with cystic hygroma</td>
</tr>
<tr>
<td>lo</td>
<td>lo</td>
<td>lo</td>
<td>trisomy 18</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>nl</td>
<td>open spina bifida, abdominal wall defects, fetal death</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>lo</td>
<td>anencephaly</td>
</tr>
<tr>
<td>hi</td>
<td>lo</td>
<td>hi</td>
<td>dates more advanced</td>
</tr>
<tr>
<td>nl</td>
<td>nl</td>
<td>very low</td>
<td>fetal death, X-linked ichthyosis (placental sulfatase deficiency), congenital adrenal hyperplasia, Smith Lemli Opitz Syndrome</td>
</tr>
</tbody>
</table>
ACOG anomalies -
<table>
<thead>
<tr>
<th>Structural Defect</th>
<th>Population Incidence</th>
<th>Aneuploidy Risk</th>
<th>Most Common Aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic hygroma</td>
<td>1/120 EU–1/6,000 B</td>
<td>60–75%</td>
<td>45X (80%); 21,18,13,XXY</td>
</tr>
<tr>
<td>Hydrops</td>
<td>1/1,500–4,000 B</td>
<td>30–80%*</td>
<td>13,21,18,45X</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3–8/10,000 LB</td>
<td>3–8%</td>
<td>13,18, triploidy</td>
</tr>
<tr>
<td>Hydranencephaly</td>
<td>2/1,000 IA</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>1/16,000 LB</td>
<td>40–60%</td>
<td>13,18,18p-</td>
</tr>
<tr>
<td>Cardiac defects</td>
<td>7–9/1,000 LB</td>
<td>5–30%</td>
<td>21,18,13,22,8,9</td>
</tr>
<tr>
<td>Complete atrioventricular canal</td>
<td></td>
<td>40–70%</td>
<td>21</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>1/3,500–4,000 LB</td>
<td>20–25%</td>
<td>13,18,21,45X</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>1/5,800 LB</td>
<td>30–40%</td>
<td>13,18</td>
</tr>
<tr>
<td>Gastrochisis</td>
<td>1/10,000–15,000 LB</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>1/10,000 LB</td>
<td>20–30%</td>
<td>21</td>
</tr>
<tr>
<td>Bladder outlet obstruction</td>
<td>1–2/1,000 LB</td>
<td>20–25%</td>
<td>13,18</td>
</tr>
<tr>
<td>Facial cleft</td>
<td>1/700 LB</td>
<td>1%</td>
<td>13,18, deletions</td>
</tr>
<tr>
<td>Limb reduction</td>
<td>4–6/10,000 LB</td>
<td>8%</td>
<td>18</td>
</tr>
<tr>
<td>Club foot</td>
<td>1.2/1,000 LB</td>
<td>6%</td>
<td>18,13,4p-,18q-</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>1%</td>
<td>Minimal</td>
<td></td>
</tr>
</tbody>
</table>

Abbreviations: B, birth; EU, early ultrasonography; LB, livebirth; IA, infant autopsy

*30% if diagnosed at 24 weeks of gestation or later; 80% if diagnosed at 17 weeks of gestation or earlier

Cystic hygroma

- Cystic hygroma – 1 in 120 (first trimester), 1 in 6000 births, 60-75% aneuploidy risk (45,X 80%, t21, t18, t13, 47,XXY)
Cystic hygroma
Cystic hygroma
Hydrops

- Hydrops – 1 in 1,500-4000 births, 30-80% aneuploidy risk (t13, t21, t18, 45,X)

- Nonimmune, immune

- Nonimmune – karyotype, FE, TORCH, parvo, FMH,
  - Essential lethal if delivered <30 weeks, after 30 weeks, guarded
Hydrops fetalis
Hydrops fetalis
Acrania (absence of skull bones)/Anencephaly (no brain/NTD)

- Lethal
- Multifactorial (NTD), 5, 10, 15%
- Maternal diabetes
- AEDs
- DDX – acrania, microcephaly, large encephalocele

Workup
- R/O spina bifida (50%)
- R/O ABS (5%)
Hydrocephalus

- Ventriculomegaly
- Hydrocephalus - 3-8/10,000 Live births; 3-8% aneuploidy risk (t13, t18, triploidy)
Ventriculomegaly/Hydrocephalus

- Definition: shrinkage/dangling of choroid plexus

- Posterior horn >10mm
  - Mild 10-12
  - Mod 12-15
  - Overt/severe >15mm

- Cannot tell hydrocephalus on ultrasound
Ventriculomegaly

- **Mild/moderate 10-15mm**
- **DDX** – normal variant, large CPC
- **Workup**
  - R/O chrom abn – 10% (T21)
  - R/O infection (TORCH)
  - R/O other anomalies
- **Prognosis** – if isolated (10% abnl neurodevelopment), 90% normal

- **Severe/overt >15mm**
- **DDX**
  - Holoprosencephaly
  - Hydranencephaly
  - Encephalocele
  - Dandy-Walker
  - Arachnoid cyst
  - Porencephaly
  - Other
- **Workup**
  - R/O OSB (25-30%)
  - R/O other anomalies (50%) – intracranial, cardiac (FE), renal GI, TORCH
- **Prognosis**
  - If isolated or with OSB (1/3, 1/3, 1/3)
  - 1/3 severe MR,
  - 1/3 moderate MR,
  - 1/3 normal
Ventriculomegaly with OSB
Hydrancephaly

Hydranencephaly – 2/1000 infant autopsies; minimal aneuploidy risk
**Prevalence:** 1-2.5:10,000 births

**Definition:** Absence of the cerebral hemispheres, incomplete or absent falx; sac-like structure containing cerebral spinal fluid surrounding the brainstem and basal ganglia.

**Etiology:** Vascular occlusion (ICA, MCA); leukomalacia formed by confluence of multiple cystic cavities; diffuse hypoxic-ischemic brain necrosis; infection - necrotizing vasculitis; thromboplastic material from a deceased co-twin.

**Pathogenesis:** Liquefaction of brain tissue in area involved (usually the hemispheres), with replacement of the neural tissue by cerebrospinal fluid and preservation of the membranes.
Holoprosencephaly

- Holoprosencephaly - absent or incomplete cleavage of forebrain (prosencephalon) into the two cerebral hemispheres and lateral ventricles.
- Prognosis of affected infants depends on the severity of holoprosencephaly.
- Associated abnormalities – trisomies, 13, 18; partial monosomies of 13q and 18q.
- Holoprosencephaly 1/16,000 LB; aneuploidy risk 40-60% (t13, t18, 18p-)
Alobar

• Alobar (most severe) - no cleavage of prosencephalon occurred
  – Instead of a ventricular system with distinct lateral and third ventricles, a monoventricle cavity is present.
  – The thalamus and corpus striatum are fused in the midline, while the midbrain, brainstem, and cerebellum may be structurally normal. Facial abnormalities associated with this type include cleft lip and palate, cyclopia, and chromosomal aberrations, usually trisomy 13, are common in the group.

• Lethal
Semilobar

- Semilobar – (moderate) - results from less severe cleavage abnormalities of the prosencephalon. Although a frontal monoventricle is present, posterior partial formation of occipital lobes occurs.
- Semilobar holoprosencephaly has an intermediate but generally quite poor, prognosis.
Lobar (mildest) - the 2 hemispheres and lateral ventricles are better separated, the hemispheres may be fused, and the lateral ventricles widely intercommunicated due to absence of the septum pellucidum.

- Outcome is variable
- Infants with the lobar type may have mild, moderate or severe mental retardation
Cardiac defects
• Cardiac defects 7-9/1,000 LB; 5-30% aneuploidy risk (t21, t18, t13, 22q11 deletion/DiGeorge, 8 and 9 deletions)
• Complete AV canal 1/2000-1/5000; aneuploidy risk 40-70% (t21)
Case –23-week scan (4CV)
Case – AV canal & pleural effusion
Diaphragmatic hernia

- Diaphragmatic hernia – 1/2500-3,500 LB; aneuploidy risk 20-25% (t13, t18, t21, 45,X)
Diaphragmatic hernia
The contralateral lung is measured by multiplying the lung’s longest axis by the longest measurement perpendicular to the former (27 by 14 mm²).

This measurement is proportionated over the head circumference, measured in the standard biparietal view, showing two symmetrical hemispheres, the septum cavum pellucidum one-third of the way from the front to the back and the posterior horns of the lateral ventricles (bottom right).
CDH - Issues

- Sporadic inheritance, recurrence risk 2% in some case series
- Work up – evaluation for associated anomalies, karyotype, fetal echocardiogram, +/- MRI, serial growth scans, fetal surveillance
- Poor prognostic variables (indicate pulmonary hypoplasia) include liver herniation, LHR < 1, polyhydramnios
- Criteria for fetal tracheal occlusion – isolated diaphragmatic hernia, liver herniated, LHR <1, normal karyotype
- Overall survival rate – variable, depends on time of diagnosis (~35% if prenatal, ~70% if postnatal)
Omphalocele

- Omphalocele – 1/4,000 - 5,800 LB; aneuploidy risk 30-40% (t13, t18)
7-7-09 –
1971g (35%ile)
33 0/7 at 33 3/7
Recurrence risk - omphalocele

- Chromosomal abnormality
  - aneuploidy = 1% or maternal age-related risk (higher)
  - Familial cases of Beckwith-Wiedemann syndrome – 50%
    - BW – Depends on mechanism – Imprinting, etc
  - Isolated – sporadic, no increased risk above general population (1/4000)

  - 1 patient had 5 consecutive pregnancies with omphalocoeles by 2 different nonconsanguineous partners
Gastroschisis

- Gastroschisis – 1/10,000-15,000 LB, actual 1 in 2,000; aneuploidy risk minimal, not increased above general population
Omphalocele vs Gastroschisis

12. Ventral Wall Defects

13. Typical features of omphalocele with extracorporeal herniation of the liver (B).

6. Typical features of gastroschisis shown on external rotation (A) and on umbilical cord (B).
Management issues

- Need karyotype, check for associated anomalies
- CD for omphalocele if defect >5cm, evidence is less convincing for CD improving outcome in cases with extracorporeal liver
- No signs on sonogram that would make you deliver a gastroschisis – nothing that correlates to outcome (no cutoff for stomach dilation, bowel dilation, bowel wall thickening, etc) ideally – deliver vaginally; follow for growth, if testing normal –
- Increased risk of IUFD, esp >37 weeks
- Deliver at 37-38 weeks if IUGR
X-linked Pedigree
X-linked

- Males affected
- Some carrier females mildly affected
- Affected males related through carrier females
- No male to male transmission
- 50% recurrence risk in males
X-linked Conditions

- Duchenne muscular dystrophy
- Hemophilia
- Fragile X- anticipation
Fragile X Syndrome

- Most common cause of inherited MR
- Males – 1 in 2,500 -4,000
- Females – 1 in 6-8,000
- Accounts for 3-6% of MR among boys with a +FHX of MR and no birth defects

- Carrier frequency (premutation 61-200 repeats)
  - 1 in 350 females, 1 in 1000 males

ACMG 2005
Fragile X – major phenotypic features

- Age at onset – childhood
- Mental deficiency
- Dysmorphic facies
- Male postpubertal macroorchidism

- Fragile site at Xq27.3 – located in 5’ untranslated region of the first exon of a gene called FMR1 (fragile X mental retardation 1)
FIGURE 2-37 • Location of genes on the X chromosome responsible for genetic diseases. (http://www.ncbi.nlm.nih.gov/disease/)
Fragile X Syndrome

- FMR1 gene product is FMRP (expressed in many cell types – mostly in neurons); may chaperone a subclass of mRNAs from the nucleus to the translational machinery.
- More than 99% of FMR1 mutations are expansions of a (CGG)n repeat sequence in the 5’ untranslated region of the gene; > 200 repeats results in hypermethylation of the CGG repeat sequence and the adjacent FMR1 promoter; this inactivates the FMR1 promoter, causing a loss of FMRP expression.
Fragile X Syndrome

- Expansion of repeated trinucleotide segment of DNA (cytosine–guanine–guanine, CGG) that leads to altered transcription of the fragile X mental retardation 1 (FMR1) gene.

- # of repeats varies – 4 groups - unaffected, intermediate, premutation, full mutation
  - 61–200 repeats - phenotypically normal, premutation

  - This condition occurs because the large number of repeats causes the FMR1 gene to become methylated and inactivated in these patients.

  - The number of repeats and the status of gene methylation are determined by use of DNA-based molecular tests (eg, Southern blot analysis and polymerase chain reaction).

  - DNA methylation is a process that controls tissue specific gene expression. Methylation "turns off" the regulatory region of a gene, thereby preventing DNA transcription. Rarely, the size of the triplet repeat and the methylation status do not correlate, making prediction of the clinical phenotype difficult.
### Table 1. Mutation in the Fragile X Mental Retardation 1 Gene

<table>
<thead>
<tr>
<th>Status of Individual</th>
<th>Number of Triplet Repeats (Cytosine–Guanine–Guanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Less than 45</td>
</tr>
<tr>
<td>Intermediate (also called &quot;grey zone&quot;)</td>
<td>45–54</td>
</tr>
<tr>
<td>Premutation</td>
<td>55–200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>More than 200</td>
</tr>
</tbody>
</table>

ACOG committee opinion 2010
AGG analysis (Nolin 2013)

- AGG interruption analysis (within the FMR1 repeat) – for patients that have 45-69 CGG repeats
  - Maternal alleles with NO interruptions - had greatest risk of unstable transmission
  - Magnitude of repeat expansion was larger for alleles lacking AGG interruptions
<table>
<thead>
<tr>
<th>Maternal Repeat Size</th>
<th>Full Mutation Expansion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>4</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
</tr>
<tr>
<td>70-79</td>
<td>31</td>
</tr>
<tr>
<td>80-89</td>
<td>58</td>
</tr>
<tr>
<td>90-99</td>
<td>80</td>
</tr>
<tr>
<td>100-200</td>
<td>98</td>
</tr>
</tbody>
</table>

ACOG CO – 2010

ACOG committee opinion 2010
X-linked Inheritance

- ½ of offspring of carrier mothers will receive the mutation and all the daughters but none of the sons of carrier fathers receive the mutation.
- Risk of expansion of the CGG repeats in a premutation allele to a full mutation overlays the transmission pattern of FXS.
  - Expansion of the premutation to the full mutation during transmission through a carrier woman is positively correlated with size of the woman’s repeat.
  - Smallest repeat to expand to a full mutation in one generation is 59 repeats.
  - Risk of expansion to the full mutation from carrier men to their daughters is rare but has occurred.
  - Premutation males pass on the premutation to their daughters typically with only small expansions or contractions.
- Males affected.
- Some carrier females mildly affected.
- Affected males related through carrier females.
- No male to male transmission.
- 50% recurrence risk in males.
X-linked Pedigree
Typical pedigree of fragile X syndrome. Note the presence of a transmitting male and anticipation with more affected individuals in later generations.

Ignatia B. Van den Veyver, MD Division of Maternal-Fetal Medicine and Reproductive Genetics, Department of Obstetrics and Gynecology and Molecular and Human Genetics, Baylor College of Medicine, Houston, Texas (Vol , Chap 74)
Fragile X Syndrome - ACOG

- Committee on Genetics recs re: testing for fragile X:
  - DNA-based molecular test (Southern blot, PCR)
    - In rare cases where there is discordancy between the triplet repeat number and the methylation status, the patient should be referred to a genetic specialist.
  - + FHx, or hx of fragile X MR – genetic counseling, offered genetic testing to assess risk for having an affected child.
  - Prenatal testing for fragile X syndrome by amniocentesis or CVS should be offered to known carriers of the fragile X premutation or mutation. Although it is reliable for determining the number of triplet repeats, CVS may not adequately determine the methylation status of the FMR1 gene.
  - Testing for fragile X syndrome should be considered in any child with developmental delay of uncertain etiology, autism, or autistic like behavior or any individual with mental retardation of uncertain etiology.
  - If a woman has ovarian failure or an elevated follicle-stimulating hormone level before the age 40 years without a known cause, fragile X carrier screening should be considered to determine whether she has a premutation.
CVS pitfall

- Chorionic villus sampling (CVS) - reliable for determining the number of triplet repeats, may not be reliable for diagnosis because of gestational age differences in ultimate methylation patterns in the trophoblast and may not adequately determine the methylation status of the \textit{FMR1} gene.
Limitations of Testing

• PCR – Accurate for # of repeats and detection of premutation carriers
  – Cannot assess methylation status
• Southern blot – Crude estimate of size of repeats, also accurate assessment of methylation status
Duodenal atresia

- Duodenal atresia – 1/10,000 LB; aneuploidy risk 20-30% (t21)
Duodenal atresia
Bladder outlet obstruction

- Bladder outlet obstruction 1-2/1,000 LB; aneuploidy risk 20-25% (t13, t18)
Bladder outlet obstruction

- Affects GU tract, GI tract, lung development, Potter sequence
- Potter IV
- Males - posterior urethral valves (1/10,000)
- Females - urethral atresia
- Cloaca case
- It accounts for 10% of all urological anomalies detected by prenatal ultrasound.
- The overall mortality is 25–50%.
- Renal insufficiency develops in up to 45% of survivors.
Table 12. Prognostic Factors in Fetuses with Posterior Urethral Valves

<table>
<thead>
<tr>
<th>Factors</th>
<th>Good prognostic indicators</th>
<th>Poor prognostic indicators</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sonographic signs</td>
<td>Normal liquor Diagnosis after 24 wk</td>
<td>Oligohydramnios Diagnosis before 24 wk</td>
</tr>
<tr>
<td></td>
<td>Asymmetric hydronephrosis</td>
<td>Echogenic kidneys with cysts</td>
</tr>
<tr>
<td></td>
<td>Urinary ascites isolated</td>
<td>Perinephric urinoma</td>
</tr>
<tr>
<td>Urine biochemistry</td>
<td>Sodium &lt;100 mEq/L</td>
<td>Associated abnormalities</td>
</tr>
<tr>
<td></td>
<td>Chlorine &lt;90 mEq/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Osmolality &lt;210 mOsml/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Calcium &lt;2 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Phosphate &lt;2 mmol/L</td>
<td></td>
</tr>
<tr>
<td></td>
<td>β₂-Microglobulins &lt;2 mg/L</td>
<td></td>
</tr>
</tbody>
</table>

Potter classification of cystic renal disease

- Type I – autosomal recessive (infantile) polycystic renal disease, RR 25%
- Type II – multicystic renal dysplasia
- Type III – autosomal dominant (adult) polycystic renal disease
- Type IV – obstructive cystic dysplasia – small echogenic kidneys; bilateral; thick bladder wall if bladder seen
Facial cleft

• Facial cleft 1/700 LB; aneuploidy risk 1% (t13, t18, deletions)
Cleft Lip with or without Cleft Palate
Limb reduction

Amniotic band syndrome

Limb reduction 4-6/10,000 LB; aneuploidy risk 8% (t18)
Club foot

- Club foot – 1-2/1000, 6% aneuploidy risk, trisomy 18, 13, 18q-
Club foot

Club foot – 1-2/1000, 6% aneuploidy risk, trisomy 18, 13, 18q-
Single umbilical artery

- SUA – 1/100 LB; aneuploidy risk minimal
Single umbilical artery

• Embryology – develop from a diverticulum/stalk of the yolk sac; between 3-5 weeks of gestation, a common umbilical artery is normally present in all embryos then it becomes shorter and right and left umbilical arteries advance within the body stalk

• 3 mechanisms of SUA
  – Primary agenesis of one of the arteries
  – Secondary atrophy/atresia of normal artery
  – Persistence of common allantoic/umbilical artery

• Incidence – 0.5-1.9%, more common in twins

• Diagnosis by ultrasound
  – Identification of 2 vessel cord, increased diameter of single artery (>50% of the UV diameter)
  – Absent intraabdominal segment of the missing UA

• Differential diagnosis – nonvisualized second UA; fused segment of 2 umbilical arteries
SUA – associated risks

• Associated anomalies - 17-44% (if found on ultrasound, check karyotype)
  • urogenital, craniospinal, Meckel syndrome, NIH; all systems potentially involved
  • If no detailed anatomy scan is done prenatally, postnatal renal sonography is needed

• Growth restriction, SGA (average BW <2500g)
  – 15-20% incidence, serial growth scans

• Prematurity – average GA at delivery 35.9w (follow for symptoms)

• Longterm outcomes – Normal growth, IQ

• Recurrence risk/genetics – none if isolated
Anomalies – ACOG -end
Genetics %

- Frequency of chromosomal abnormalities
  - Live births 0.6%
  - With congenital anomaly + MR = 23%
  - Congenital heart disease = 13%
  - Institutional individual with MR = 12%
  - Couples with multiple sabs = 5%
  - Stillbirths/perinatal deaths = 6%
  - Spontaneous abortion 1st trim = 60%
Genetics %

- Chromosomal abnormalities in newborns (freq at birth)
  - Balanced translocation (1 in 500)
  - Unbalanced translocation (1 in 2000)
  - Pericentric inversion (1 in 100)
  - Tri 21 (1 in 700)
  - Tri 18 (1 in 6000)
  - Trisomy 13 (1 in 10,000)
  - 47,XXY (1 in 1000 males)
  - 47,XYY (1 in 1000 males)
  - 47,XXX (1 in 1000 females)
  - 45X (1 in 5000 females)
Genetics %

- Examples of numerical abnormalities
  - 45,x
  - 45,XY,-9 (monosomy 9)
  - 47,XX,+13 (trisomy 13)
  - 47,XXY (Klinefelter's syndrome – XXY is all you need for Klinefelter's syndrome – can have 48XXYY, 49XXXYY)
- 1st trimester spontaneous abortions – SAB
- Normal chromosomes – 40%
- Abnormal chromosomes – 60%
  - Autosomal trisomy – 50%; trisomy 16 (most common, 100% abort); trisomy 18 (98% abort); trisomy 21 (78% abort)
  - 45,X – 25% (99% abort)
  - Triploid, tetraploid – 20%
- Structural abnormalities <5%
- Most chromosomal abnormalities end as prenatal lethals
Genetics % End
Above –session 1
Below – possible session 2
Perinatal infections

• Related anomalies
CMV – most common congenital infection

- Primary infection – 40% fetal infection rate
  - <20 weeks, infection rate less, more severe infection,
  - >20 weeks, esp >28 weeks, infection rate higher, less severe infection
- 90/10 rule of primary infection
  - 90% asymptomatic at birth, 10% with symptoms at 2 yo (hearing loss, chorioretinitis
  - 10% symptomatic at birth (30% mortality rate), 90% of these will have long term complications;
- Nonprimary recurrent infection 10-15% risk of long term complications, usually not symptomatic at birth
CMV sonogram findings

- IUGR
- Microcephaly
- Intracranial calcifications
- Ventriculomegaly
- Echogenic bowel

- Complications
- Chorioretinitis
- Hearing loss
- Thrombocytopenia
- Hyperbilirubinemia
- Hepatitis

- Therapy – CMV IVIG, Gancyclovir
Toxoplasmosis

- Protozoan that affects humans via ingestion of contaminated meat or cat feces
- 0.8/10,000 US; 10/10,000 France
- 400-4000 estimate new cases of congenital toxoplasmosis each year
- 50% of US women with evidence of prior exposure

- 40% risk of congenital infection – risk is greatest in 3rd trimester; severity of infection is worse in first trimester
- Rate of infection at 13 wks - 6%, at 36 weeks 72%;
- If infection <20 weeks, 11% of newborns had congenital infection
- If infection >20 weeks, 45% had congenital infection
Toxoplasmosis

- Disseminated rash, hepatosplenomegaly, chorioretinitis, uveitis, seizures, MR
- Diagnosis: Serologic testing performed by standardized reference lab (send if + to lab Palo Alto California), toxoplasmosis PCR in amniotic fluid
- Sonogram findings: IUGR, ascites, ventriculomegaly, periventricular calcifications
- Treatment: Spiramycin to reduce risk and severity of congenital infection, confirmed by PCR in amniotic fluid or by reference lab
  - Spiramycin to prevent infection; treatment if primary maternal infection; reduces risk of congenital infection; does not treat active infection
  - If fetal infection diagnosed (sono findings, + PCR) treatment is with pyrimethamine, sulfadiazine, folinic acid
  - Controversial if + maternal infection and neg PCR late in pregnancy as whether to give other medications in addition to spiramycin
Toxoplasmosis

- Which of the following is true about fetal rates of toxoplasmosis infection related to fetal age at the time of maternal infection?
  - A- Risk of fetal infection increases with advancing fetal age
  - B- Risk of fetal infection decreases with advancing fetal age
  - C- Severity of fetal infection is much greater in late pregnancy
  - D- Risk and severity of fetal infection are not dependent on gestational age

- Williams OB
Varicella

- Diagnosis – disseminated, pruritic, vesicular rash often associated with fever; varicella pneumonia (admission, IV ACV, respiratory support)
  - Anti-VZV IgM antibodies
- Congenital varicella – very rare (<1% in first trimester, <2% in second trimester)
  - Ultrasound findings – IUGR, microcephaly, ventriculomegaly, echogenic foci in liver, limb anomalies
  - Highest rate of infection at term
  - Chorioretinitis, microophthalmia, skin or bone defects
- Neonatal varicella – maternal varicella 5 days before to 2 days after delivery; disseminated mucocutaneous lesions, visceral infection, pneumonia, encephalitis
- Treatment – within 72-96 hours of exposure
  - VZIG (not in US)
  - Acyclovir 800mg po 5x/d x 7 days or valacyclovir 1000mg po TID x7 days
  - Respiratory support (oxygen, ABG, pH, CO2 in pregnancy)
  - No varicella vaccination in pregnancy
  - No evidence that tocolysis at term works
  - VariZIG - Canada
- Varicella zoster – Treatment with acyclovir
  - No increased risk of fetal infection
Rubella

• Rubella – fetal infection rate
• 1\textsuperscript{st} trimester infection increased rate of infection – 80-90% 
• 13-20 weeks - 54% infection rate 
• Late 2\textsuperscript{nd} – early 3\textsuperscript{rd} trimester – 25% infection rate, then increases late in 3\textsuperscript{rd} trim
• Most common defect – Sensorineural deafness, second is heart defects, PDA, pulmonary artery stenosis
Rubella

Classic findings of fetal rubella syndrome: renal disorders, hypospadias, cryptorchidism, meningocele, glaucoma, patent ductus arteriosus, and peripheral pulmonary stenosis.
The risk for congenital infection from an infected mother is between 10% to 20% and is highest in the first and second trimesters.

Pathophys - Aplastic anemia, High output cardiac failure, Myocardial damage from virus, Decreased oncotic pressure (anemia)
Listeriosis

- Gram + rod
- Risks of IUFD, PTL, fetal infection
- Early onset – sepsis, IUFD
- Late onset – meningitis, hydrocephalus, MR
- Hematogenous infection, leads to placental abscesses, fetal sepsis, IUFD
- Avoid unpasteurized cheeses, meats (uncooked hot dogs)
- Tx Ampicillin

Placental villitis is shown here with a small microabscess containing mostly neutrophils in a case of congenital infection with Listeria monocytogenes. Listeriosis is generally not life-threatening to the mother, but is potentially a cause for fetal demise. http://library.med.utah.edu/WebPath/PLACHTML/PLAC034.html
Lyme Disease

- Lyme:
- Borrelia burgdorferi
- Erythema chronicum migrans (60-80%)
- Erythema is later followed by meningitis or Bell’s palsy and peripheral radiculopathies
- 5-10% of patients will have cardiac disease-AV block
- late infection associated with arthritis
- associated with poor pregnancy outcome—but no pattern of teratogenesis (rash, syndactaly, IUG)
- may treat with amox 500 qid x 14-30 days
- ceftriaxone 2gm IV daily for 14 days crosses blood brain barrier well
Syphilis

- *Syphilis*
- Incubate 10-90 days
- Primary lesion disappears in 2-6 weeks
- Secondary, or bacteremic stage lasts 2-6 weeks
- Early latent – may again get lesions, bacteremia up to 4 yrs
- Late latent - not infectious sexually
- Tertiary develops in 33% of patients
- Primary or secondary has 50% transmission, with 50% death rate
- Early latent 40% transmission and 20% death rate
- Late-10% transmission
- Early signs—rash, hepatosplenomegaly, snuffles, chorioretinitis
- Late-Hutchinson’s teeth, saber shins, saddle nose, cardiac
- After treatment VDRL should become neglibile in 12 months. Do titers every 3 months for 1 year
- 2.4 mill units benzathine X 1 for primary and seconday or latent < 1 yr, other wise repeat X 3
ACOG anomalies - end
High Yield Select Topics

• Added here 2015-2016
Sickle cell anemia – Overview

- **Definition** – AR hemoglobin disease due β-globin chain (chromosome 11) missense mutation that substitutes valine for glutamic acid at amino acid 6 (β-globin glu6val mutation); HB C lysine sub for glutamate
- **Incidence** – 1 in 700 (African), carrier rate ~1 in 10
- **Pathogenesis** – the glu6val mutation **DECREASES** the solubility and deformability of the β-globin chain so that after repeated cycles oxygenation and attendant sickling, the chains become permanently ‘sickled’ and occlude capillaries causing infarctions (painful crisis, acute chest syndrome, asplenia); irreversible sickled cells are removed by the spleen and the rate of removal of erythrocytes from the circulation exceeds the production capacity of the bone marrow and causes a hemolytic anemia
- **Diagnosis** – Peripheral smear; Hemoglobin electrophoresis identifying Hb SS (p100 Gehleter) – normal adult A (97.5%), A2 (2%), F (0.5%)
- Alpha globin chain on chromosome 16
Sickle Cell Disease & Pregnancy

- Increased risk of morbidity/mortality – depends on severity of anemia
  - Hb SS and to lesser extent Hb SC - Risks include infection, acute chest syndrome, pain crises, dehydration, severe anemia, cholecystitis, preterm birth, low-birth weight infants (<2500g), fetal growth restriction, hospitalization, IUFD
  - Folic acid supplementation – 4mg/day
  - Painful crisis (tx with pain control, oxygen, IV hydration) – avoid cold temp, heavy exertion, dehydration, stress
  - Acute chest syndrome (fever, tachypnea, chest pain, hypoxia)
  - Autosomal recessive implications for offspring
  - Prophylactic or exchange transfusion – goal of Hct - >21% (ideal ~30%) – decreases risk of painful crises, severe anemia, not necessarily associated with improved pregnancy outcome, less crises, less anemia (ACOG 2007)
  - Vaccinations – Pneumococcal vaccine and Meningococcal and Haemophilus influenza type B
  - Serial Urine cultures -
Hardy-Weinberg example

• Williams quest – What is approximate incidence of sickle cell anemia in African Americans if carrier rate is 1/12?

• $1=p+q$

• $1=p^2 + 2pq + q^2$

• $p =$ dominant allele

• $q =$ recessive allele

• $\frac{1}{12} \times \frac{1}{12} \times \frac{1}{4} = 1 \text{ in } 576$
HW – PKU example

• PKU
• Frequency of affected homozygotes in the population can be determined accurately through newborn screening programs
• Heterozygotes – asymptomatic silent carriers, population incidence is impossible to measure directly from phenotype
• HW law allows estimate of heterozygote frequency to be made and used subsequently for counseling
• Frequency of PKU 1 in 4500 – 1/4500 in Ireland
  – Frequency of affected individuals = 1/4500 = q², q =0.015, and 2pq = 0.029 or approx ~3%
• Carrier frequency in the Irish population ~3%
• If pt is a known carrier – Partner is Irish (3% heterozygote rate)
  – Chance of affected offspring – 0.5 x 0.03 x 0.25 = 1 in 267
  – Chance of carrier offspring - 0.5 x 0.03 x 0.5 = 1 in 133
• If pt is known carrier – Partner is from Finland (PKU frequency 1/200,000)
  – Frequency of affected individuals = 1/200,000 = q², q =0.002, and 2pq = 0.004 = 0.4% = carrier rate
  – Chance of affected offspring = 0.5 x 0.004 x 0.25 = 1 in 2000
  – Chance of carrier offspring = 0.5 x 0.004 x 0.5 = 1 in 1000
Multiples
Epidemiology

- United States, twin births accounted for 3.2 percent of live births in 2006 (Natl Vital Statistics)
- Of all twins...without ART
  - Dizygotic twins (~70%)
    - Ethnic variation in incidence of DZ twinning
  - Monozygotic twins (~30%)
    - Incidence of MZ twins is relatively stable worldwide at 3 to 5 per 1000 births
    - 70% MCDA, 30% DCDA
- Triplets...
- Quadruplets...
Placentation

• Multiple gestations – (e.g. twins)
• Dependent on when zygote splits post-fertilization in monozygotic pregnancy
  • the earlier the split the more tissue each pregnancy gets to itself
    – <3 dichorionic
    – 3-8 diamniotic
    – 8-12 monoamniotic
    – >12 conjoined
  – dichorionic placentation (two placentas, in all dizygotic and some monozygotic twins)
  – monochorionic placentation
    • monozygotic twins develop with only one placenta
    • higher risk of complications during pregnancy
    • preeclampsia
    • shunting of blood from 1 twin to the other (TTTS)
  – monoamniotic placentation
2 placentas
2 amnions
2 chorions
(dizygotic twins or monozygotic twins with cleavage of zygote during first 3 days after fertilization)
Lambda sign/twin peak

1 placenta
2 amnions
1 chorion
(monozygotic twins with cleavage of zygote days 4-8 post-fertilization)

1 placenta
1 amnion
1 chorion
(monozygotic twins with cleavage of zygote days 8-12 post-fertilization)

*Twin peak
*T sign

*if split occurs after 12 days post-fertilization, conjoined twins result
Twinning

• Determine early in gestation
  – Location, fetal sex, insertion sites, thickness of membranes

• Why do we care about placentation?
  – Predicting risk...
    • Monochorionic, diamniotic
      – Risk of sharing a placenta; shunting, anastomosis
      – unequal blood distribution - TTTS
      – 15% occurrence rate
    • Monoamniotic (cord entanglement)
      – 1/10,000 of all pregnancies
        » 1-5% of monozygotic twins
Dichorionic twin pregnancy (lambda sign)
Thick interdividing membrane of dichorionic twin pregnancy
Thin intertwin membrane characteristic of monochorionic diamniotic twin pregnancy
Twin to twin transfusion syndrome (TTTS)

- Incidence
  - 15% in monochorionic-diamniotic twin pregns
- Diagnosis
  - Monochorionic-diamniotic pregnancy (same sex, thin membrane, no twin peak, 1 placenta)
  - Polyhydramnios (>8cm) - recipient; oligohydramnios (<2cm) - donor
- Etiology - TYPE OF ANASTOMOSIS, not necessarily number; discordant placental sharing
  - A-V- unidirectional flow; intravillous (placental surface single unpaired artery carrying blood from donor twin to placental cotyledon together with single unpaired vein carrying blood from that cotyledon back to the recipient twin)
  - A-A, V-V- superficial on chorionic plate; bidirectional flow; “protective”
- Less A-A, V-V anastomoses increases probability of A-V anastomoses leading to TTTS
TTTS

- Classification (no good system for prediction of progression or prognosis)
- Quintero staging system (good for monitoring disease progression, not predicting outcomes)
  - Stage I: + Poly/oligo (POS); +bladder in donor
  - Stage II: +POS; NO bladder seen in donor; normal Dopplers
  - Stage III: +POS; NO bladder seen in donor; abnormal Dopplers
  - Stage IV: + POS, hydrops in either twin
  - Stage V: Fetal demise of either or both twins
- Staging system based on presence of A-A anastomoses (Jain et al); not widely used
End 2015-2016 CREOG review
CREOG review continued with Genetics
Genetics Review
Serum Screening
ALPHA-FETOPROTEIN

• STRUCTURALLY AND FUNCTIONALLY RELATED TO ALBUMIN

• PRODUCED BY THE FETAL YOLK SAC, G-I TRACT AND LIVER

• PEAK FETAL SERUM CONCENTRATION AT END OF FIRST TRIMESTER
ALPHA-FETOPROTEIN

- AFP leaves the fetus in fetal urine and by diffusion across membranes.
- AF-AFP enters maternal circulation by diffusion across placenta (2/3) and amnion (1/3).
FETAL SERUM AFP

(A)
AMNIOTIC FLUID AFP

![Graph showing the concentration of AFP in amniotic fluid over gestation](image)

- **AFP (μg/ml)**
- **Gestation (weeks)**
MATERNAL SERUM AFP

![Graph showing maternal serum AFP levels over gestation in weeks. The graph includes curves for 2.5 percentile, 50.0 percentile, and 97.5 percentile.](C)
INTERPRETATION

Maternal serum alpha-fetoprotein level
(Multiples of the median)

- Unaffected
- Open spina bifida
- Anencephaly
CAUSES OF ELEVATED MSAFP VALUES

- NEURAL TUBE DEFECT
- MULTIPLE GESTATION
- WRONG DATES
- ABDOMINAL WALL DEFECT
- PLACENTAL PROBLEMS
- FETAL-MATERNAL BLEED
- IUFD
- FETAL RENAL PROBLEMS
- MATERNAL TUMORS
- SACROCOCCYGEAL TERATOMA
MSAFP & DOWN SYNDROME

![Graph showing maternal serum AFP levels for Down syndrome, unaffected individuals, and spina bifida.](image-url)
<table>
<thead>
<tr>
<th>AFP</th>
<th>hCG</th>
<th>uE3</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>lo</td>
<td>hi</td>
<td>lo</td>
<td>Down syndrome, dates less advanced, Turner syndrome with cystic hygroma</td>
</tr>
<tr>
<td>lo</td>
<td>lo</td>
<td>lo</td>
<td>trisomy 18</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>nl</td>
<td>open spina bifida, abdominal wall defects, fetal death</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>lo</td>
<td>anencephaly</td>
</tr>
<tr>
<td>hi</td>
<td>lo</td>
<td>hi</td>
<td>dates more advanced</td>
</tr>
<tr>
<td>nl</td>
<td>nl</td>
<td>very</td>
<td>fetal death, X-linked ichthyosis (placental sulfatase deficiency),</td>
</tr>
<tr>
<td></td>
<td></td>
<td>low</td>
<td>congenital adrenal hyperplasia, Smith Lemli Opitz Syndrome</td>
</tr>
</tbody>
</table>
### Table 1. Down Syndrome Screening Tests and Detection Rates (5% Positive Screen Rate)

<table>
<thead>
<tr>
<th>Screening Test</th>
<th>Detection Rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>First Trimester</strong></td>
<td></td>
</tr>
<tr>
<td>NT measurement</td>
<td>64–70*</td>
</tr>
<tr>
<td>NT measurement, PAPP-A, free or total β-hCG†</td>
<td>82–87*</td>
</tr>
<tr>
<td><strong>Second trimester</strong></td>
<td></td>
</tr>
<tr>
<td>Triple screen (MSAFP, hCG, unconjugated estriol)</td>
<td>69*</td>
</tr>
<tr>
<td>Quadruple screen (MSAFP, hCG, unconjugated estriol, inhibin A)</td>
<td>81*</td>
</tr>
<tr>
<td>Screening Test</td>
<td>Detection Rate (%)</td>
</tr>
<tr>
<td>----------------</td>
<td>--------------------</td>
</tr>
<tr>
<td><strong>First Plus Second Trimester</strong></td>
<td></td>
</tr>
<tr>
<td>Integrated (NT, PAPP-A, quad screen)</td>
<td>94–96*</td>
</tr>
<tr>
<td>Serum integrated (PAPP-A, quad screen)</td>
<td>85–88*</td>
</tr>
</tbody>
</table>
| Stepwise sequential  
First-trimester test result:  
Positive: diagnostic test offered  
Negative: second-trimester test offered  
Final: risk assessment incorporates first and second results | 95* |
| Contingent sequential  
First-trimester test result:  
Positive: diagnostic test offered  
Negative: no further testing  
Intermediate: second-trimester test offered  
Final: risk assessment incorporates first and second results | 88–94%‡ |
Single Gene Disorders

- Autosomal Dominant
- Autosomal Recessive
- X-linked
Pedigree Symbols (Thompson/Thompson)

Figure 7-1 Symbols commonly used in pedigree charts. Although there is no uniform system of pedigree notation, the symbols used here are according to recent recommendations made by professionals in the field of genetic counseling. (From Bennett RL, Steinhaus KA, Uhrich SB, et al: Recommendations for standardized pedigree nomenclature. J Genet Couns 4:267-279, 1995.)
Figure 7-2  Relationships within a kindred. The proband, III-5 (arrow), represents an isolated case of a genetic disorder. She has four siblings, III-3, III-4, III-7, and III-8. Her partner/spouse is III-6, and they have three children (their F1 progeny). The proband has nine first-degree relatives (her parents, siblings, and offspring), nine second-degree relatives (grandparents, uncles and aunts, nieces and nephews, and grandchildren), two third-degree relatives (first cousins), and four fourth-degree relatives (first cousins once removed). IV-3, IV-5, and IV-6 are second cousins of IV-1 and IV-2. IV-7 and IV-8, whose parents are consanguineous, are doubly related to the proband: second-degree relatives through their father and fourth-degree relatives through their mother.
Autosomal Dominant

- Males and females equally affected
- Affected person has an affected parent
- Many are structural
- Many are new mutations
- Penetrance and expressivity are important
  - Penetrance – If you inherit the gene, will you show the disease
  - Expressivity – If you show the disease, how severe will you show it
- Age of onset is important
- 50% recurrence risk
Autosomal Dominant Pedigree
Autosomal Dominant Conditions

- Neurofibromatosis
- Autosomal dominant polycystic kidney disease
- Huntington’s disease
- Waardenburg syndrome
- Achondroplasia
- Tuberous sclerosis
Autosomal Recessive

- Males and females equally affected
- Carrier parents are usually normal
- Most are biochemical disorders
- Most are usually the first case in the family
- Consanguinity
- 25% recurrence risk
Autosomal Recessive Pedigree
## Autosomal recessive

<table>
<thead>
<tr>
<th></th>
<th>A</th>
<th>a</th>
</tr>
</thead>
<tbody>
<tr>
<td>AAA</td>
<td>Aa</td>
<td></td>
</tr>
<tr>
<td>aA</td>
<td>aa</td>
<td></td>
</tr>
</tbody>
</table>
Autosomal Recessive Conditions

- Cystic fibrosis
- Sickle cell anemia
- Spinal muscular atrophy
- Congenital adrenal hyperplasia
- Phenylketonuria
- Autosomal recessive polycystic kidney disease
- Meckel-Gruber syndrome
Sickle cell anemia – Overview

• Definition – AR hemoglobin disease due β-globin chain (chromosome 11) missense mutation that substitutes valine for glutamic acid at amino acid 6 (β-globin glu6val mutation)
• Incidence – 1 in 700 (African), carrier rate ~1 in 10
• Pathogenesis – the glu6val mutation DECREASES the solubility and deformability of the β-globin chain so that after repeated cycles oxygenation and attendant sickling, the chains become permanently ‘sickled’ and occlude capillaries causing infarctions (painful crisis, acute chest syndrome, asplenia); irreversible sickled cells are removed by the spleen and the rate of removal of erythrocytes from the circulation exceeds the production capacity of the bone marrow and causes a hemolytic anemia
• Diagnosis – Peripheral smear; Hemoglobin electrophoresis identifying Hb SS (p100 Gehleter) – normal adult A (97.5%), A2 (2%), F (0.5%)
Hgb electrophoresis
Electric field
Sickle (glu6val) valine in place of glutamine
Glutamine has a more Negative charge thus it travels further than Valine (S) or lysine (C)
-A = glutamine has the most negative charge – thus it goes far on the gel
-S = glutamine to valine (middle charge b/n +/-)
-C = glutamine to lysine (more + charge thus it does not goes as far on the gel)
-A2 (most positive charge, thus it does not go far on the gel)
Sickle Cell Disease and genetic principles

- Heterozygote advantage, plays role in ethnic variation in allele frequency
- Novel property mutation - sickle cell disease is an exception to the allelic heterogeneity rule in that one specific mutation is responsible for the unique ‘novel’ properties of sickle Hb; Hb C is less soluble than Hb A and tends to crystallize in red cells, decreasing the deformability in capillaries and this also creates mild hemolysis, but Hb C does not sickle or form the rod shaped polymers like Hb S
## Sickle cell mutation frequencies (Nussbaum 4th ed) — California cohort data

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>Hb SS</th>
<th>Hb AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1/700</td>
<td>1/14</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>0/1600</td>
<td>1/700</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/46,000</td>
<td>1/180</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0/22,000</td>
<td>1/360</td>
</tr>
<tr>
<td>Native American</td>
<td>1/17,000</td>
<td>1/180</td>
</tr>
<tr>
<td>White</td>
<td>1/160,000</td>
<td>1/600</td>
</tr>
<tr>
<td>Asian</td>
<td>0/200,000</td>
<td>1/1300</td>
</tr>
</tbody>
</table>
Sickle cell disease & Pregnancy

- Increased risk of morbidity/mortality – depends on severity of anemia
  - Hb SS and to lesser extent Hb SC - Risks include infection, acute chest syndrome, pain crises, dehydration, severe anemia, cholecystitis, preterm birth, low-birth weight infants (<2500g), fetal growth restriction, hospitalization
  - Folic acid supplementation – 4mg/day
  - Painful crisis (tx with pain control, oxygen, IV hydration) – avoid cold temp, heavy exertion, dehydration, stress
  - Acute chest syndrome (fever, tachypnea, chest pain, hypoxia)
  - Autosomal recessive implications for offspring
  - Prophylactic or exchange transfusion – goal of Hct - >21% (ideal ~30%) – decreases risk of painful crises, severe anemia, not necessarily associated with improved pregnancy outcome, less crises, less anemia (ACOG 2007)
Screening in pregnancy (ACOG, 2007)

- CBC, hemoglobin electrophoresis, ferritin (<10 mcg/dL – iron deficiency)
- Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be screened
- Carriers or affected patients – genetic counseling, prenatal diagnosis if mutations have been defined in the parents for thalassemia – DNA mutation analysis for sickle cell disease is available 2 carriers or affected patients
- MCV < 80fL, normal ferritin – screen with hemoglobin electrophoresis
Fig. 1. Specialized antepartum evaluation for hematologic assessment of patients of African, Southeast Asian, or Mediterranean descent. Patients of Southeast Asian or Mediterranean descent should undergo electrophoresis if their blood test results reveal anemia. Abbreviations: CBC = complete blood count; RBC = red blood cell; MCV = mean corpuscular volume; Hb = hemoglobin.
Genetic principles (cont)
X-linked

- Males affected
- Some carrier females mildly affected
- Affected males related through carrier females
- No male to male transmission
- 50% recurrence risk in males
X-linked Pedigree
X-linked Conditions

- Duchenne muscular dystrophy
- Hemophilia
- Fragile X
Fragile X Syndrome

- FMR1 gene product is FMRP (expressed in many cell types – mostly in neurons); may chaperone a subclass of mRNAs from the nucleus to the translational machinery.
- More than 99% of FMR1 mutations are expansions of a (CGG)n repeat sequence in the 5’ untranslated region of the gene; > 200 repeats results in hypermethylation of the CGG repeat sequence and the adjacent FMR1 promoter; this inactivates the FMR1 promoter, causing a loss of FMRP expression.
Fragile X Syndrome

• Expansion of repeated trinucleotide segment of DNA (cytosine–guanine–guanine, CGG) that leads to altered transcription of the fragile X mental retardation 1 (FMR1) gene.

• # of repeats varies – 4 groups - unaffected, intermediate, premutation, full mutation
  – 61–200 repeats - phenotypically normal, premutation
  – This condition occurs because the large number of repeats causes the FMR1 gene to become methylated and inactivated in these patients.
  – The number of repeats and the status of gene methylation are determined by use of DNA-based molecular tests (eg, Southern blot analysis and polymerase chain reaction).
  – DNA methylation is a process that controls tissue specific gene expression. Methylation "turns off" the regulatory region of a gene, thereby preventing DNA transcription. Rarely, the size of the triplet repeat and the methylation status do not correlate, making prediction of the clinical phenotype difficult.
FIGURE 6-4 • Diagram of the FMR1 gene and the first exon in normal, premutation, and full mutation alleles. The oval immediately to the left of the start site of transcription represents the promoter region of the FMR1 gene. The open symbol represents active transcription, and the black symbol, silenced transcription. The vertical lines indicate CGG trinucleotides upstream of the methionine codon (AUG) at the translocational start site. (Reprinted with permission from Warren ST, Nelson DL: Advances in molecular analysis of fragile X syndrome. JAMA 271:536, 1994.)
Fragile X syndrome

<table>
<thead>
<tr>
<th>Status of Individual</th>
<th>Number of Triplet Repeats (Cytosine–Guanine–Guanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Less than 45</td>
</tr>
<tr>
<td>Intermediate</td>
<td>45-54</td>
</tr>
<tr>
<td>(also called &quot;grey zone&quot;)</td>
<td></td>
</tr>
<tr>
<td>Premutation</td>
<td>55–200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>More than 200</td>
</tr>
</tbody>
</table>

ACOG committee opinion 2010
**Full Mutation Expansion from Maternal Premutation Allele**

<table>
<thead>
<tr>
<th>Maternal Repeat Size</th>
<th>Full Mutation Expansion (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>55-59</td>
<td>4</td>
</tr>
<tr>
<td>60-69</td>
<td>5</td>
</tr>
<tr>
<td>70-79</td>
<td>31</td>
</tr>
<tr>
<td>80-89</td>
<td>58</td>
</tr>
<tr>
<td>90-99</td>
<td>80</td>
</tr>
<tr>
<td>100-200</td>
<td>98</td>
</tr>
</tbody>
</table>

ACOG CO – 2010

ACOG committee opinion 2010
X-linked Inheritance

- ½ of offspring of carrier mothers will receive the mutation and all the daughters but none of the sons of carrier fathers receive the mutation
- Risk of expansion of the CGG repeats in a premutation allele to a full mutation overlays the transmission pattern of FXS
  - Expansion of the premutation to the full mutation during transmission through a carrier woman is positively correlated with size of the woman’s repeat.
  - Smallest repeat to expand to a full mutation in one generation is 59 repeats
  - Risk of expansion to the full mutation from carrier men to their daughters is rare but has occurred
  - Premutation males pass on the premutation to their daughters typically with only small expansions or contractions
- Males affected
- Some carrier females mildly affected
- Affected males related through carrier females
- No male to male transmission
- 50% recurrence risk in males
Polygenic/multifactorial

- More than one gene involved and possibly environmental factors
- Many are surgically treatable
- Threshold risk
- 2-5% recurrence risk
- Sex of proband may influence recurrence
Polygenic/multifactorial Conditions

- Neural tube defects
- Congenital heart disease
- Cleft lip with or without cleft palate (males)
- Cleft palate (females)
- Club foot
Genetic principles – break here, do cardiac disease, then resume genetic principles
Cardiac disease in pregnancy - Maternal
Cardiac Disease in Pregnancy

Darren Farley, MD
Clinical Assistant Professor
Division of Maternal-Fetal Medicine
Dept. of Obstetrics and Gynecology
University of Kansas School of Medicine – Wichita
Objectives

• Epidemiology
• Cardiac changes in pregnancy
• Issues in cardiac patients
  – Risk assessment
  – Anticoagulation
  – Anesthesia consult
  – L&D, invasive monitoring
  – Endocarditis prophylaxis
  – Mode of delivery
Epidemiology

• Cardiac disease complicates 1-4% of all pregnancies in the US
  – 10-25% of maternal mortality

• Etiology
  – Rheumatic most common worldwide
  – Congenital heart disease most common in North America

(Foley 2003)
Heart disease complicates more than 1% of pregnancies and is now the leading cause of indirect maternal deaths. The spectrum and severity of heart disease observed in reproductive-aged women is changing. Today, congenital heart disease accounts for more than half of cardiac disease in pregnancy, and ischemic heart disease is on the rise as a result of obesity, hypertension, diabetes, and delayed childbearing. Pregnancy is still contraindicated in women with pulmonary hypertension, severe systemic ventricular dysfunction, dilated aortopathy, and severe left-sided obstructive lesions, but advances in medical and surgical management have resulted in an increasing number of patients with congenital heart defects reaching childbearing age who are interested in pregnancy. A multidisciplinary approach can best determine whether acceptable outcomes can be expected and what management strategies may improve the prognosis for pregnant women with heart disease.

(Obstet Gynecol 2012;119:345–59)
DOI: 10.1097/AOG.0b013e318242e260
Cardiovascular Changes of Pregnancy

<table>
<thead>
<tr>
<th>Variable</th>
<th>First Trimester</th>
<th>Second Trimester</th>
<th>Third Trimester</th>
<th>Eight wk Postpartum</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart rate (beats/min)</td>
<td>70±8</td>
<td>77±10</td>
<td>80±10</td>
<td>66±10</td>
</tr>
<tr>
<td>Cardiac output (L/min)</td>
<td>6.8±1.6</td>
<td>7.6±1.5</td>
<td>7.9±1.6</td>
<td>6.0±1.2</td>
</tr>
<tr>
<td>Stroke volume (mL)</td>
<td>95±20</td>
<td>99±20</td>
<td>99±19</td>
<td>87±17</td>
</tr>
<tr>
<td>Mean arterial pressure (mm Hg)</td>
<td>71±5</td>
<td>70±5</td>
<td>70±6</td>
<td>71±6</td>
</tr>
<tr>
<td>Left ventricle mass (g)</td>
<td>131±36</td>
<td>141±31</td>
<td>147±36</td>
<td>140±34</td>
</tr>
</tbody>
</table>

Data are mean±standard deviation.
Blood volume increases 50%
Cardiovascular Changes of Pregnancy

- **Systemic Vascular Resistance** - Drops
- **Central Venous Pressure** - Unchanged (10 mm Hg)

*Figure 3-6. Change in systemic vascular resistance (S.V.R.) during normal pregnancy and the first year postpartum in nulliparous and parous women. Open circles, 15 nulliparous women; open squares, 15 parous women. Data are presented as mean ± SEM. 52PP, 52 weeks postpartum; NP, nonpregnant. (From Clapp J, Capeless E: Cardiovascular function before, during and after the first and subsequent pregnancies. Am J Cardiol 80:1469, 1997, with permission.)*
Stroke Volume Increases Across Gestation

Adapted from Uptodate - Citation Bonica 1994 Obstetrical Anesthesia
Heart Rate Increases Across Gestation

Adapted from Uptodate - Citation Bonica 1994 Obstetrical Anesthesia
Cardiac Output Across Gestation

Cardiac Output Increased by 30-50%
Twin Pregnancy: Add another 15%
Starts Early and Peaks at 20 Weeks

Adapted from Uptodate - Citation Bonica 1994 Obstetrical Anesthesia
Effect of Labor on Cardiac Output

Figure 3–9. Changes in cardiac output and stroke volume during normal labor. (From Hunter S, Robson S: Adaptation of the maternal heart in pregnancy. Br Heart J 68:540, 1992, with permission.)

(Hunter 1992)
Estimation of Maternal Risk in Patients With Cardiac Disease
New York Heart Association (NYHA) Functional Classification

- **I** – No limitation of physical activity
- **II** – Symptoms with ordinary physical activity, but no symptoms at rest
- **III** – Less than ordinary physical activity precipitates symptoms that markedly limit activity; no symptoms at rest
- **IV** – Symptoms with any physical activity & at rest

- **Group 1** – Minimal risk of complications (mortality <1%)
  - Atrial septal defect
  - Ventricular septal defect
  - Patent ductus arteriosus
  - Pulmonic/tricuspid disease
  - Corrected tetralogy of Fallot
  - Bioprosthetic heart valve
  - Mitral stenosis – NYHA class I and II
  - Marfan syndrome with normal aorta (root < 40mm)

• Group 2 – Moderate risk of complications (mortality 5-15%)
  – Mitral stenosis with atrial fibrillation
  – Artificial valve
  – Mitral stenosis – NYHA class III and IV
  – Aortic stenosis
  – Coarctation of aorta, uncomplicated
  – Uncorrected tetralogy of Fallot
  – Previous myocardial infarction *(2 week rule)
Previous MI – 2 week rule

- 1996 – retrospective review of 125 cases of acute MI in 123 pregnancies
  - Angina, ECG & enzymatic changes
    - 6 cases excluded
  - More common > 33 years of age, 3rd trimester
  - Maternal Mortality – 21%
    - Fetal death rate – 13%
    - Maternal death most often occurred at the time of infarct or within 2 weeks, often associated with the labor and delivery process
- Confirmed Hankins 1985 data on 68 cases

Martin 2004, Roth 1996
Table 2. Maternal Mortality in Relation to Duration of Pregnancy and Timing of Delivery in 68 Women Sustaining a Myocardial Infarction During Pregnancy or Delivery

<table>
<thead>
<tr>
<th>Pregnancy outcome</th>
<th>First trimester</th>
<th>Second trimester</th>
<th>Third trimester</th>
<th>Total</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. women</td>
<td>Deaths</td>
<td>No. women</td>
<td>Deaths</td>
</tr>
<tr>
<td>Died, undelivered</td>
<td>0</td>
<td>0</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Delivered within 14 days of initial infarction</td>
<td>1</td>
<td>1</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Delivered more than 14 days after initial infarction</td>
<td>8</td>
<td>0</td>
<td>12</td>
<td>0</td>
</tr>
<tr>
<td>Recurrent infarction</td>
<td>0</td>
<td>0</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td>Total</td>
<td>9</td>
<td>1</td>
<td>17</td>
<td>5</td>
</tr>
</tbody>
</table>

N=68, Hankins – 1985

- **Group 3** – Major risk of complications or death (mortality > 25%)
  - Pulmonary hypertension (correct diagnosis)
    - Eisenmenger’s syndrome
  - Coarctation of the aorta, complicated*
  - Marfan syndrome with aortic involvement (root >40mm)
  - Dilated cardiomyopathy
Pulmonary Hypertension

- Elevated pulmonary artery pressure with right ventricular failure
  - > 25 mmHg at rest with PA catheter (normal 8-20)
  - > 40 mmHg (estimated with echocardiography which requires an adequate tricuspid regurgitant jet) – limitations in diagnosis
    - Limitation during pregnancy
- Eisenmenger syndrome
**Pulmonary Hypertension**

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>30</td>
<td>27</td>
<td>17</td>
</tr>
<tr>
<td>Secondary</td>
<td>56</td>
<td>25</td>
<td>33</td>
</tr>
<tr>
<td>Associated with congenital heart disease*</td>
<td>36</td>
<td>73</td>
<td>28</td>
</tr>
</tbody>
</table>

* Includes cases with Eisenmenger syndrome.

Complicated Coarctation of the Aorta

- Uncorrected, with aneurysmal dilation or associated cardiac lesions such as pulmonary hypertension, VSD
- Functional class
  - Entering pregnancy at NYHA class > II
Marfan syndrome - 40 mm rule (Rossiter et al, 1995)

- N=45 pregnancies in 21 patients
- 1983-92; prospective study (Johns Hopkins)
Marfan syndrome

- Issues
  - aortic dissection
  - Risk for having a child with the syndrome (50%)
  - Risk for peripartum aortic dissection is especially high in women in whom aortic root dilatation is diagnosed before pregnancy
    - Normal root ≠ normal pregnancy
      - 350 unselected cases of Marfan syndrome the expected rate of aortic dissection is ~3%: 1% in patients with aortic root diameters <40 mm and 10% in patients with diameters >40 mm.

- Exclude dilated aortic root prior to pregnancy
- TEE or MRI preferred noninvasive assessment of dilation before and during pregnancy; avoid contrast aortograms for diagnosis of dissection due to risk of radiation to fetus
- Prophylactic use of beta-blockers - preventing aortic dilatation
- Surgery during gestation when root is 5-5.5cm

Elkayam 1995
Marfan syndrome

Elkayam 1995

• Issues
  – Mode of delivery
    • Vaginal delivery can be done in patients with the Marfan syndrome who do not have cardiovascular system abnormalities.
    • In patients with aortic dilatation, aortic dissection, or other important cardiac abnormalities, cesarean section should be the preferred method of delivery as labor may precipitate rupture of an aneurysm or aortic dissection

  – Offspring
Assessing the aortic root – MRI?
Echo?
(A) Parasagittal breath hold T1 magnetic resonance (MR) image showing pronounced dilatation of the aortic root with slight dilatation of the descending aorta in a young adult with Marfan syndrome.
Cardiac MRI vs echocardiography for assessing the aortic root

- Patient populations – Turner syndrome, Marfan syndrome, Ehlers-Danlos syndrome
- MRI and echo comparable for assessing aortic root and arch (N=75, Lanzarini 2007)
- Progression of normal root to dilated root in Turner syndrome patients - minimal change in 3yr study (Lanzarini 2007)
  - Lymphedema at birth predictor for change
- Patient with dilated root incidentally found?
should be avoided. Overall, the maternal mortality associated with Marfan syndrome is approximately 1% but increases to more than 20% in cases of aortic dissection.\textsuperscript{27,36}

Table 5. Risk of Dissection or Rupture Based on Aortic Root Size

<table>
<thead>
<tr>
<th>Aortic Root Diameter (cm)</th>
<th>Risk of Dissection or Rupture</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 4</td>
<td>1% during pregnancy</td>
</tr>
<tr>
<td>4 or more</td>
<td>10% during pregnancy</td>
</tr>
<tr>
<td>4.0–4.9</td>
<td>2% yearly rate</td>
</tr>
<tr>
<td>5.0–5.9</td>
<td>3% yearly rate</td>
</tr>
<tr>
<td>6 or more</td>
<td>7% yearly rate</td>
</tr>
</tbody>
</table>

CARPREG study

• Prospective multicenter study in women with heart disease (N=562 women, 599 pregnancies)

• During pregnancy - 4 predictors identified of ensuing cardiac event (heart failure, arrhythmia, TIA, stroke)
  – New York Heart Association Class III or greater
  – Left heart Obstruction (mitral valve <2cm²; aortic valve <1.5cm²; peak left ventricular outflow tract gradient >30mmHg)
  – Prior cardiac event before pregnancy
  – Ejection fraction <40%

• Should pregnancy be attempted if above are present - NOPE

(Siu 2001)
CARPREG study
Cardiac death rate – 1%

Table 1. Predictors of Major Cardiac Event in Pregnant Patients With Heart Disease*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Odds Ratio (95% Confidence Interval)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prior cardiac event or arrhythmia</td>
<td>6 (3–14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Transient ischemic attack</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke before pregnancy</td>
<td></td>
<td></td>
</tr>
<tr>
<td>New York Heart Association class greater than II or cyanosis</td>
<td>6 (2–22)</td>
<td>.009</td>
</tr>
<tr>
<td>Left heart obstruction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mitral valve area less than 2 cm²</td>
<td>6 (3–14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Aortic valve area less than 1.5 cm²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peak left ventricular outflow tract gradient greater than 30 mm Hg by echocardiography</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Systemic ventricular dysfunction</td>
<td>11 (4–34)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Ejection fraction less than 40%</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Major cardiac event=pulmonary edema, arrhythmia requiring treatment, stroke, cardiac arrest, cardiac death; 0 predictor=5% risk; one predictor=27% risk; two or more predictors=75% risk.


Frequency of maternal primary cardiac events, as predicted by the risk index and observed in the derivation and validation groups, expressed as a function of the number of cardiac predictors or points.
• Select lesions
Aortic Stenosis

• Definition – narrowing of aortic valve
  – Normal area of tricuspid aortic valve – 2-3 cm²
    • Severe stenosis when < 1.0 cm² or peak valvular gradient > 75 mmHg
  – Our patient – 0.9 cm² - original valve was a congenital stenotic bicuspid aortic valve
    • EF – 52%
      – Physical exam – SEM, systolic ejection ‘click’
      – Diagnosis with echocardiography

• Most common of rheumatic disease
• Congenital bicuspid valve represents 5% of all congenital cardiac lesions

(Clark 1987, 2003)
Aortic stenosis

- Inability to maintain CO can lead to sudden death
  - Vs mitral stenosis and fixed cardiac output
- Because hypovolemia (from blood loss, regional anesthesia, or supine venal caval occlusion) is a greater threat to the patient than pulmonary edema, ‘mild hypervolemia’ (CVP – 15-17 mm Hg) is the goal
  - Vs mitral stenosis where pulmonary edema is a greater risk, but tachycardia (regardless of etiology) can decrease the already fixed CO

- Overall mortality reported as high as 17%

(Clark 1987, 2003)
Aortic stenosis

• Preconceptional counseling
  – Strong consideration for surgical correction prior to attempting pregnancy
    • Valvular gradient > 75 mmHg
    • Left ventricular ejection fraction < 55%
    • Aortic valve area < 1.0 cm²
Heart Valves

- Mechanical – St. Judes
  - Long-lasting
  - Need for anticoagulation

- *Biologic - ‘bioprosthetic’, porcine
  - Less durable, no need for anticoagulation long term

http://my.clevelandclinic.org/heart/disorders/valve/valvetreatment.aspx
Indications For Anticoagulation

- Mechanical heart valve
  - Risk of thromboembolic event is significant enough to warrant life-long anticoagulation
  - Overall mortality – 3%

- Atrial fibrillation – common in patients with mitral stenosis

- NYHA class III or greater

- Eisenmenger syndrome

(Martin, Foley 2003)
Mechanical Heart Valves - Anticoagulation Options

- **Warfarin** – absolutely contraindicated according to manufacturer
  - Risk of miscarriage, pregnancy loss – 21-30%
    - Especially with use in the 1st trimester
  - Risk of anomalies (nasal, limb hypoplasia, epiphyseal stippling)
    - Greatest risk in 1st trimester – 8%
  - Risk of intracranial hemorrhage – cesarean section if delivery required before warfarin can be discontinued
- **Therapeutic goal** – INR 2.5-3.5

(Martin, Foley 2003)
Mechanical Heart Valves - Anticoagulation Options

- **Warfarin**
  - Use throughout gestation
  - VTE risk – 3.9%, risk of death 1.8%

- **Heparin**
  - Use throughout gestation
  - VTE risk – 25%, risk of death 6.7%

- **Combination of heparin in 1st/3rd trimesters and warfarin 13-36 weeks**
  - VTE risk 9.2%, risk of death 4.2%

(Chan review 2000; Martin, Foley 2003)
Elkayam 2005

- First-generation PHV (e.g., Starr-Edwards, Bjork-Shiley) in the mitral position, atrial fibrillation, history of thromboembolism on anticoagulation
- Warfarin (INR 2.5–3.5) for 35 wk
  followed by
  UFH (mid-interval aPTT >2.5) or LMWH (pre-dose anti-Xa \(\approx 0.7\)) + ASA 80–100 mg qd
- UFH (aPTT 2.5–3.5) or LMWH (pre-dose anti-Xa \(\approx 0.7\)) for 12 wk
  followed by
  Warfarin (INR 2.5–3.5) to 35th wk
  then
  UFH (mid-interval aPTT >2.5) or LMWH (pre-dose anti-Xa \(\approx 0.7\)) + ASA 80–100 mg qd
Elkayam 2005

- Second-generation PHV (e.g., St. Jude Medical, Medtronic-Hall) and any mechanical PHV in the aortic position.
- SC UFH (mid-interval aPTT, 2.0–3.0) or LMWH (pre-dose anti-Xa ≈ 0.6) for 12 wk
  
  *followed by*
  
  Warfarin (INR 2.5–3.0) for 35 wk
  
  *then*
  
  SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa ≈ 0.6)

- SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa ≈ 0.6) throughout pregnancy
American College of Chest Physicians

- **ANTITHROMBOTIC THERAPY FOR PROPHYLAXIS IN PATIENTS WITH MECHANICAL HEART VALVES**

1. Aggressive adjusted-dose UFH, q12h SC throughout pregnancy; mid-interval aPTT time maintained at >2× control levels, or anti-Xa heparin level maintained at 0.35 to 0.70 IU/mL OR

2. LMWH throughout pregnancy, in doses adjusted according to weight or as necessary to maintain a 4-h postinjection anti-Xa heparin level of about 1.0 IU/mL OR

3. UFH or LMWH, as above, until the 13th week; then change to warfarin until the middle of the third trimester, then restart UFH or LMWH therapy until delivery
Mechanical Heart Valves - Anticoagulation Options

- **Enoxaparin**
  - Black box warning from drug company in pregnancy in women with mechanical heart valves due to 2 maternal and 2 fetal deaths during a clinical research trial in patients receiving 80mg twice daily of Lovenox

(Martin, Foley 2003)
Patient on Warfarin Needing Emergent Delivery

- Vitamin K – 10 mg IV over 20-60 minutes
- Fresh frozen plasma as needed for continued bleeding despite vitamin K
- Cesarean delivery to prevent risk of fetal intracranial hemorrhage
Mitral Stenosis + Atrial Fibrillation
Another Indication for Anticoagulation

• Congenital mitral stenosis is rare – the most common valvular lesion from rheumatic heart disease is mitral stenosis

• Normal valve area – 4-5 cm²
  – No symptoms until < 2 cm²
  – Moderate stenosis – 1.0 – 1.5 cm²
  – Severe stenosis - < 1 cm²

• Maximize diastolic filling time (hypervolemia and rate control)
Cardiomyopathy – various forms

- Dilated – contraindication to pregnancy even if heart failure is compensated
  - 20% of cases genetic in origin
- Peripartum – 1 in 3000, heart failure in the ABSENCE of other causes
  - Risk present even if interval echo is normal
    - 20-50% risk of cardiac decompensation/death in subsequent pregnancies
- Idiopathic hypertrophic – dominant inheritance; sudden death is significant concern due to LVOT obstruction

- Vaginal delivery is best
Peripartum Cardiomyopathy

Although peripartum cardiomyopathy comprises less than 1% of cardiac events in pregnancy, it accounts for an increasing number of pregnancy-related deaths. The diagnosis is based on the following:

- cardiac failure in the last month of pregnancy or within 5 months postpartum
- no other identifiable cause of heart failure
- absence of heart disease before the last month of pregnancy
- left ventricular systolic dysfunction (left ventricular ejection fraction less than 45%)

Table 6. Outcome of Subsequent Pregnancies After Peripartum Cardiomyopathy

<table>
<thead>
<tr>
<th>History of Peripartum Cardiomyopathy</th>
<th>n</th>
<th>Congestive Heart Failure (%)</th>
<th>Maternal Mortality (%)</th>
<th>Preterm Delivery (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Normalization of left ventricle function</td>
<td>28</td>
<td>21</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>Nonnormalization of left ventricle function</td>
<td>16</td>
<td>44</td>
<td>19</td>
<td>37</td>
</tr>
</tbody>
</table>

Fetal Risk in Women With Cardiac Disease

- Small for gestational age – 20%
- Preterm birth – 20%
- Recurrence of congenital heart disease – 5-10%

CARPREG - Siu
2001
General Principles – Antepartum

- Cardiology, Anesthesia consults
- Frequent surveillance
- Attention to subtle changes in activity status, symptoms
- Fetal Echo exam if maternal congenital heart disease (risk of recurrence of CHD – 5-10%)
- Fetal growth surveillance, testing
- Anticoagulation
  - Therapeutic if mechanical heart valve, mitral stenosis with atrial fibrillation
  - Prophylactic anticoagulation in patients with pulmonary hypertension, Eisenmenger’s syndrome, class III/IV

(Foley 2003)
Cardiac Patient – Intrapartum Issues

- Fluid overload vs. cardiac under-perfusion
  - +/- pulmonary artery catheter
  - LiDCO – injection of lithium chloride to measure cardiac output using an arterial line
- Unable to measure central venous pressure

PA catheter no effect on mortality
1900+ ICU nonpregnant patients
(Conners 1996, Sandham 2003)
Indications for invasive monitoring in pregnancy

• Critical aortic stenosis (<1cm²) or mitral stenosis (<1.5cm²)
• Eisenmenger’s syndrome
• NYHA class III or IV cardiac disease

• Intraoperative or intrapartum cardiovascular decompensation
• Peripartum or perioperative coronary artery disease
• Refractory pulmonary edema or oliguria in the setting of severe PIH
• Unexplained or refractory pulmonary edema, heart failure or oliguria
• Normals –
• CO – 5.5 – 7.5 L/min
• CVP 4-10 mmHg
• PCWP – 6-12 mmHg
• SVR 1000-1400 dynes/sec/cm-5
• LVSWI 40-55 gM/m2
Cardiac Patient – Intrapartum Issues

• Labor in left lateral decubitus position, supplemental oxygen

• Anesthesia – epidural using lidocaine is [relatively] contraindicated in the following lesions:
  • Coarctation of aorta
  • Aortic stenosis
  • Tetralogy of Fallot (uncorrected)
  • Pulmonary hypertension
  • Idiopathic hypertrophic subaortic stenosis
  • Eisenmenger’s syndrome

• Assisted second stage
Anesthesia issues

- Controlled regional anesthetic may be preferred method
- Left sided lesions – avoid sudden drop in CO
- Important in controlling catecholamine release from pain
- Important for cardiac patients to consult with Anesthesia at least once in the antepartum period
Mode of delivery

- In general use cesarean for obstetrical indications
  - Surgery vs labor
  - Catecholamine release from surgery is just as or more physiologically stressful as labor and delivery
- Forceps delivery to decrease cardiac work
- CD – indications – recent MI, need for emergent delivery in patient on warfarin, Marfan syndrome >40mm/aneurysm
Indications for Cesarean

of choice in most cases. Despite the increased risks of hemorrhage, infection, and large fluid shifts, there are a few conditions in which labor is ill-advised and cesarean delivery is recommended:

- dilated aortic root (more than 4 cm) or aortic aneurysm
- acute severe congestive heart failure
- a history of recent myocardial infarction
- severe symptomatic aortic stenosis
- warfarin administration within 2 weeks of delivery
- need for emergency valve replacement immediately after delivery
Effect of Labor on Cardiac Output

Figure 3–9. Changes in cardiac output and stroke volume during normal labor. (From Hunter S, Robson S: Adaptation of the maternal heart in pregnancy. Br Heart J 68:540, 1992, with permission.)

(Hunter 1992)
Endocarditis Prophylaxis

• Recent change in AHA guidelines (2007)
  – Endocarditis is typically from ‘random bacteremia’ and not invasive procedures
  – Prophylaxis may prevent a small number of cases
  – Risks of antibiotic associated adverse events

• Delivery – vaginal or cesarean
  – Propylaxis is recommended if active infection (pyelonephritis, chorioamnionitis) is present AND a high risk cardiac condition is present

AHA 2007, ACOG 2008
High-Risk Cardiac Conditions For Which Endocarditis Prophylaxis is Reasonable

- Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
- History of endocarditis
- Congenital Heart Disease
  - Unrepaired cyanotic CHD, including palliative shunts and conduits
  - Completely repaired CHD with prosthetic material
  - Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
- Cardiac transplantation patients with valve disease

ACOG 2008
SBE prophylaxis regimens

- **No PCN allergy** – Ampicillin 2g IV or Cefazolin/ceftriaxone 1g IV 30-60 min before procedure
- **PCN allergy** - Cefazolin/ceftriaxone 1g IV if no significant sensitivity; clindamycin 600mg IV 30-60 min before procedure
  - If enterococcus a concern, vancomycin 1gm IV over 1-2 ours before procedure
- **Oral** (recommendation is for IV route) – amoxicillin 2g PO 30-60 minutes before procedure

AHA 2007, ACOG 2008
Preconception Counseling
Fig. 1. Preconception assessment.
### Table 7. Congenital Heart Disease: Estimated Risk of Cardiac Complications in Pregnancy

<table>
<thead>
<tr>
<th>High Risk of Complications or Death</th>
<th>Moderate Risk of Complications (5–15%)</th>
<th>Low Risk of Complications (Less Than 1%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Left-to-right shunt with pulmonary hypertension</td>
<td>Mild-to-moderate aortic stenosis</td>
<td>Isolated atrial septal defect, repaired or un repaired</td>
</tr>
<tr>
<td>Reversal of shunt with Eisenmenger’s syndrome</td>
<td>Marfan syndrome with normal aorta</td>
<td>Isolated ventricular septal defect, repaired or un repaired</td>
</tr>
<tr>
<td>Marfan syndrome with aortic root dilation</td>
<td>Unrepaired cyanotic defects such as tetralogy of Fallot</td>
<td>Pulmonic or tricuspid valve disease</td>
</tr>
<tr>
<td>Coarctation of aorta, uncorrected with proximal aortic dilation</td>
<td>Systemic right ventricle such as complete and congenitally corrected transposition of great arteries</td>
<td>Coarctation, repaired with normal proximal aortic size</td>
</tr>
<tr>
<td>Severe symptomatic left-sided obstructive lesions such as aortic stenosis, hypertrophic cardiomyopathy</td>
<td>Well-functioning Fontan palliation for hypoplastic ventricles, complex defects</td>
<td>Repaired tetralogy of Fallot with normal right ventricular function and competent pulmonic valve</td>
</tr>
<tr>
<td>Palliated tetralogy of Fallot with severe pulmonic regurgitation and right ventricular dysfunction</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Conclusions

- Risk assessment
- Contraindications to pregnancy –
  - NYHA Class III or greater
  - Left heart Obstruction (mitral valve >2cm; aortic valve >1.5cm; peak left ventricular outflow tract gradient >30mmHg)
  - Prior cardiac event before pregnancy
  - Ejection fraction <40%
  - 3 No, no’s - Marfan > 40mm, complicated aortic coarctation, pulmonary hypertension
Conclusions

- Anesthesia issues
- Mode of delivery – vaginal best in most cases
- Anticoagulation if necessary
- Recurrence of congenital cardiac disease 5-10%
- Change in endocarditis prophylaxis
Cardiac disease in pregnancy above
END – above sent PDF 1-13-16
Genetic principles continued
You perform a CVS at 13 weeks gestation on your patient because of advanced maternal age (she is 38 years of age). The report from the cytogenetics laboratory is: 47,XY,+15/46,XY. Then you perform a high level ultrasound and an amniocentesis at 16 weeks. The ultrasound is normal and only cells with a 46,XY karyotype are found. Because of these results, you order a methylation analysis of chromosome 15 on the amniocyte DNA? Why? What is the chance that the methylation analysis will be abnormal? What would the physical characteristics be, if the methylation pattern was abnormal?

- **a-** Methylation studies of amniocyte DNA were done to check for uniparental disomy from possible trisomic rescue post-fertilization.

- **b-** Chance that methylation status is abnormal and is likely due to nondisjunction of maternal meiosis I is 33% - meaning that there is 1/3 chance that the 1 of the 3 chromosome 15s is rescued (loss of a paternal chromosome 15 from a conceptus with chromosome 15 trisomy due to maternal meiosis I nondisjunction (80% - slide 81/104 - Mitosis/Meiosis errors lecture Dr. Moore), not present. If the paternal 15 chromosome is knocked out - then the 2 remaining maternal 15s would have an inactive region (15q11-q13) that would give rise to Prader Willi syndrome (hypotonia, feeding difficulties, hypogonadism, then later in life hyperphagia, marked obesity
1. (2 pts) What is the most likely mode of inheritance in this pedigree? Affected individuals have reported migraine headaches or seizures, muscle weakness and/or cardiac disease. What is the chance that individual III-7 will have affected children?

-a- Mode of inheritance is maternal inheritance of mitochondrial DNA mutation; 
-b- chance that III-7 will have affected children (assuming no consanguinity higher in the pedigree) is essentially zero as this is a maternal inheritance disorder and the mitochondrial DNA is passed through maternal lineage, not paternal, so III-7 should not have affected children because she does not carry the mitochondrial DNA that is abnormal from her father, she inherits it from her normal mother and her mother and her siblings are unaffected suggesting it is isolated to the left side of the pedigree (maternal inheritance).
Fragile X, CF, spinal muscular atrophy
Fragile X

• X-linked mental retardation disorder; mutation in the FMR1 gene on Xq27.3
• 16-25 per 100,000 in general male population
  – 8 per 100,000 in general female population
  – Accounts for 3-6% of MR among boys with a +FHX of MR and no birth defects
• FMR1 gene product is FMRP (expressed in many cell types – mostly in neurons; may chaperone a subclass of mRNAs from the nucleus to the translational machinery
• More than 99% of FMR1 mutations are expansions of a (CGG)n repeat sequence in the 5’ untranslated region of the gene; > 200 repeats results in hypermethylation of the CGG repeat sequence and the adjacent FMR1 promoter; this inactivates the FMR1 promoter, causing a loss of FMRP expression
Fragile X – major phenotypic features

- Age at onset – childhood
- Mental deficiency
- Dysmorphic facies
- Male postpubertal macroorchidism

- Fragile site at Xq27.3 – located in 5’ untranslated region of the first exon of a gene called FMR1 (fragile X mental retardation 1)
# Fragile X syndrome

### Table 1. Mutation in the Fragile X Mental Retardation 1 Gene

<table>
<thead>
<tr>
<th>Status of Individual</th>
<th>Number of Triplet Repeats (Cytosine–Guanine–Guanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Less than 40</td>
</tr>
<tr>
<td>Intermediate (also called &quot;grey zone&quot;)</td>
<td>41–60</td>
</tr>
<tr>
<td>Premutation</td>
<td>61–200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>More than 200</td>
</tr>
</tbody>
</table>

ACOG committee opinion 2006
Fragile X syndrome

- CVS pitfall
- Fragile X syndrome - X-linked recessive
- Expansion of repeated trinucleotide segment of DNA (cytosine–guanine–guanine, CGG) that leads to altered transcription of the fragile X mental retardation 1 (FMR1) gene.
- # of repeats varies – 4 groups - unaffected, intermediate, premutation, full mutation
  - 61–200 repeats - phenotypically normal, premutation
  - This condition occurs because the large number of repeats causes the FMR1 gene to become methylated and inactivated in these patients.
  - The number of repeats and the status of gene methylation are determined by use of DNA-based molecular tests (eg, Southern blot analysis and polymerase chain reaction).
  - Chorionic villus sampling (CVS) - reliable for determining the number of triplet repeats, may not be reliable for diagnosis because of gestational age differences in ultimate methylation patterns in the trophoblast and may not adequately determine the methylation status of the FMR1 gene.
  - DNA methylation is a process that controls tissue specific gene expression. Methylation "turns off" the regulatory region of a gene, thereby preventing DNA transcription. Rarely, the size of the triplet repeat and the methylation status do not correlate, making prediction of the clinical phenotype difficult.
Fragile X syndrome

- Triplet repeat expansion – massive expansion nearly always occurs during female gametogenesis; Normal number of repeats up to 60; several thousand occur in fragile X; > 200 copies of the repeat lead to excessive methylation of cytosines in the promoter of FMR1; this interferes with replication or chromatin condensation or both, producing the characteristic chromosomal fragile site, a form of DNA modification that prevents normal promoter function or blocks translation.

- Somatic mosaicism- a mutation affecting morphogenesis and occurring during embryonic development might be manifested as a segmental or patchy abnormality, depending on the stage at which the mutation occurred and the lineage of the somatic cell in which it originated – ex: NF1 is sometimes segmental, affecting only one part of the body. Segmental NF1 is caused by mosaicism for a mutation that occurred after conception. In such cases the patient has normal parents, but if he or she has an affected child, the child’s phenotype is typical for NF1, that is, not segmental. In such cases, the mutation has to be in the patient’s gametes and therefore must have occurred before separation of germline cells from the somatic cell line that carries the mutation.
Fragile X

- Sex-specific anticipation – Every child of an affected mother has a more severe form than the mother did, may only have a mild expression of the disease and may not know she is affected
- DNA methylation – the major form of DNA modification in the human genome involves methylation of cytosine residues (to form 5-methylcytosine), specifically when they are located immediately 5’ to a guanine (i.e. as the dinucleotide 5’-CG-3’). Hotspot for mutation in the human genome as it upstream from coding exons
- Haplotype effect – a given set of alleles at a locus or cluster of loci on a chromosome is referred to as a haplotype; the set of HLA alleles at the different class I and class loci on a given chromosome together from a haplotype; risk of premutation expansion to a full mutation increases as the repeat length of the premutation increases. Not all premutations, however, are equally predisposed to expand. Although premutations are relatively common, progression to a full mutation has been observed only on a limited number of haplotypes; that is, there is a haplotype predisposition to expansion. This haplotype predisposition may relate partly to the presence of a few AGG triplets embedded within the string of CGG repeats; these AGG triplets appear to inhibit expansion of the string of CGG repeats, and their absence in some haplotypes, therefore, may predispose to expansion
Fragile X syndrome

- Committee on Genetics recs re: testing for fragile X:
  - DNA-based molecular test (Southern, PCR)
    - In rare cases where there is discordancy between the triplet repeat number and the methylation status, the patient should be referred to a genetic specialist.
  - + FHx, or hx of fragile X MR – genetic counseling, offered genetic testing to assess risk for having an affected child.
- Prenatal testing for fragile X syndrome by amniocentesis or CVS should be offered to known carriers of the fragile X premutation or mutation. Although it is reliable for determining the number of triplet repeats, CVS may not adequately determine the methylation status of the \( FMR1 \) gene.
- Testing for fragile X syndrome should be considered in any child with developmental delay of uncertain etiology, autism, or autistic-like behavior or any individual with mental retardation of uncertain etiology.
- If a woman has ovarian failure or an elevated follicle-stimulating hormone level before the age 40 years without a known cause, fragile X carrier screening should be considered to determine whether she has a premutation.
Fragile X syndrome
CF – major phenotypic features

- Age at onset – neonatal to adulthood
- Progressive pulmonary disease
- Exocrine pancreatic insufficiency
- Obstructive azoospermia
- Elevated sweat chloride concentration by pilocarpine iontophoresis
  - Normal - <40 mmol/L
  - Indeterminate – 40-60 mmol/L
  - Elevated - >60 mmol/L
- Growth failure
- Meconium ileus
Cystic Fibrosis – ACOG info

- Cystic fibrosis is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, gastrointestinal, biliary, and reproductive systems. Individuals with cystic fibrosis typically present with cough, wheezing, failure to thrive, loose stools, abdominal pain, and, in males, infertility secondary to congenital bilateral absence of the vas deferens. Treatment involves pancreatic enzymes, proper nutrition, and respiratory therapy with aggressive treatment of infection. The current median survival is approximately 30 years, and the cause of death usually is respiratory failure. Approximately 15% of individuals with cystic fibrosis are pancreatic sufficient and have a milder disease course and a median survival of 56 years.

- Cystic fibrosis is an autosomal recessive genetic condition. Therefore, when a patient and her partner are both carriers of a mutation in the cystic fibrosis gene, they have a one-in-four chance of having a child with cystic fibrosis. More than 1,300 mutations have been identified in the gene for cystic fibrosis, but screening for 23 common mutations is available and can reduce a couple's risk for having a child with cystic fibrosis. The risk of being a carrier depends on an individual's ethnicity and family history.
• Disease etiology and incidence, pathogenesis
  • Autosomal recessive; disorder of epithelial ion transport caused by mutations in the CF transmembrane conductance regulator gene (CFTR)
    – cAMP-regulated chloride channel that regulates other channels; maintains hydration of secretions in airways and ducts that secrete mucus – resp tract, pancreas, biliary system, male genitalia, intestine, sweat glands
• Live birth incidence – 1 in 313 (Alberta, Canada)
  • 1 in 90000 among Asian pop in Hawaii
  • 1 in 3200 among all US whites
  • Typically diagnosed in childhood
• Median survival 33 years old (depends on progression of lung disease)
  – Most patients die of respiratory failure and right ventricular failure secondary to the destruction of lung parenchyma and high pulmonary vasuclar resistance (cor pulmonale);
• 5-15% do not have pancreatic insufficiency; 95% of male patients are azospermic (CBAVD)
• Management – accurate diagsosis; symptomatic management, control of infection, pancreatic enzymes, nutrition; lung transplant
• Inheritance risk – if no family history and are northern European descent – 1 in 29; couple’s risk of an affected child is 1 in 3200; for couples with an affected child, this risk for future children being affected is 1 in 4
• ‘Prenatal diagnosis is based on identification of the CFTR mutations in DNA from fetal tissue, such as chorionic villi or amniocytes. Effective identification of affected fetuses usually requires that the mutations responsible for CF in a family have already been identified.’ Nussbaum

CF (Nussbaum p 252)
Cystic fibrosis

- Ethnic variation - table; differences in frequencies of alleles that cause genetic disease; reason why you can check a panel of allele mutations in 1 population and cut the risk of being carrier substantially, but in another population, the panel is different and larger; other ex is in North America, when persons of Mediterranean descent are at risk of having a child with B-thalassemia, testing of parental DNA for just seven mutant alleles has more than 90% probability of providing the information needed for prenatal diagnosis.

- Variable expressivity - severity of expression of the phenotype among individuals with the same disease-causing genotype; when the severity of disease differs in people who have the same genotype the phenotype is said to have variable expressivity; even in the same kindred, 2 individuals carrying the same mutant genes may have some signs and symptoms in common, whereas their other disease manifestations may be quite different, depending on which tissues or organs happen to be affected.

  - Vs penetrance which is present or not – if there is ANY demonstration of some sign of the disease then it’s said to be penetrant (neurofibromatosis – all individuals have penetrance, but there is variable expression.)
CF – genetic principles

- Tissue-specific expression of mutations (lung, pancreas, GI tract, reproductive tract); some patients present with slow growth, chronic respiratory disease, malnutrition due to pancreatic insufficiency, infertility due to congenital bilateral absence of the vas deferens.

- Genetic modifiers: correlation between particular CFTR mutant alleles and disease severity exists only for pancreatic insufficiency; secondary mutations or polymorphisms within a CFTR allele may alter the efficiency of splicing or protein maturation and thereby extend the spectrum of disease associated with some mutations; in addition, some mutations in CFTR cause disease manifestations only in certain tissues; for example, some mutations affecting the efficiency of splicing have a greater effect on wolffian duct derivatives than in other tissues because of a tissue-specific need for full-length transcript and protein.

- Environmental modifiers: ex – cigarette smoke exposure markedly worsens the severity of lung disease among patients with CF.
### Cystic Fibrosis

#### Table 1. Cystic Fibrosis Detection and Carrier Rates Before and After Testing

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<tr>
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ACOG committee opinion 2006
CF committee on Genetics recs

- Information about cystic fibrosis screening should be made available to all couples. It is reasonable to offer cystic fibrosis carrier screening to all couples regardless of race or ethnicity as an alternative to selective screening.

- Cystic fibrosis carrier screening should be offered before conception or early in pregnancy when both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity. Patients may elect to use either sequential or concurrent carrier screening; the latter option may be preferred if there are time constraints for decisions regarding prenatal diagnostic testing or termination of the affected pregnancy.

- For individuals with a family history of cystic fibrosis, medical records indicating the CFTR mutation in the affected family member should be obtained whenever possible. If the mutation has not been identified, screening with an expanded panel of mutations or, in some cases, complete analysis of the CFTR gene by sequencing may be indicated. Genetic counseling in this situation usually is beneficial.

- Individuals who have a reproductive partner with cystic fibrosis or congenital bilateral absence of the vas deferens may benefit from screening with an expanded panel of mutations or, in some cases, a complete analysis of the CFTR gene by sequencing.

- When both partners are cystic fibrosis carriers, genetic counseling is recommended to review prenatal testing and reproductive options. Prenatal diagnosis by chorionic villus sampling or amniocentesis, using DNA-based testing of the fetal cells, should be offered. If the partner is unavailable for testing, genetic counseling may be helpful.

- Cystic fibrosis carrier screening may identify individuals with two cystic fibrosis mutations who have not previously received a diagnosis of cystic fibrosis. These individuals may have a milder form of cystic fibrosis and should be referred to a specialist in cystic fibrosis for further evaluation. Genetic counseling also is beneficial.
Cystic Fibrosis
Spinal muscular atrophy

• Accepted criteria that a candidate disease should meet before widespread screening is instituted
  • the disease significantly impairs health in the affected offspring;
  • there is a high frequency of carriers in the population to be screened;
  • technically and clinically valid screening methods are available to the population, and screening is cost-effective;
  • testing is voluntary, and informed consent and pretest and posttest counseling are available and effective;
  • fetal testing is available for couples whose screening results are positive and reproductive options are readily available in a time-sensitive manner.

• In addition to these well-accepted criteria, it is imperative that any screening program be carried out in a manner by which a patient’s privacy is protected so that risks of discrimination and stigmatization in the community are minimized. Nevertheless, public awareness campaigns regarding the disease and carrier screening availability will enhance knowledge of SMA and SMA testing in the prenatal population. This may lead to patients requesting SMA carrier testing.
Spinal muscular atrophy

• Spinal muscular atrophy (SMA) - autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness.

• - caused by a mutation in the gene known as the survival motor neuron gene (SMN1), which is responsible for the production of a protein essential to motor neurons.
Spinal muscular atrophy

- Complex genetics, limitations in molecular diagnostic assays available, accurate prediction of the phenotype in affected fetuses may be not be possible.
- Incidence - 1 in 10,000 live births
- Leading genetic cause of infant death
- Carrier frequencies are estimated at 1 in 40-60
- No effective treatment
- Types 1-3
  - Type I – most severe ; (Wernig–Hoffman), has symptomatic onset of the disease before 6 months of age and death from respiratory failure within the first 2 years of life.
  - Type II, most common form of SMA disease, ; intermediate severity; onset <2 yr old; Affected children are able to sit but few are able to stand or walk unaided. Respiratory insufficiency is a frequent cause of death during adolescence; life expectancy is 2 years to 20s;
  - Type III (Kugelberg–Welander), ; mild form ; onset >18months old ; variable sx profile; most reach major motor milestones, but function ranges from requiring wheelchair assistance in childhood to completely unaided ambulation into adulthood with minor muscular weakness. Many patients have normal life expectancies. There are other forms of SMA-like disorders with similar symptoms as those described previously, but they are linked to genes other than SMN1.
Spinal muscular atrophy

- **Molecular Genetics**
- 2 nearly identical survival motor neuron genes present in humans, SMN1, SMN2
- SMN1 is considered the active gene for survival motor neuron protein production and more than 98% of patients with SMA have an abnormality in both SMN1 genes, which can be caused by a deletion (95%), or other mutation.
- There is generally one, but occasionally two, copies of SMN1 per chromosome and a variable number of SMN2 gene copies (ranging from zero to three).
- SMN2 gene does not produce much in the way of functional survival motor neuron protein. However, the primary genetic feature, which determines the severity of SMA, appears to be the number of gene copies of SMN2 in a given individual. Studies have shown that a higher number of SMN2 copies correlates with generally milder clinical phenotypes.
- The modulation of clinical severity due to variable copy numbers of SMN2 is the result of a small amount of full-length survival motor neuron transcripts and the protein generated by SMN2.
- This protein product can partially compensate for the complete absence of protein from the SMN1 alleles. However, accurate prediction of the SMA phenotype based on SMN2 copy number is not possible. Although most of the population has one to three copies of SMN2, approximately 15% of normal individuals have no SMN2 gene.
Spinal muscular atrophy

- **DNA Assay**

- For diagnosis of SMA, it is sufficient to simply detect the classic SMN1 deletion using DNA analysis in both SMN1 alleles.
  - 95% sensitive (100% specific) for pt with SMA symptoms
  - Not sufficient for ID of heterozygotes/carriers for SMN1 deletion
  - Carrier testing requires a quantitative PCR assay that provides a measure of SMN1 copy number. Detection of a single normal copy of SMN1 would indicate the carrier state.
  - Limitations of this assay to determine carrier status
  - ~3-4% of the general population, having two SMN1 copies on one chromosome and no copies on the other, will be incorrectly identified as being negative, or not carriers of SMA.
  - These individuals are carriers because one of their chromosomes is missing the SMN1 allele.
  - Another 2% of the general population has SMN1 mutations that are not detectable by the polymerase chain reaction method of SMN1 dosage analysis.
  - Therefore, the counseling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from SMA affected families.
Spinal muscular atrophy

• Carrier Screening

• In current practice, patients with a family history of SMA are being offered carrier screening for the SMN1 deletion mutations. Recent marketing and public awareness campaigns by laboratories and advocacy organizations are promoting widespread population-based carrier screening for SMA in the prenatal or preconception setting, regardless of family history.

• Proponents of testing (American College of Medical Genetics) of carrier screening in general population because of severity of the disease and relatively high carrier frequency, as well as the advent of improved DNA diagnostic assays for mutations in the disease causing gene (SMN1).

• The American College of Medical Genetics has recently recommended offering carrier testing to all couples regardless of race or ethnicity (1). However, to date, no pilot studies have been completed in the United States that would determine best practices for pretest and posttest education and counseling with specific regard to SMA screening. In addition, there have been no studies to date to determine patient preferences and utility measures that would allow the completion of an analysis of the cost-effectiveness of widespread carrier screening for SMA.
Spinal muscular atrophy

- However, the American College of Obstetricians and Gynecologists’ Committee on Genetics agrees that preconception and prenatal screening for SMA is not recommended in the general population at this time.
Review select diseases that illustrate genetic principles
ADRENAL

http://ocw.tufts.edu/data/14/265915/132195_medium.jpg
Congenital adrenal hyperplasia - Overview

- CAH – Deficiency of enzymes of cortisol production; most due to 21α-hydroxylase deficiency; cortisol is not produced (adrenal hyperplasia due to ACTH stimulation); >100 different mutations of CYP21A1 have been reported (Forrester 2004)
  - precursors proximal (17-OHP accumulates b/c it does not get converted to 11-deoxycortisol) to the block are produced in excess as are products of other pathways (testosterone production results in virilization of female fetuses)
- Incidence – 1 in 12,500 (Nussbaum, p110)
- Diagnosis – 17OHP – classic (>20,000 ng/dL), non-classic (2-15,000ng/dL);
  - normal newborn 10-20ng/mL (Forest 2004);
  - TEXAS premature cohort – EFW >2500g (>40ng/mL); if <2500g (>65ng/mL) due to functional peak at 29 weeks (White 2000)
  - Plasma renin activity – markedly elevated in salt-wasting form, less so in simple virilizing form (OMIM)
Adrenal gland steroid biosynthesis

Cholesterol

Pregnenolone

\[17\alpha\rightarrow\]

17-hydroxypregnenolone

\[3\beta\rightarrow\]

Progesterone

\[17\alpha\rightarrow\]

17-hydroxyprogesterone

\[17,20\rightarrow\]

Androstenedione

DHEA

\[3\beta\rightarrow\]

SL

DHEAS

\[\rightarrow\]

SK

21 alpha hydroxylase

Deoxycorticosterone

\[11\beta\rightarrow\]

Corticosterone

\[18\rightarrow\]

Aldosterone

11-deoxycortisol

\[11\beta\rightarrow\]

Cortisol

Dihydrotestosterone

\[5\alpha R\rightarrow\]

Estradiol

\[17\beta R\rightarrow\]

Estrone

\[A\rightarrow\]
<table>
<thead>
<tr>
<th>Enzyme deficiency</th>
<th>Salt-wasting (hypoaldost induced lose Na, cannot excrete K)</th>
<th>HT N</th>
<th>Female external genitalia at birth?</th>
<th>Male external genitalia at birth</th>
<th>Post-natal virilization</th>
</tr>
</thead>
<tbody>
<tr>
<td>21α hydroxylase</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>classic form</td>
<td>Yes</td>
<td>No</td>
<td>Ambiguous</td>
<td>Male</td>
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<tr>
<td>simple virilizing</td>
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<td>No</td>
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<tr>
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<td>No</td>
<td>Female</td>
<td>Male</td>
<td>Yes</td>
</tr>
<tr>
<td>11-β hydroxylase</td>
<td>No</td>
<td>Yes</td>
<td>Ambiguous</td>
<td>Male</td>
<td>Yes</td>
</tr>
<tr>
<td>3β hydroxysteroid dehydrog</td>
<td>Yes</td>
<td>No</td>
<td>Mild virilization</td>
<td>Ambiguous</td>
<td>Yes</td>
</tr>
</tbody>
</table>
CAH – genetic principles

- Gene map locus – 6p21.3 (OMIM) – gene CYP21A2
- Inheritance/recurrence risk - Autosomal recessive implications – 25% risk of affected offspring, 50% risk of carrier offspring
  - 1% of mutations occur de novo
CAH and Pregnancy - prenatal testing and tx for fetuses at risk for 21OHD CAH, panel of cyp21A2 mutations available for testing OMIM, Genetest review 2009 (Nimkarn 2009)
Adrenal hyperplasia – thefetus.net

- Suchet MD, 2006 Canada
- female fetus with an adrenal hyperplasia. The mother received steroids during the gestation to prevent virilization. The baby was born without any sign of ambiguous genitalia. The final diagnosis was a congenital adrenal hyperplasia due to 21-hydroxylase deficiency. – bilateral adrenal hyperplasia
SEX CHROMOSOME, GONADAL ABNORMALITIES
-if Y (TDF, SRY) present, medullary tissue forms testes, seminiferous tubules, Leydig cells which secrete androgens (HCG helps) to support male development, mitosis of primordial germ cells, etc.

- if no Y, gonad develops into ovary by 8th week, cortex develops, medullary region regresses, oogonia develop in follicles - oogonia meiosis I begins (12wk), then arrests in dictyotene (M1) until ovulation occurs many years later.

**GONADS - Ovarian, Testicular Development** 
(Nussbaum p100)

by 6 weeks – migration to gonadal ridges, surrounded by sex cords; bipotential gonads regardless of XX, XY; -ovarian vs testis depends on Y chromosome (TDF/SRY gene), if present diverts development into male pathway.
Female, male differentiation

- Normal male differentiation –
  - Leydig cells produce testosterone (6-7 wks)
  - Sertoli cells produce anti-Mullerian [protein] hormone (AMH; also known as Mullerian Inhibiting Factor) at 8 weeks

- AMH – involution of Mullerian duct system; allows development of the Wolffian ducts into male internal genitalia
  - IF no AMH, Mullerian ducts develop into female internal genital organs
Male factors

- Sperm development
  - AZF gene in formation of sperm
  - Severe oligo/azoospermia
  - Y chromosome deletions
- Klinefelter syndrome (XXY)
- XYY syndrome
- Androgen insensitivity
Y chromosome – and disorders of sexual differentiation (figure 6-10, Nussbaum, p101)

Pseudoautosomal region of X and Y chromosomes – pairing segment (identical on X, Y) undergoes homologous recombination in meiosis I

Y – 50 genes
AZF in formation of sperm

- AZF – ‘azospermia factors’ – located on Y chromosome –
- 3 overlapping regions on Yq (AZFa, AZFb, and AZFc)
- Deleted in azospermia (DAZ - deleted in azospermia) – AZFc region contains the DAZ genes that encode RNA-binding proteins expressed only in the premeiotic germ cells of the testes
- De novo deletions of AZFc arise in 1 in 4000 males and are mediated by recombination b/n long repeated sequences – give rise to azospermia but mechanism is not completely known

(Nussbaum p110)
Severe oligo/azoospermia & Y chromosome deletions

• 2% of healthy males have severe oligospermia/azospermia (Significant proportion due to de novo deletions or mutations)

• Y-linked genes in spermatogenesis –
  – interstitial deletions in Yq have been associated with at least 10% of cases of nonobstructive azoospermia (no detectable sperm in semen) and with 6% of cases of severe oligospermia
  – an example of a de novo point mutation has been described in one Y-linked gene, USP9Y, the function of which is unknown but appears to be needed for normal spermatogenesis
  – men with idiopathic infertility - karyotype, Y chromosome testing for mutations/deletions should be offered before initiation of assisted reproduction (to detect Y chromosome deletions/mutations)

(Nussbaum p110)
Androgen insensitivity; X-linked (AR gene on Xq11-q12); 1 in 20,000

- **Diagnosis** - 46,XY, infertile female; female external genitalia, blind vaginal pouch, no Mullerian structures; sparse axillary/pubic hair; gonads (testicles) present in abdomen or inguinal canal; breast development; serum testosterone (male level) (OMIM AIS, Gotlieb)

- **Pathogenesis** – testes secrete androgen normally, but NO androgen receptors in end organs thus no complex with testosterone/DHT (transcription of target genes required for male differentiation does not occur);
  - **Mutation** – complete AR gene deletion or point mutation

- **Counseling** – Carrier females – 50% risk of transmitting the AR gene mutation; DNA testing for AR gene possible
Androgen insensitivity (wikipedia, google images)
Klinefelter’s syndrome (47, XXY)

- **Phenotype** – Tall male, infertile, Gynecomastia development greatly increases breast cancer risk
- **Nondisjunction error of paternal M1 (51%); maternal meiosis (34%)** postzygotic mitotic errors leading to mosaicism (15%) (Moore, c10, s92; Nussbaum, p107)
  - Failure of Xp/Yp recombination in the pseudoautosomal region
  - Variants with increasing numbers of X chromosomes have greater degrees of dysmorphism, defective sexual development, MR
- **Counseling - Recurrence risk** – 1% or age related risk

1 in 1000 male live births

XYY syndrome

- 47,XYY – incidence 1 in 1000 among male live births
- Male phenotype not obviously abnormal from 46,XY individuals
- Origin of error – paternal meiosis II nondisjunction error that produces YY sperm (Moore, c10, s94; p107 Nussbaum)
  - Less common XXYY, XXXYY share features of Klinefelter’s (47,XXY) and XYY also due to nondisjunction error of paternal M1, M2
  - Developmental delays, normal fertility
  - Behavioral abnormalities of hyperactivity, impulsiveness, NOT aggressive psychopathological behavior (Nussbaum p107)
- Counseling - Recurrence risk – 1%
Gonadal dysgenesis

- **Swyer syndrome** – 46,XY complete gonadal dysgenesis
  - Phenotypically female (uterus, fallopian tubes, female external genitalia present), lack of secondary sexual characteristics, no menstruation, streak gonads (OMIM – Swyer 1955)
  - Gonadal neoplastic risk – 25% - reason to remove gonads (gonadoblastomas and dysgerminomas)
  - One form of the disorder - due to mutations in the SRY gene (Yp11.3) (OMIM)
  - Inheritance, recurrence risk – de novo mutations, general population risk
Female factors

- 45,X
- Multiple X syndrome
- Premature ovarian failure
Female factors

- Turner syndrome (45,X) →
  - Complete/partial absence of 2nd X chromosome
  - 1 in 4-5,000 female live births; 1-2% of all conceptuses; 99% abort; make up 25% of first trimester spontaneous abortions (Moore,c10,s19)
  - Error is paternal nondisjunction (70%), maternal (30%); (Moore,c10,s77)
  - Clinically – short stature, webbed neck, gonadal dysgenesis, characteristic facies, renal/CV abnormalities (hypoplastic left heart syndrome, coarctation of the aorta); 10% with mild MR
  - Counseling - Recurrence risk – nominal -1% or age related risk
Case – 45,X

- 26 yo P0 at 13 weeks seen in consultation for cystic hygroma;
- Amniocentesis at 15+ weeks – karyotype – 45,X
Female factors

- Multiple X syndrome
  - Trisomy X (47,XXX) – 1/1000 female births, slightly above average stature; normal puberty; increased risk of chromosomally abnormal offspring (p107, Nussbaum); 70% with learning disability; severe psychiatric disease is rare
  - Nondisjunction Error in maternal meiosis 1 - 78% are maternal M1 events (Moore, class 10/slide 77)
  - X chromosome inactivation (2 of X chromosomes are inactivated, but more likely for some of the material on the extra X chromosomes to not be inactivated) (p108 Nussbaum)
  - Recurrence risk – 1% or age-related risk
Female factors - Premature ovarian failure

- Cessation of ovarian function before age 40 (FSH>30 mIU/mL)
- Incidence - 1% of women
- Etiology – idiopathic (majority), infection, autoimmune, radiation, chemotherapy
- CGG trinucleotide premutation carrier (Fragile X syndrome carrier; 60-200 CGG repeats)
  - Risk of POF – 20% (Saul, OMIM)
  - No risk with full mutation (>200 repeats)
  - No consensus on risk of women with high normal or intermediate # of CGG repeats (30-60 repeats)
  - Suggestion that FMR1 gene plays a role in menopause

Bankowski p 402
Development of Male and Female Internal Genitalia

OUTFLOW TRACT & CF

Ostrer 2008 – Genereview, OMIM
CBAVD (Outflow tract) & Cystic Fibrosis

• Congenital bilateral absence of the vas deferens (CBAVD)

• Diagnosis of CFTR-related CBAVD in males established by obstructive azoospermia (due to lack of Wolffian duct structures), low volume of ejaculated semen, absence of vas deferens on clinical or ultrasound examination, and at least one disease-causing mutation in CFTR

• Patients with CF - Infertility/obstructive azospermia - > 95% of male infants with CF have azospermia due to CBAVD

• Male infertility - CBAVD - accounts for 1-2% of male infertility; ~80% of men with CBAVD have at least 1 mutation in CFTR gene (OMIM, Moskowitz)
EFFECTS OF CYSTIC FIBROSIS
Multisystem disease

- Severe chronic bacterial infection of airways
- Severe hepatobiliary disease (5–10% of cases)
- Pancreatic exocrine insufficiency
- Meconium ileus at birth (15–20% of cases)
- Sweat chloride value: usually 90–110 mmol/liter, sometimes 60–90 mmol/liter
- Obstructive azoospermia
- Chronic bacterial infection of airways (later onset, but variable)
- Adequate pancreatic exocrine function (usually); pancreatitis (5–20% of cases)
- Sweat chloride value usually 60–90 mmol/liter; sometimes normal (<40 mmol/liter)
- Obstructive azoospermia
Cystic Fibrosis – Overview

- **Definition** - AR disease (neonatal-adulthood onset) multisystem disease of epithelial ion transport caused by mutations in the CF transmembrane conductance regulator gene (CFTR)

- **Incidence** – 1 in 1600-3200 US whites affected with CF (1 in 20 carrier rate)

- **Pathogenesis** – (gene for CFTR is on 7p) CFTR is a cAMP regulated Cl-channel that regulates other ion channels; CFTR maintains hydration of secretions of airways and ducts through the transport of chloride and inhibition of Na uptake; CFTR dysfunction affects many organs that secrete mucous (respiratory/GI tract, pancreas, biliary system, male genitalia, sweat glands)

- **Diagnosis** – 1+ phenotypic features (pulmonary, meconium ileus, growth failure, obstructive azospermia, exocrine pancreatic insufficiency) + 2 CFTR mutations or abnormal sweat chloride (>60 MEQ/L)
Hyphaerated lungs, pulmonary blebs
Cystic fibrosis – genetic principles

• Ethnic variation - CFTR mutation detection rate varies by test method and ethnic background; in some affected and carrier individuals the disease-causing mutation is not detectable

• Genetic modifiers -
  – correlation between particular CFTR mutant alleles and disease severity (pancreatic insufficiency) or spectrum of disease associated with a particular disease causing mutation that alters protein production
  – some mutations in CFTR cause disease manifestations only in certain tissues (e.g. some mutations affecting the efficiency of splicing have a greater effect on Wolffian duct derivatives than in other tissues because of a tissue-specific need for full-length transcript and protein)

• Environmental modifiers - cigarette smoke worsens severity of lung disease
## Cystic Fibrosis

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ACOG committee opinion 2006
Cystic fibrosis & Pregnancy

- **Inheritance, recurrence risk** – autosomal recessive inheritance implications, depends on ethnic background
- ‘Prenatal diagnosis is based on identification of the CFTR mutations in DNA from fetal tissue…effective identification of affected fetuses usually requires that the mutations responsible for CF in a family have already been identified.’ (Nussbaum case review)
- **Predictors of poor pregnancy outcome** – FEV-1 <40-50% (OMIM, Moskowitz)
- **Management** – accurate/confirmed diagnosis, symptomatic management, control of infection, pancreatic enzymes, nutrition, lung transplant
Review select diseases that illustrate genetic principles
Marfan syndrome – overview

- **Definition** – connective tissue disease from mutation of fibrillin 1 gene (15q21.1 – OMIM)
- **Incidence** – 1 in 10,000
- **Pathogenesis** – FBN1 encodes fibrillin 1 (ECM glycoprotein) - polymerizes to form micro-fibrils in both elastic and nonelastic tissues, such as the aortic adventitia, ciliary zonules and skin. Mutations affect fibrillin 1 synthesis, processing, secretion, polymerization, or stability.
- **Diagnosis** – clinical (need following)
  - aortic root dilation/dissection; lens displaced superiorly; spontaneous pneumothorax or apical blebs; striae or recurrent hernia; 4 of 8 specific skeletal features; +FHx + genetic testing for FBN1 mutation or haplotype around FBN1; diagnosis must include anthropometric measurements
Marfan syndrome – genetic principles

• Autosomal dominant; 25-35% of patients result from de novo mutations making the mutation unique to the family

• Dominant negative mutations - Studies of fibrillin 1 deposition and cell culture expression assays suggest a dominant negative pathogenesis (i.e. production of mutant fibrillin 1 inhibits formation of normal microfibrils by normal fibrillin 1 or stimulates inappropriate proteolysis of extracellular microfibrils) – (Nussbaum, p286)

• Variable expressivity (varying degrees of severity)
Marfan syndrome & Pregnancy

- Prenatal diagnosis – requires linkage analysis of the mutation that is unique to the family
- AD – 50% chance of affected offspring
- Aortic root cutoff – 40mm for excess risk (Rossiter 1995) - reason is <40mm is less likely to have significant expansion during pregnancy and less likely to dissect
  - β-blockade to prevent aortic root dilation (HR <90)
  - Echocardiogram q6-10 weeks
  - L&D – labor in lateral decubitus, oxygen, assisted 2nd stage,
  - Risk if increased until 6-8 weeks PP
40 mm aortic root cutoff in pregnancy (Rossiter et al, 1995)

- N=45 pregnancies in 21 patients
- 1983-92; prospective study (Johns Hopkins)

Fig. 1. Aortic root diameter measurements before, during, and after pregnancy. Least-squares linear regression lines, each extending through measurements of aortic root diameter from last study before pregnancy, all studies during pregnancy, and studies after pregnancy.
Hemophilia - overview

- **Def** – bleeding diathesis due to deficient/dysfunctional factors 8 and 9
- **Incidence** - A – 1 in 5-10000; B – 1 in 100,000
- **Pathogenesis** – inability to form fibrin clot
- **Diagnosis** - Factor levels (predict clinical severity)
  - hemophilia A – VIII activity <30-35%, NL 50-150%
    need normal/functional von Willebrand factor; genetic testing reveals DNA mutations in 98% of patients with hemophilia A
  - Hemophilia B – IX activity level <30%
Lockwood 2002
Hemophilia – genetic principles

- Factor IX – various mutations
- Factor VIII - partial inversion in F8 gene
  - Inversion deletion of carboxyl terminus (X chromosome) of factor VIII
  - Accounts for mutations in severe disease
  - Inversion involves intrachromosomal recombination between sequences in intron 22 of F8 and homologous sequences telomeric to F8
  - Variable expressivity – according to level of activity of factor
    - severe disease (<1% of activity); moderate (1-5% of activity); mild (5-25% of activity)
  - X-linked recessive -
    - carrier males affected (daughters obligate carriers) carrier females (50% of sons will be affected, and 50% of daughters carriers)
Hemophilia – pregnancy implications

- Factor VIII replacement (if <50%) – DDAVP - (0.4mcg/kg loading dose) IV - helps treat most bleeding; single IV dose triples factor VIII clotting activity, caution fluid overload, hyponatremia (with massive fluid admin, oxytocin)
  - Recombinant Factor VIII or IX
  - Cryoprecipitate has high concentrations of Factor VIII
  - If factor level > 50IU/dL or >50% - and coagulation profile normal
    - Regional anesthetic not contraindicated
- Establish carrier status if possible
- Fetal intracranial hemorrhage risk (3-25% with vaginal and CD, 60% with vacuum) reason to know gender – males at risk – avoid scalp electrodes, vacuum, prolonged labor/2nd stage, CD not necessarily protective if easy outlet forceps can be performed, otherwise low threshold for CD (Lee 2006, OMIM)
- Factor VIII levels increase throughout pregnancy – protects against PPH, but delayed PPH can ensue once factor VIII clotting levels return to baseline 48hr PP (Lee 2006)

(ACOG, OMIM)
Osteogenesis Imperfecta - overview

- Def - fragile bone disease due to mutations in collagen structural genes (4 types)
- Incidence: all 4 types – 1 in 15,000 (Nussbaum, p372)
- Pathogenesis – each collagen chain is made as a type 1 procollagen ‘triple-helix’ that is secreted into the extracellular space where it undergoes cleavage (of amino and carboxy terminal ends) that forms collagen; mature collagen fibrils are assembled and ultimately mineralized in bone
  - OI – 2 classes of mutations (>800 different mutations) –
    - Mutations that affect synthesis (reduction in amount of type 1 procollagen that is made)
    - Mutations affecting structure of molecules that make up procollagen 1
- Diagnosis – clinical (depends on type)
- Recurrence risk – 50% if dominant inheritance
OI – Genetic principles

- Inheritance – Autosomal dominant (most types and mutations); new mutation (type 2)
- Proα1 – chromosome 17; proα2 – chromosome 7
- Dominant negative – one type of mutation interferes with the production of normal pro-collagen molecules
  - Stoichiometry – normally have 2 proα1 molecules and 1 proα2 chain; if mutation is in proα1 then as the collagen molecule polymerizes, 3 of 4 pro-collagen chains are potentially affected, vs if proα2 is affected, then 1 of 2 collagen pro-collagen chains are potentially affected
    - proα1 - Ratio of normal:mutant molecules 1:3
    - Proα2 – ratio of normal:mutant molecules 1:1 (may be less severe)
  - “It’s better to have a mutation that produces no gene product, than one that produces an abnormal procollagen molecule” (Nussbaum p375)
OI – pregnancy implications

• Case of type I OI – 26 yo P0 -15 weeks prenatal care
  – Blue sclera, multiple childhood fractures, 4’11”; appropriate, symmetric long bones; AD pedigree
  – Normal 17 week ultrasound; 50% risk of affected child
  – Risk of in-utero/intrapartum fracture
  – Maternal uterine rupture confirmed to be abnormal collagen on uterine biopsy (case reports – Krishnamoorthy, 2002; Christodoulou 2004)

• Prenatal diagnosis – typically of type 2 OI
Type 2 OI

- AD, most are new mutations
- “Perinatal lethal” (Nussbaum p373)
- Severe skeletal disease (fractures and deformities); dark sclera; lethal malformation
  - Sonographically – short bones, small thorax, angulation of bones from fx, decreased ossification of skull, irregular ribs
- Gene defect is missense mutation of glycine codons for α1 and α2 procollagen chains
- If detected prenatally – counseling should include option of termination
- Recurrence risk – 2-5% for T2 OI (Nyberg p698)
Ex of in-utero fracture
Type 2 OI – hypomineralized and short bones, frontal bossing, fractures
Thefetus.net
Hemoglobinopathies

• Definition –
  – qualitative (sickle cell – Beta globin gene mutation)
  – quantitative (thalassemia, unbalance of alpha or beta globin chains) abnormality in the hemoglobin molecule

• Incidence – allele frequency depends on ethnicity;
  – worldwide > 270 million heterozygous carriers;
  – > 300,000 affected homozygotes or compound heterozygotes born each year (ACOG 2007)
Thalassemias –
Beta globin gene -- chromosome 11
Alpha globin gene -- chromosome 16

Pathogenesis
Gelehter p 105

Life span
Of RBC 120d
### Classification of α/β-Thalassemias (ACOG bulletin, Nussbaum, Gelehter)

<table>
<thead>
<tr>
<th>Number of functional Globin Genes (ratio of α/β globin)</th>
<th>Genotype</th>
<th>Description</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (1)</td>
<td>αα/αα</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3 (0.8)</td>
<td>α-/αα</td>
<td>Heterozygous α-thal trait (silent carrier)</td>
<td>Asymptomatic (silent carrier)</td>
</tr>
<tr>
<td>2 (0.6)</td>
<td>α-/α-αα/--</td>
<td>“α-thal trait” affected</td>
<td>Mild anemia</td>
</tr>
<tr>
<td>1 (0.3)</td>
<td>α-/-- 1α, rest β</td>
<td>Hb H disease (β4 tetramers detected)</td>
<td>Hb H – marked hemolytic anemia at birth (MCV &lt;50mm3)</td>
</tr>
<tr>
<td>0 (0)</td>
<td>--/--</td>
<td>Hb Bart’s – no alpha globin</td>
<td>Hb Bart's (hydrops fetalis)</td>
</tr>
</tbody>
</table>

- **α thalassemia** – diagnosed by DNA based testing (S. blot, PCR, ASO)
- **βthalassemia** - βchain deficiency (Hb electrophoresis - >0.5% F, >3.5%% A2)
α-thalassemia

- Autosomal recessive; Classification table
- Chromosome 16 – 2 functioning α genes
  - Heterozygous α thal 2 (α-/αα) – silent carrier
  - ‘α thal trait’ – α thal 1 (2 of 4 α globin genes deleted)
    - Southeast Asians – (αα/--) heterozygous for α 1, 2
    - Blacks – (α-/α-) – homozygous for α thal 2 chromosome
    - MCV slightly reduced, asymptomatic
  - Hb H → α-/-- essentially all 4 Beta chains, severe anemia
  - Hb Barts – hydrops (--/--) all gamma chains
- Most common abnormality – leads to loss of 1 α-globin gene on a chromosome – unequal crossing over of α-globin cluster on chromosome 16
  - High degree of homology of nucleotide sequences around α1 and α2 genes

Gelehrter p107-109
β thalassemia

- Autosomal recessive; β-globin gene Chromosome 11
- Large number of mutations that can result in decreased or absent function of β-globin gene
- Due to 1 β globin gene per chromosome 11, chance for unequal crossing over is much reduced (vs α thal)
- Classes
  - Minor – 1 normal β-gene, 1 nonfunctional gene
  - Intermedia – abnormality of both β-globin chains, anemic, symptomatic, but not transfusion dependent
  - Major – No β-globin made (both genes mutated), no Hb A made, severe anemia, transfusion dependent

Gelehrter p107-109
Thalassemia (α/β) – overview

- **Definition** – quantitative abnormality of the globin chains
- **Incidence** – α-thal trait - 0.01% in nonmalarial exposed populations Iceland, UK, Japan; 49% in southwest Pacific islanders
  - Hb H disease, hydrops fetalis – restricted to Mediterranean and SE Asia
  - β-thal trait – 1-2% Africans and African Americans; 30% in Sardinia
- **Pathogenesis** - deficient synthesis of α-globin or β-globin chain that forms the hemoglobin molecule, unbalanced accumulation of alpha/beta subunits (Gelehrter, p96); childhood onset, hypochromic microcytic anemia, HSM, extramedullary hematopoiesis
  - ~80% untreated pts die within 5 years;
  - Transfusion therapy alone – death <30yo (due to infection, hemochromotosis)
  - Iron chelation therapy can reduce chance of hemochromotosis and cardiac, hepatic complications - from repeated transfusions

(OMIM)
Thalassemia – genetic principles

• Heterozygote advantage – carriers of trait display resistance to malaria; prevalence in an ethnic group reflects past and present exposure of a population to malaria
  – Ethnic variation in allele frequencies

• Gene dosage – amount of gene present affects degree of symptoms
Thalassemia & Pregnancy

- Thalassemia trait not increased risk
- Autosomal recessive implications, Screening at risk ethnic groups (Asians, Mediterranean, Blacks)
- Thalassemia major (little to no $\beta$ chain production)- pregnancy is recommended if normal cardiac function, Hb > 10g/dL after hypertransfusion and iron chelation therapy (ACOG 2007)
  - During pregnancy Hb goal >10 g/dL ; Deferoxamine stopped
  - Fetal testing (serial growth scans, weekly testing); CD for obstetric indications
- $\beta$-thalassemia minor – mild anemia; only ppx iron; fetal testing (ACOG 2007)
- Supportive therapy – Hct >21% (Hb >6g/dL); ideal Hct > 30%
Sickle cell anemia – Overview

• Definition – AR hemoglobin disease due βglobin chain (chromosome 11) missense mutation that substitutes valine for glutamic acid at amino acid 6 (β-globin glu6val mutation)
• Incidence – 1 in 700 (African), carrier rate ~1 in 10
• Pathogenesis – the glu6val mutation DECREASES the solubility and deformability of the βglobin chain so that after repeated cycles oxygenation and attendant sickling, the chains become permanently ‘sickled’ and occlude capillaries causing infarctions (painful crisis, acute chest syndrome, asplenia); irreversible sickled cells are removed by the spleen and the rate of removal of erythrocytes from the circulation exceeds the production capacity of the bone marrow and causes a hemolytic anemia
• Diagnosis – Peripheral smear; Hemoglobin electrophoresis identifying Hb SS (p100 Gehleter) – normal adult A (97.5%), A2 (2%), F (0.5%)
Hgb electrophoresis
Electric field
Sickle (glu6val) valine in place of glutamine
Glutamine has a more Negative charge thus it travels further than Valine (S) or lysine (C)
-A = glutamine has the most negative charge – thus it goes far on the gel
-S = glutamine to valine (middle charge b/n +/-)
-C = glutamine to lysine (more + charge thus it does not go as far on the gel)
-A2 (most positive charge, thus it does not go far on the gel)
Sickle Cell Disease and genetic principles

- Heterozygote advantage, plays role in ethnic variation in allele frequency
- Novel property mutation - sickle cell disease is an exception to the allelic heterogeneity rule in that one specific mutation is responsible for the unique ‘novel’ properties of sickle Hb; Hb C is less soluble than Hb A and tends to crystallize in red cells, decreasing the deformability in capillaries and this also creates mild hemolysis, but Hb C does not sickle or form the rod shaped polymers like Hb S
### Sickle cell mutation frequencies (Nussbaum 4th ed) — California cohort data

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>HB SS</th>
<th>Hb AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1/700</td>
<td>1/14</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>0/1600</td>
<td>1/700</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/46,000</td>
<td>1/180</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0/22,000</td>
<td>1/360</td>
</tr>
<tr>
<td>Native American</td>
<td>1/17,000</td>
<td>1/180</td>
</tr>
<tr>
<td>White</td>
<td>1/160,000</td>
<td>1/600</td>
</tr>
<tr>
<td>Asian</td>
<td>0/200,000</td>
<td>1/1300</td>
</tr>
</tbody>
</table>
Sickle cell disease & Pregnancy

- Increased risk of morbidity/mortality – depends on severity of anemia
  - Hb SS and to lesser extent Hb SC - Risks include infection, acute chest syndrome, pain crises, dehydration, severe anemia, cholecystitis, preterm birth, low-birth weight infants (<2500g), fetal growth restriction, hospitalization
  - Folic acid supplementation – 4mg/day
  - Painful crisis (tx with pain control, oxygen, IV hydration) – avoid cold temp, heavy exertion, dehydration, stress
  - Acute chest syndrome (fever, tachypnea, chest pain, hypoxia)
  - Autosomal recessive implications for offspring
  - Prophylactic or exchange transfusion – goal of Hct - >21% (ideal ~30%) – decreases risk of painful crises, severe anemia, not necessarily associated with improved pregnancy outcome, less crises, less anemia (ACOG 2007)
Screening in pregnancy (ACOG, 2007)

- CBC, hemoglobin electrophoresis, ferritin (<10 mcg/dL – iron deficiency)
- Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be screened
- Carriers or affected patients – genetic counseling, prenatal diagnosis if mutations have been defined in the parents for thalassemia – DNA mutation analysis for sickle cell disease is available for 2 carriers or affected patients
- MCV < 80fL, normal ferritin – screen with hemoglobin electrophoresis
Fig. 1. Specialized antepartum evaluation for hematologic assessment of patients of African, Southeast Asian, or Mediterranean descent. Patients of Southeast Asian or Mediterranean descent should undergo electrophoresis if their blood test results reveal anemia. Abbreviations: CBC = complete blood count; RBC = red blood cell; MCV = mean corpuscular volume; Hb = hemoglobin.
Conclusions

- Keep inheritance patterns and recurrence risk straight
- Use OMIM, GeneTest for review and options for prenatal diagnosis and counseling
• QUESTIONS ??
Texas Newborn Screening
http://www.dshs.state.tx.us/LAB/NBSdisorderList.pdf

- **Amino Acid Disorders** - Phenylketonuria (PKU), Maple Syrup Urine Disease (MSUD), Homocystinuria (HCY), Tyrosinemia Type I (TYR I), Argininosuccinic acidemia (ASA), Citrullinemia (CIT)

- **Fatty Acid Disorders** - Medium chain Acyl-CoA dehydrogenase deficiency (MCAD), Very Long chain Acyl-CoA dehydrogenase deficiency (VLCAD), Long Chain Hydroxy Acyl-CoA dehydrogenase deficiency (LCHAD), Trifunctional protein deficiency (TFP), Carnitine uptake defect (CUD),

- **Organic Acid Disorders** - Isovaleric Acidemia (IVA), Glutaric Aciduria Type I (GA-I), 3-hydroxy-3-methylglutaryl CoA lyase deficiency (HMG), Multiple carboxylase deficiency(MCD), Methylmalonic Acidemia/Methylmalonyl-CoA mutase (MUT), Methylmalonic Acidemia/Vitamin B12 Disorders (Cbl A,B), 3-methylcrotonyl-CoA carboxylase deficiency (3MCC), Propionic Acidemia (PROP), Beta ketothiolase deficiency (BKT),

- **Hemoglobinopathies** - Sickle Cell Anemia (SCA), Sickle C Disease (HB S/C), Sickle Beta Thalassemia (HB S/Th)

- **Other Disorders** - Hypothyroidism (HYPOTH), Biotinidase deficiency (BIO), Congenital Adrenal Hyperplasia (CAH), Transferase Deficient Galactosemia (GALT), Cystic Fibrosis (CF), Hearing (HEAR)
Kansas Newborn Screening
http://www.kdheks.gov/newborn_screening/disorder_listing.htm

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CREOG Review - Done
CREOG – extra slides, notes from genetics -start
Malaria
Pedigree Symbols

[Diagram showing various symbols used in pedigrees, such as male, female, deceased, affected, heterozygote, carrier of X-linked trait, and symbols for married and abortion/marriage.]
Fragile X, CF, spinal muscular atrophy
Fragile X

- X-linked mental retardation disorder; mutation in the FMR1 gene on Xq27.3
- 16-25 per 100,000 in general male population
  - 8 per 100,000 in general female population
  - Accounts for 3-6% of MR among boys with a +FHX of MR and no birth defects
- FMR1 gene product is FMRP (expressed in many cell types – mostly in neurons; may chaperone a subclass of mRNAs from the nucleus to the translational machinery)
- More than 99% of FMR1 mutations are expansions of a (CGG)n repeat sequence in the 5’ untranslated region of the gene; > 200 repeats results in hypermethylation of the CGG repeat sequence and the adjacent FMR1 promoter; this inactivates the FMR1 promoter, causing a loss of FMRP expression
Fragile X – major phenotypic features

- Age at onset – childhood
- Mental deficiency
- Dysmorphic facies
- Male postpubertal macroorchidism

- Fragile site at Xq27.3 – located in 5’ untranslated region of the first exon of a gene called FMR1 (fragile X mental retardation 1)
# Fragile X syndrome

## Table 1. Mutation in the Fragile X Mental Retardation 1 Gene

<table>
<thead>
<tr>
<th>Status of Individual</th>
<th>Number of Triplet Repeats (Cytosine–Guanine–Guanine)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Unaffected</td>
<td>Less than 40</td>
</tr>
<tr>
<td>Intermediate</td>
<td>41–60</td>
</tr>
<tr>
<td>(also called &quot;grey zone&quot;)</td>
<td></td>
</tr>
<tr>
<td>Premutation</td>
<td>61–200</td>
</tr>
<tr>
<td>Full mutation</td>
<td>More than 200</td>
</tr>
</tbody>
</table>

ACOG committee opinion 2006
Fragile X syndrome

- CVS pitfall
- Fragile X syndrome - X-linked recessive
- Expansion of repeated trinucleotide segment of DNA (cytosine–guanine–guanine, CGG) that leads to altered transcription of the fragile X mental retardation 1 (FMR1) gene.
- # of repeats varies – 4 groups - unaffected, intermediate, premutation, full mutation
  - 61–200 repeats - phenotypically normal, premutation
  - This condition occurs because the large number of repeats causes the FMR1 gene to become methylated and inactivated in these patients.
  - The number of repeats and the status of gene methylation are determined by use of DNA-based molecular tests (eg, Southern blot analysis and polymerase chain reaction).
  - Chorionic villus sampling (CVS) - reliable for determining the number of triplet repeats, may not be reliable for diagnosis because of gestational age differences in ultimate methylation patterns in the trophoblast and may not adequately determine the methylation status of the FMR1 gene.
  - DNA methylation is a process that controls tissue specific gene expression. Methylation "turns off" the regulatory region of a gene, thereby preventing DNA transcription. Rarely, the size of the triplet repeat and the methylation status do not correlate, making prediction of the clinical phenotype difficult.
Fragile X syndrome

• Triplet repeat expansion – massive expansion nearly always occurs during female gametogenesis; Normal number of repeats up to 60; several thousand occur in fragile X; > 200 copies of the repeat lead to excessive methylation of cytosines in the promoter of FMR1; this interferes with replication or chromatin condensation or both, producing the characteristic chromosomal fragile site, a form of DNA modification that prevents normal promoter function or blocks translation

• Somatic mosaicism- a mutation affecting morphogenesis and occurring during embryonic development might be manifested as a segmental or patchy abnormality, depending on the stage at which the mutation occurred and the lineage of the somatic cell in which it originated – ex: NF1 is sometimes segmental, affecting only one part of the body. Segmental NF1 is caused by mosaicism for a mutation that occurred after conception. In such cases the patient has normal parents, but if he or she has an affected child, the child’s phenotype is typical for NF1, that is, not segmental. In such cases, the mutation has to be in the patient’s gametes and therefore must have occurred before separation of germline cells from the somatic cell line that carries the mutation.
Fragile X

- **Sex-specific anticipation** – Every child of an affected mother has a more severe form than the mother did, may only have a mild expression of the disease and may not know she is affected.

- **DNA methylation** – the major form of DNA modification in the human genome involves methylation of cytosine residues (to form 5-methylcytosine), specifically when they are located immediately 5’ to a guanine (i.e. as the dinucleotide 5’-CG-3’). Hotspot for mutation in the human genome as it upstream from coding exons.

- **Haplotype effect** – a given set of alleles at a locus or cluster of loci on a chromosome is referred to as a haplotype; the set of HLA alleles at the different class I and class loci on a given chromosome together form a haplotype; risk of premutation expansion to a full mutation increases as the repeat length of the premutation increases. Not all premutations, however, are equally predisposed to expand. Although premutations are relatively common, progression to a full mutation has been observed only on a limited number of haplotypes; that is, there is a haplotype predisposition to expansion. This haplotype predisposition may relate partly to the presence of a few AGG triplets embedded within the string of CGG repeats; these AGG triplets appear to inhibit expansion of the string of CGG repeats, and their absence in some haplotypes, therefore, may predispose to expansion.
Fragile X syndrome

- Committee on Genetics recs re: testing for fragile X:
- DNA-based molecular test (Southern, PCR)
  - In rare cases where there is discordancy between the triplet repeat number and the methylation status, the patient should be referred to a genetic specialist.
- + FHx, or hx of fragile X MR – genetic counseling, offered genetic testing to assess risk for having an affected child.
- Prenatal testing for fragile X syndrome by amniocentesis or CVS should be offered to known carriers of the fragile X premutation or mutation. Although it is reliable for determining the number of triplet repeats, CVS may not adequately determine the methylation status of the FMR1 gene.
- Testing for fragile X syndrome should be considered in any child with developmental delay of uncertain etiology, autism, or autistic-like behavior or any individual with mental retardation of uncertain etiology.
- If a woman has ovarian failure or an elevated follicle-stimulating hormone level before the age 40 years without a known cause, fragile X carrier screening should be considered to determine whether she has a premutation.
Fragile X syndrome
CF – major phenotypic features

- Age at onset – neonatal to adulthood
- Progressive pulmonary disease
- Exocrine pancreatic insufficiency
- Obstructive azoospermia
- Elevated sweat chloride concentration by pilocarpine iontophoresis
  - Normal - <40 mmol/L
  - Indeterminate – 40-60 mmol/L
  - Elevated - >60 mmol/L
- Growth failure
- Meconium ileus
Cystic Fibrosis – ACOG info

- Cystic fibrosis is a progressive, multisystem disease that primarily affects the pulmonary, pancreatic, gastrointestinal, biliary, and reproductive systems. Individuals with cystic fibrosis typically present with cough, wheezing, failure to thrive, loose stools, abdominal pain, and, in males, infertility secondary to congenital bilateral absence of the vas deferens. Treatment involves pancreatic enzymes, proper nutrition, and respiratory therapy with aggressive treatment of infection. The current median survival is approximately 30 years, and the cause of death usually is respiratory failure. Approximately 15% of individuals with cystic fibrosis are pancreatic sufficient and have a milder disease course and a median survival of 56 years.

- Cystic fibrosis is an autosomal recessive genetic condition. Therefore, when a patient and her partner are both carriers of a mutation in the cystic fibrosis gene, they have a one-in-four chance of having a child with cystic fibrosis. More than 1,300 mutations have been identified in the gene for cystic fibrosis, but screening for 23 common mutations is available and can reduce a couple's risk for having a child with cystic fibrosis. The risk of being a carrier depends on an individual's ethnicity and family history.
• Disease etiology and incidence, pathogenesis
  • Autosomal recessive; disorder of epithelial ion transport caused by mutations in the CF transmembrane conductance regulator gene (CFTR)
    – cAMP-regulated chloride channel that regulates other channels; maintains hydration of secretions in airways and ducts that secrete mucus – resp tract, pancreas, biliary system, male genitalia, intestine, sweat glands
  • Live birth incidence – 1 in 313 (Alberta, Canada)
    • 1 in 90000 among Asian pop in Hawaii
    • 1 in 3200 among all US whites
    • Typically diagnosed in childhood
  • Median survival 33 years old (depends on progression of lung disease)
    – Most patients die of respiratory failure and right ventricular failure secondary to the destruction of lung parenchyma and high pulmonary vascuclar resistance (cor pulmonale);
  • 5-15% do not have pancreatic insufficiency; 95% of male patients are azospermic (CBAVD)
  • Management – accurate diagnsosis; symptomatic management, control of infection, pancreatic enzymes, nutrition; lung transplant
  • Inheritance risk – if no family history and are northern European descent – 1 in 29; couple’s risk of an affected child is 1 in 3200; for couples with an affected child, this risk for future children being affected is 1 in 4
  • ‘Prenatal diagnosis is based on identification of the CFTR mutations in DNA from fetal tissue, such as chorionic villi or amniocytes. Effective identification of affected fetuses usually requires that the mutations responsible for CF in a family have already been identified.’ Nussbaum
Cystic fibrosis

- Ethnic variation - table; differences in frequencies of alleles that cause genetic disease; reason why you can check a panel of allele mutations in 1 population and cut the risk of being carrier substantially, but in another population, the panel is different and larger; other ex is in North America, when persons of Mediterranean descent are at risk of having a child with B-thalassemia, testing of parental DNA for just seven mutant alleles has more than 90% probability of providing the information needed for prenatal diagnosis.

- Variable expressivity - severity of expression of the phenotype among individuals with the same disease-causing genotype; when the severity of disease differs in people who have the same genotype the phenotype is said to have variable expressivity; even in the same kindred, 2 individuals carrying the same mutant genes may have some signs and symptoms in common, whereas their other disease manifestations may be quite different, depending on which tissues or organs happen to be affected.
  - Vs penetrance which is present or not – if there is ANY demonstration of some sign of the disease then it’s said to be penetrant (neurofibromatosis – all individuals have penetrance, but there is variable expression.)
• Tissue-specific expression of mutations (lung, pancreas, GI tract, reproductive tract); some patients present with slow growth, chronic respiratory disease, malnutrition due to pancreatic insufficiency, infertility due to congenital bilateral absence of the vas deferens

• Genetic modifiers- correlation between particular CFTR mutant alleles and disease severity exists only for pancreatic insufficiency; secondary mutations or polymorphisms within a CFTR allele may alter the efficiency of splicing or protein maturation and thereby extend the spectrum of disease associated with some mutations; in addition, some mutations in CFTR cause disease manifestations only in certain tissues; for example, some mutations affecting the efficiency of splicing have a greater effect on wolffian duct derivatives than in other tissues because of a tissue-specific need for full-length transcript and protein.

• Environmental modifiers- ex – cigarette smoke exposure markedly worsens the severity of lung disease among patients with CF
# Cystic Fibrosis

<table>
<thead>
<tr>
<th>Racial or Ethnic Group</th>
<th>Detection Rate</th>
<th>Carrier Rate Before Testing</th>
<th>Carrier Risk After Negative Test Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ashkenazi Jewish</td>
<td>94%</td>
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</table>
CF- committee on Genetics recs

- Information about cystic fibrosis screening should be made available to all couples. It is reasonable to offer cystic fibrosis carrier screening to all couples regardless of race or ethnicity as an alternative to selective screening.
- Cystic fibrosis carrier screening should be offered before conception or early in pregnancy when both partners are of Caucasian, European, or Ashkenazi Jewish ethnicity. Patients may elect to use either sequential or concurrent carrier screening; the latter option may be preferred if there are time constraints for decisions regarding prenatal diagnostic testing or termination of the affected pregnancy.
- For individuals with a family history of cystic fibrosis, medical records indicating the CFTR mutation in the affected family member should be obtained whenever possible. If the mutation has not been identified, screening with an expanded panel of mutations or, in some cases, complete analysis of the CFTR gene by sequencing may be indicated. Genetic counseling in this situation usually is beneficial.
- Individuals who have a reproductive partner with cystic fibrosis or congenital bilateral absence of the vas deferens may benefit from screening with an expanded panel of mutations or, in some cases, a complete analysis of the CFTR gene by sequencing.
- When both partners are cystic fibrosis carriers, genetic counseling is recommended to review prenatal testing and reproductive options. Prenatal diagnosis by chorionic villus sampling or amniocentesis, using DNA-based testing of the fetal cells, should be offered. If the partner is unavailable for testing, genetic counseling may be helpful.
- Cystic fibrosis carrier screening may identify individuals with two cystic fibrosis mutations who have not previously received a diagnosis of cystic fibrosis. These individuals may have a milder form of cystic fibrosis and should be referred to a specialist in cystic fibrosis for further evaluation. Genetic counseling also is beneficial.
Cystic Fibrosis
Spinal muscular atrophy

- Accepted criteria that a candidate disease should meet before widespread screening is instituted
  - the disease significantly impairs health in the affected offspring;
  - there is a high frequency of carriers in the population to be screened;
  - technically and clinically valid screening methods are available to the population, and screening is cost-effective;
  - testing is voluntary, and informed consent and pretest and posttest counseling are available and effective;
  - fetal testing is available for couples whose screening results are positive and reproductive options are readily available in a time-sensitive manner.

- In addition to these well-accepted criteria, it is imperative that any screening program be carried out in a manner by which a patient’s privacy is protected so that risks of discrimination and stigmatization in the community are minimized. Nevertheless, public awareness campaigns regarding the disease and carrier screening availability will enhance knowledge of SMA and SMA testing in the prenatal population. This may lead to patients requesting SMA carrier testing.
Spinal muscular atrophy

- Spinal muscular atrophy (SMA) - autosomal recessive neurodegenerative disease that results from degeneration of spinal cord motor neurons leading to atrophy of skeletal muscle and overall weakness.
- caused by a mutation in the gene known as the survival motor neuron gene (SMN1), which is responsible for the production of a protein essential to motor neurons.
Spinal muscular atrophy

- Complex genetics, limitations in molecular diagnostic assays available, accurate prediction of the phenotype in affected fetuses may be not be possible.
- Incidence - 1 in 10,000 live births
- leading genetic cause of infant death
- Carrier frequencies are estimated at 1 in 40-60
- No effective treatment
- Types 1-3
  - Type I – most severe ; (Wernig–Hoffman), has symptomatic onset of the disease before 6 months of age and death from respiratory failure within the first 2 years of life.
  - Type II, most common form of SMA disease, ; intermediate severity; onset <2 yr old; Affected children are able to sit but few are able to stand or walk unaided. Respiratory insufficiency is a frequent cause of death during adolescence; life expectancy is 2 years to 20s;
  - Type III (Kugelberg–Welander), ; mild form ; onset >18months old ; variable sx profile; most reach major motor milestones, but function ranges from requiring wheelchair assistance in childhood to completely unaided ambulation into adulthood with minor muscular weakness. Many patients have normal life expectancies. There are other forms of SMA-like disorders with similar symptoms as those described previously, but they are linked to genes other than SMN1.
Spinal muscular atrophy

- **Molecular Genetics**
  - 2 nearly identical survival motor neuron genes present in humans, SMN1, SMN2
  - SMN1 is considered the active gene for survival motor neuron protein production and more than 98% of patients with SMA have an abnormality in both SMN1 genes, which can be caused by a deletion (95%), or other mutation.
  - There is generally one, but occasionally two, copies of SMN1 per chromosome and a variable number of SMN2 gene copies (ranging from zero to three).
  - SMN2 gene does not produce much in the way of functional survival motor neuron protein. However, the primary genetic feature, which determines the severity of SMA, appears to be the number of gene copies of SMN2 in a given individual. Studies have shown that a higher number of SMN2 copies correlates with generally milder clinical phenotypes.
  - The modulation of clinical severity due to variable copy numbers of SMN2 is the result of a small amount of full-length survival motor neuron transcripts and the protein generated by SMN2.
  - This protein product can partially compensate for the complete absence of protein from the SMN1 alleles. However, accurate prediction of the SMA phenotype based on SMN2 copy number is not possible. Although most of the population has one to three copies of SMN2, approximately 15% of normal individuals have no SMN2 gene.
Spinal muscular atrophy

- DNA Assay
- For diagnosis of SMA, it is sufficient to simply detect the classic SMN1 deletion using DNA analysis in both SMN1 alleles.
  - 95% sensitive (100% specific) for pt with SMA symptoms
  - Not sufficient for ID of heterozygotes/carriers for SMN1 deletion
  - Carrier testing requires a quantitative PCR assay that provides a measure of SMN1 copy number. Detection of a single normal copy of SMN1 would indicate the carrier state.
  - Limitations of this assay to determine carrier status
  - ~3-4% of the general population, having two SMN1 copies on one chromosome and no copies on the other, will be incorrectly identified as being negative, or not carriers of SMA.
  - These individuals are carriers because one of their chromosomes is missing the SMN1 allele.
  - Another 2% of the general population has SMN1 mutations that are not detectable by the polymerase chain reaction method of SMN1 dosage analysis.
  - Therefore, the counseling of patients who are tested for carrier status must account for the residual risk present when carrier screening assay results are negative, particularly in patients from SMA affected families.
Spinal muscular atrophy

• Carrier Screening
• In current practice, patients with a family history of SMA are being offered carrier screening for the SMN1 deletion mutations. Recent marketing and public awareness campaigns by laboratories and advocacy organizations are promoting widespread population-based carrier screening for SMA in the prenatal or preconception setting, regardless of family history.
• Proponents of testing (American College of Medical Genetics) of carrier screening in general population because of severity of the disease and relatively high carrier frequency, as well as the advent of improved DNA diagnostic assays for mutations in the disease causing gene (SMN1).
• The American College of Medical Genetics has recently recommended offering carrier testing to all couples regardless of race or ethnicity (1). However, to date, no pilot studies have been completed in the United States that would determine best practices for pretest and posttest education and counseling with specific regard to SMA screening. In addition, there have been no studies to date to determine patient preferences and utility measures that would allow the completion of an analysis of the cost-effectiveness of widespread carrier screening for SMA.
Spinal muscular atrophy

• However, the American College of Obstetricians and Gynecologists’ Committee on Genetics agrees that preconception and prenatal screening for SMA is not recommended in the general population at this time.
Congenital adrenal hyperplasia - Overview

- CAH – Deficiency of enzymes of cortisol production; most due to 21α-hydroxylase deficiency; cortisol is not produced (adrenal hyperplasia due to ACTH stimulation); >100 different mutations of CYP21A1 have been reported (Forrester 2004)
  - precursors proximal (17-OHP accumulates b/c it does not get converted to 11-deoxycortisol) to the block are produced in excess as are products of other pathways (testosterone production results in virilization of female fetuses)
- Incidence – 1 in 12,500 (Nussbaum, p110)
- Diagnosis – 17OHP – classic (>20,000 ng/dL), non-classic (2-15,000ng/dL);
  - normal newborn 10-20ng/mL (Forest 2004);
  - TEXAS premature cohort – EFW >2500g (>40ng/mL); if <2500g (>65ng/mL) due to functional peak at 29 weeks (White 2000)
  - Plasma renin activity – markedly elevated in salt-wasting form, less so in simple virilizing form (OMIM)
Adrenal gland steroid biosynthesis

21 alpha hydroxylase

Uptodate
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<th>HT N</th>
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<td>No</td>
<td>Mild virilization</td>
<td>Ambiguous</td>
<td>Yes</td>
</tr>
</tbody>
</table>
CAH – genetic principles

- Gene map locus – 6p21.3 (OMIM) – gene CYP21A2
- Inheritance/recurrence risk - Autosomal recessive implications – 25% risk of affected offspring, 50% risk of carrier offspring
  - 1% of mutations occur de novo
CAH and Pregnancy - prenatal testing and tx for fetuses at risk for 21OHD CAH, panel of cyp21A2 mutations available for testing OMIM, Genetest review 2009 (Nimkarn 2009)

- Pregnancy at risk <9 weeks after last menstrual period
  - Begin dexamethasone 20 μg/kg/day in 3 divided doses per maternal pre-pregnancy weight
  - Chorionic villus sampling (CVS) 9-11 weeks
  - Karyotyping

- 46,XY
  - Stop dexamethasone

- 46,XX
  - CYP21A2 genotype
    - Affected
      - Continue dexamethasone until term
    - Not affected
      - Stop dexamethasone
Adrenal hyperplasia

• Suchet MD, 2006 Canada
• female fetus with an adrenal hyperplasia. The mother received steroids during the gestation to prevent virilization. The baby was born without any sign of ambiguous genitalia. The final diagnosis was a congenital adrenal hyperplasia due to 21-hydroxylase deficiency. – bilateral adrenal hyperplasia
SEX CHROMOSOME,
GONADAL ABNORMALITIES
-if Y (TDF, SRY) present, medullary tissue forms testes, seminiferous tubules, Leydig cells which secrete androgens (HCG helps) to support male development, mitosis of primordial germ cells, etc.

GONADS - Ovarian, Testicular Development (Nussbaum p100)
by 6 weeks – migration to gonadal ridges, surrounded by sex cords; bipotential gonads regardless of XX, XY; -ovarian vs testis depends on Y chromosome (TDF/SRY gene), if present diverts development into male pathway

- if no Y, gonad develops into ovary by 8th week, cortex develops, medullary region regresses, oogonia develop in follicles -oogonia meiosis I begins (12wk), then arrests in dictyotene (M1) until ovulation occurs many years later
Female, male differentiation

- Normal male differentiation –
  - Leydig cells produce testosterone (6-7 wks)
  - Sertoli cells produce anti-Mullerian [protein] hormone (AMH; also known as Mullerian Inhibiting Factor) at 8 weeks

- AMH – involution of Mullerian duct system; allows development of the Wolffian ducts into male internal genitalia
  - IF no AMH, Mullerian ducts develop into female internal genital organs
Male factors

• Sperm development
  – AZF gene in formation of sperm
  – Severe oligo/azoosperimia
  – Y chromosome deletions

• Klinefelter syndrome (XXY)

• XYY syndrome

• Androgen insensitivity
Y chromosome – and disorders of sexual differentiation (figure 6-10, Nussbaum, p101)

Pseudoautosomal region of X and Y chromosomes – pairing segment (identical on X, Y) undergoes homologous recombination in meiosis I

Y - 50 genes
AZF in formation of sperm

• AZF – ‘azospermia factors’ – located on Y chromosome –
• 3 overlapping regions on Yq (AZFa, AZFb, and AZFc)
• Deleted in azospermia (DAZ - deleted in azospermia) – AZFc region contains the DAZ genes that encode RNA-binding proteins expressed only in the premeiotic germ cells of the testes
• de novo deletions of AZFc arise in 1 in 4000 males and are mediated by recombination b/n long repeated sequences – give rise to azospermia but mechanism is not completely known

(Nussbaum p110)
Severe oligo/azoospermia & Y chromosome deletions

- 2% of healthy males have severe oligospermia/azospermia (Significant proportion due to de novo deletions or mutations)
- Y-linked genes in spermatogenesis –
  - interstitial deletions in Yq have been associated with at least 10% of cases of nonobstructive azoospermia (no detectable sperm in semen) and with 6% of cases of severe oligospermia
  - an example of a de novo point mutation has been described in one Y-linked gene, USP9Y, the function of which is unknown but appears to be needed for normal spermatogenesis
  - men with idiopathic infertility - karyotype, Y chromosome testing for mutations/deletions should be offered before initiation of assisted reproduction (to detect Y chromosome deletions/mutations)

(Nussbaum p110)
Androgen insensitivity; X-linked (AR gene on Xq11-q12); 1 in 20,000

- **Diagnosis** - 46,XY, infertile female; female external genitalia, blind vaginal pouch, no Mullerian structures; sparse axillary/pubic hair; gonads (testicles) present in abdomen or inguinal canal; breast development; serum testosterone (male level) (OMIM AIS, Gotlieb)

- **Pathogenesis** – testes secrete androgen normally, but NO androgen receptors in end organs thus no complex with testosterone/DHT (transcription of target genes required for male differentiation does not occur);
  - Mutation – complete AR gene deletion or point mutation

- **Counseling** – Carrier females – 50% risk of transmitting the AR gene mutation; DNA testing for AR gene possible
Androgen insensitivity (wikipedia, google images)
Klinefelter’s syndrome (47,XXY)

- Phenotype – Tall male, infertile, Gynecomastia development greatly increases breast cancer risk

- Nondisjunction error of paternal M1 (51%); maternal meiosis (34%) postzygotic mitotic errors leading to mosaicism (15%) (Moore,c10,s92; Nussbaum, p107)
  - Failure of Xp/Yp recombination in the pseudoautosomal region
  - Variants with increasing numbers of X chromosomes have greater degrees of dysmorphism, defective sexual development, MR

- Counseling - Recurrence risk – 1% or age related risk

1 in 1000 male live births

XYY syndrome

- 47,XYY – incidence 1 in 1000 among male live births
- Male phenotype not obviously abnormal from 46,XY individuals
- Origin of error – paternal meiosis II nondisjunction error that produces YY sperm (Moore, c10, s94; p107 Nussbaum)
  - Less common XXYY, XXXYY share features of Klinefelter’s (47,XXY) and XYY also due to nondisjunction error of paternal M1, M2
  - Developmental delays, normal fertility
  - Behavioral abnormalities of hyperactivity, impulsiveness, NOT aggressive psychopathological behavior (Nussbaum p107)
- Counseling - Recurrence risk – 1%
Gonadal dysgenesis

- **Swyer syndrome** – 46,XY complete gonadal dysgenesis
  - Phenotypically female (uterus, fallopian tubes, female external genitalia present), lack of secondary sexual characteristics, no menstruation, streak gonads (OMIM – Swyer 1955)
  - Gonadal neoplastic risk – 25% - reason to remove gonads (gonadoblastomas and dysgerminomas)
  - One form of the disorder - due to mutations in the SRY gene (Yp11.3) (OMIM)
  - Inheritance, recurrence risk – de novo mutations, general population risk
Female factors

• 45,X
• Multiple X syndrome
• Premature ovarian failure
Female factors

- Turner syndrome (45,X) →
  - Complete/partial absence of 2\(^{nd}\) X chromosome
  - 1 in 4-5,000 female live births; 1-2% of all conceptuses; 99% abort; make up 25% of first trimester spontaneous abortions (Moore,c10,s19)
  - Error is paternal nondisjunction (70%), maternal (30%); (Moore,c10,s77)
  - Clinically – short stature, webbed neck, gonadal dysgenesis, characteristic facies, renal/CV abnormalities (hypoplastic left heart syndrome, coarctation of the aorta); 10% with mild MR
  - Counseling - Recurrence risk – nominal -1% or age related risk
Case – 45,X

- 26 yo P0 at 13 weeks seen in consultation for cystic hygroma; - Amniocentesis at 15+ weeks – karyotype – 45,X
Female factors

- **Multiple X syndrome**
  - Trisomy X (47,XXX) – 1/1000 female births, slightly above average stature; normal puberty; increased risk of chromosomally abnormal offspring (p107, Nussbaum); 70% with learning disability; severe psychiatric disease is rare
  - Nondisjunction Error in maternal meiosis 1 - 78% are maternal M1 events (Moore, class 10/slide 77)
  - X chromosome inactivation (2 of X chromosomes are inactivated, but more likely for some of the material on the extra X chromosomes to not be inactivated) (p108 Nussbaum)
  - Recurrence risk – 1% or age-related risk
Female factors - Premature ovarian failure

- Cessation of ovarian function before age 40 (FSH>30 mIU/mL)
- Incidence - 1% of women
- Etiology – idiopathic (majority), infection, autoimmune, radiation, chemotherapy
- CGG trinucleotide premutation carrier (Fragile X syndrome carrier; 60-200 CGG repeats)
  - Risk of POF – 20% (Saul, OMIM)
  - No risk with full mutation (>200 repeats)
  - No consensus on risk of women with high normal or intermediate # of CGG repeats (30-60 repeats)
  - Suggestion that FMR1 gene plays a role in menopause

Bankowski p 402
OUTFLOW TRACT & CF

Ostrer 2008 – Genereview, OMIM
CBAVD (Outflow tract) & Cystic Fibrosis

- Congenital bilateral absence of the vas deferens (CBAVD)
- Diagnosis of CFTR-related CBAVD in males established by obstructive azoospermia (due to lack of Wolffian duct structures), low volume of ejaculated semen, absence of vas deferens on clinical or ultrasound examination, and at least one disease-causing mutation in CFTR
- Patients with CF - Infertility/obstructive azospermia - > 95% of male infants with CF have azospermia due to CBAVD
- Male infertility - CBAVD - accounts for 1-2% of male infertility; ~80% of men with CBAVD have at least 1 mutation in CFTR gene (OMIM, Moskowitz)
EFFECTS OF CYSTIC FIBROSIS
Multisystem disease

Severe chronic bacterial infection of airways
Severe hepatobiliary disease (5–10% of cases)
Pancreatic exocrine insufficiency
Meconium ileus at birth (15–20% of cases)
Sweat chloride value usually 90–110 mmol/liter; sometimes 60–90 mmol/liter
Obstructive azoospermia

Chronic bacterial infection of airways (later onset, but variable)
Adequate pancreatic exocrine function (usually); pancreatitis (5–20% of cases)
Sweat chloride value usually 60–90 mmol/liter; sometimes normal (<40 mmol/liter)
Obstructive azoospermia

Cystic Fibrosis – Overview

• Definition - AR disease (neonatal-adulthood onset) multisystem disease of epithelial ion transport caused by mutations in the CF transmembrane conductance regulator gene (CFTR)

• Incidence – 1 in 1600-3200 US whites affected with CF (1 in 20 carrier rate)

• Pathogenesis – (gene for CFTR is on 7p) CFTR is a cAMP regulated Cl-channel that regulates other ion channels; CFTR maintains hydration of secretions of airways and ducts through the transport of chloride and inhibition of Na uptake; CFTR dysfunction affects many organs that secrete mucous (respiratory/GI tract, pancreas, biliary system, male genitalia, sweat glands)

• Diagnosis – 1+ phenotypic features (pulmonary, meconium ileus, growth failure, obstructive azospermia, exocrine pancreatic insufficiency) + 2 CFTR mutations or abnormal sweat chloride (>60 MEQ/L)
Hyperaerated lungs, pulmonary blebs
Cystic fibrosis – genetic principles

- Ethnic variation - CFTR mutation detection rate varies by test method and ethnic background; in some affected and carrier individuals the disease-causing mutation is not detectable
- Genetic modifiers-
  - correlation between particular CFTR mutant alleles and disease severity (pancreatic insufficiency) or spectrum of disease associated with a particular disease causing mutation that alters protein production
  - some mutations in CFTR cause disease manifestations only in certain tissues (e.g. some mutations affecting the efficiency of splicing have a greater effect on Wolffian duct derivatives than in other tissues because of a tissue-specific need for full-length transcript and protein)
- Environmental modifiers - cigarette smoke worsens severity of lung disease
## Cystic Fibrosis

### Table 1. Cystic Fibrosis Detection and Carrier Rates Before and After Testing

<table>
<thead>
<tr>
<th>Racial or Ethnic Group</th>
<th>Detection Rate</th>
<th>Carrier Rate Before Testing</th>
<th>Carrier Risk After Negative Test Result</th>
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<tr>
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ACOG committee opinion 2006
Cystic fibrosis & Pregnancy

- Inheritance, recurrence risk – autosomal recessive inheritance implications, depends on ethnic background
- ‘Prenatal diagnosis is based on identification of the CFTR mutations in DNA from fetal tissue…effective identification of affected fetuses usually requires that the mutations responsible for CF in a family have already been identified.’ (Nussbaum case review)
- Predictors of poor pregnancy outcome – FEV-1 <40-50% (OMIM, Moskowitz)
- Management – accurate/confirmed diagnosis, symptomatic management, control of infection, pancreatic enzymes, nutrition, lung transplant
Review select diseases that illustrate genetic principles.
Marfan syndrome – overview

• Definition – connective tissue disease from mutation of fibrillin 1 gene (15q21.1 – OMIM)

• Incidence – 1 in 10,000

• Pathogenesis – FBN1 encodes fibrillin 1 (ECM glycoprotein) - polymerizes to form micro-fibrils in both elastic and nonelastic tissues, such as the aortic adventitia, ciliary zonules and skin. Mutations affect fibrillin 1 synthesis, processing, secretion, polymerization, or stability.

• Diagnosis – clinical (need following)
  – aortic root dilation/dissection; lens displaced superiorly; spontaneous pneumothorax or apical blebs; striae or recurrent hernia; 4 of 8 specific skeletal features; +FHx + genetic testing for FBN1 mutation or haplotype around FBN1; diagnosis must include anthropometric measurements
Marfan syndrome – genetic principles

- Autosomal dominant; 25-35% of patients result from de novo mutations making the mutation unique to the family.
- Dominant negative mutations - Studies of fibrillin 1 deposition and cell culture expression assays suggest a dominant negative pathogenesis (i.e. production of mutant fibrillin 1 inhibits formation of normal microfibrils by normal fibrillin 1 or stimulates inappropriate proteolysis of extracellular microfibrils) – (Nussbaum, p286)
- Variable expressivity (varying degrees of severity)
Marfan syndrome & Pregnancy

- Prenatal diagnosis – requires linkage analysis of the mutation that is unique to the family
- AD – 50% chance of affected offspring
- Aortic root cutoff – 40mm for excess risk (Rossiter 1995) - reason is <40mm is less likely to have significant expansion during pregnancy and less likely to dissect
  - β-blockade to prevent aortic root dilation (HR <90)
  - Echocardiogram q6-10 weeks
  - L&D – labor in lateral decubitus, oxygen, assisted 2nd stage,
  - Risk if increased until 6-8 weeks PP
40 mm aortic root cutoff in pregnancy (Rossiter et al, 1995)

- N=45 pregnancies in 21 patients
- 1983-92; prospective study (Johns Hopkins)

Fig. 1. Aortic root diameter measurements before, during, and after pregnancy. Least-squares linear regression lines, each extending through measurements of aortic root diameter from last study before pregnancy, all studies during pregnancy, and period of follow-up after delivery.
Hemophilia - overview

- **Def** – bleeding diathesis due to deficient/dysfunctional factors 8 and 9
- **Incidence** - A – 1 in 5-10000; B – 1 in 100,000
- **Pathogenesis** – inability to form fibrin clot
- **Diagnosis** - Factor levels (predict clinical severity)
  - hemophilia A – VIII activity <30-35%, NL 50-150%
    need normal/functional von Willebrand factor; genetic testing reveals DNA mutations in 98% of patients with hemophilia A
  - Hemophilia B – IX activity level <30%
Diagram of the coagulation cascade and fibrinolytic system. Key components include:

- **XIIa/platelets** activating IX to IXa.
- **TF/VIIa** and **X** activating Xa.
- **VIIIa** activated by **APC/PS**.
- **IIa** activated by **APC/PS**.
- Platelet activation.
- **XIIIa** converting to Fibrin.
- **PAI-I** inhibited by **tPA**.
- **FDP** formation from Fibrinogen.

Additional interactions include:

- **AT** inhibiting the cascade.

Source: Lockwood 2002
Hemophilia – genetic principles

- Factor IX – various mutations
- Factor VIII - partial inversion in F8 gene
  - Inversion deletion of carboxyl terminus (X chromosome) of factor VIII
  - Accounts for mutations in severe disease
  - inversion involves a intrachromosomal recombination b/n sequences in intron 22 of F8 and homologous sequences telomeric to F8
  - Variable expressivity – according to level of activity of factor
    - severe disease (<1% of activity); moderate (1-5% of activity); mild (5-25% of activity)
  - X-linked recessive -
    - carrier males affected (daughters obligate carriers) carrier females (50% of sons will be affected, and 50% of daughters carriers)
Hemophilia – pregnancy implications

- Factor VIII replacement (if <50%) – DDAVP - (0.4mcg/kg loading dose) IV - helps treat most bleeding; single IV dose triples factor VIII clotting activity, caution fluid overload, hyponatremia (with massive fluid admin, oxytocin)
  - Recombinant Factor VIII or IX
  - Cryoprecipitate has high concentrations of Factor VIII
  - If factor level > 50IU/dL or >50% - and coagulation profile normal
    - Regional anesthetic not contraindicated
- Establish carrier status if possible

- Fetal intracranial hemorrhage risk (3-25% with vaginal and CD, 60% with vacuum) reason to know gender – males at risk – avoid scalp electrodes, vacuum, prolonged labor/2nd stage, CD not necessarily protective if easy outlet forceps can be performed, otherwise low threshold for CD (Lee 2006, OMIM)

- Factor VIII levels increase throughout pregnancy – protects against PPH, but delayed PPH can ensue once factor VIII clotting levels return to baseline 48hr PP (Lee 2006)
Osteogenesis Imperfecta - overview

• Def - fragile bone disease due to mutations in collagen structural genes (4 types)

• Incidence: all 4 types – 1 in 15,000 (Nussbaum, p372)

• Pathogenesis – each collagen chain is made as a type 1 procollagen ‘triple-helix’ that is secreted into the extracellular space where it undergoes cleavage (of amino and carboxy terminal ends) that forms collagen; mature collagen fibrils are assembled and ultimately mineralized in bone

  – OI – 2 classes of mutations (>800 different mutations) –
    • Mutations that affect synthesis (reduction in amount of type 1 procollagen that is made )
    • Mutations affecting structure of molecules that make up procollagen 1

• Diagnosis – clinical (depends on type)

• Recurrence risk – 50% if dominant inheritance
OI – Genetic principles

- Inheritance – Autosomal dominant (most types and mutations); new mutation (type 2)
- Proα1 – chromosome 17; proα2 – chromosome 7
- Dominant negative – one type of mutation interferes with the production of normal pro-collagen molecules
  - Stoichiometry – normally have 2 proα1 molecules and 1 proα2 chain; if mutation is in proα1 then as the collagen molecule polymerizes, 3 of 4 pro-collagen chains are potentially affected, vs if proα2 is affected, then 1 of 2 collagen pro-collagen chains are potentially affected
    - proα1 - Ratio of normal:mutant molecules 1:3
    - Proα2 – ratio of normal:mutant molecules 1:1 (may be less severe)
  - “It’s better to have a mutation that produces no gene product, than one that produces an abnormal procollagen molecule” (Nussbaum p375)
OI – pregnancy implications

- Case of type I OI – 26 yo P0 - 15 weeks prenatal care
  - Blue sclera, multiple childhood fractures, 4’11”; appropriate, symmetric long bones; AD pedigree
  - Normal 17 week ultrasound; 50% risk of affected child
  - Risk of in-utero/intrapartum fracture
  - Maternal uterine rupture confirmed to be abnormal collagen on uterine biopsy (case reports – Krishnamoorthy, 2002; Christodoulou 2004)

- Prenatal diagnosis – typically of type 2 OI
Type 2 OI

- AD, most are new mutations
- “Perinatal lethal” (Nussbaum p373)
- Severe skeletal disease (fractures and deformities); dark sclera; lethal malformation
  - Sonographically – short bones, small thorax, angulation of bones from fx, decreased ossification of skull, irregular ribs
- Gene defect is missense mutation of glycine codons for $\alpha_1$ and $\alpha_2$ procollagen chains
- If detected prenatally – counseling should include option of termination
- Recurrence risk – 2-5% for T2 OI (Nyberg p698)
Ex of in-utero fracture
Type 2 OI – hypomineralized and short bones, frontal bossing, fractures
Thefetus.net

©2003 Ian Suchet
Hemoglobinopathies

• **Definition** –
  - qualitative (sickle cell – Beta globin gene mutation)
  - quantitative (thalassemia, unbalance of alpha or beta globin chains) abnormality in the hemoglobin molecule

• **Incidence** – allele frequency depends on ethnicity;
  - worldwide > 270 million heterozygous carriers;
  - > 300,000 affected homozygotes or compound heterozygotes born each year (ACOG 2007)
Thalassemias –
Beta globin gene -- chromosome 11
Alpha globin gene -- chromosome 16

Life span
Of RBC 120d
**Classification of α/β-Thalassemias** (ACOG bulletin, Nussbaum, Gelehter)

<table>
<thead>
<tr>
<th>Number of functional Globin Genes (ratio of α/β globin)</th>
<th>Genotype</th>
<th>Description</th>
<th>Clinical Features</th>
</tr>
</thead>
<tbody>
<tr>
<td>4 (1)</td>
<td>αα/αα</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>3 (0.8)</td>
<td>α-/αα</td>
<td>Heterozygous α-thal trait (silent carrier)</td>
<td>Asymptomatic (silent carrier)</td>
</tr>
<tr>
<td>2 (0.6)</td>
<td>α-/α-αα/--</td>
<td>“α-thal trait” affected</td>
<td>Mild anemia</td>
</tr>
<tr>
<td>1 (0.3)</td>
<td>α--1α, rest β</td>
<td>Hb H disease (β4 tetramers detected)</td>
<td>Hb H – marked hemolytic anemia at birth (MCV &lt;50mm3)</td>
</tr>
<tr>
<td>0 (0)</td>
<td>--/--All 4 γ</td>
<td>Hb Bart’s – no alpha globin</td>
<td>Hb Bart's (hydrops fetalis)</td>
</tr>
</tbody>
</table>

α thalassemia – diagnosed by DNA based testing (S. blot, PCR, ASO)

βthalassemia - βchain deficiency (Hb electrophoresis - >0.5% F, >3.5%% A2)
α-thalassemia

- Autosomal recessive; Classification table
- Chromosome 16 – 2 functioning α genes
  - Heterozygous α thal 2 (α-/αα) – silent carrier
  - ‘α thal trait’ – α thal 1 (2 of 4 α globin genes deleted)
    - Southeast Asians – (αα/--–) heterozygous for α 1, 2
    - Blacks – (α-/α-) – homozygous for α thal 2 chromosome
      - MCV slightly reduced, asymptomatic
  - Hb H → α-/-- essentially all 4 Beta chains, severe anemia
  - Hb Barts – hydrops (/----) all gamma chains
- Most common abnormality – leads to loss of 1 α-globin gene on a chromosome – unequal crossing over of α-globin cluster on chromosome 16
  - High degree of homology of nucleotide sequences around α1 and α2 genes

Gelehrter p107-109
β thalassemia

- Autosomal recessive; β-globin gene Chromosome 11
- Large number of mutations that can result in decreased or absent function of β-globin gene
- Due to 1 β globin gene per chromosome 11, chance for unequal crossing over is much reduced (vs α thal)
- Classes
  - Minor – 1 normal β-gene, 1 nonfunctional gene
  - Intermedia – abnormality of both β-globin chains, anemic, symptomatic, but not transfusion dependent
  - Major – No β-globin made (both genes mutated), no Hb A made, severe anemia, transfusion dependent
Thalassemia ($\alpha/\beta$) – overview

- Definition – quantitative abnormality of the globin chains
- Incidence – $\alpha$-thal trait - 0.01% in nonmalarial exposed populations Iceland, UK, Japan; 49% in southwest Pacific islanders
  - Hb H disease, hydrops fetalis – restricted to Mediterranean and SE Asia
  - $\beta$-thal trait – 1-2% Africans and African Americans; 30% in Sardinia
- Pathogenesis - deficient synthesis of $\alpha$-globin or $\beta$-globin chain that forms the hemoglobin molecule, unbalanced accumulation of alpha/beta subunits (Gelehrter, p96); childhood onset, hypochromic microcytic anemia, HSM, extramedullary hematopoiesis
  - ~80% untreated pts die within 5 years;
  - Transfusion therapy alone – death <30yo (due to infection, hemochromotosis)
  - Iron chelation therapy can reduce chance of hemochromotosis and cardiac, hepatic complications - from repeated transfusions

(OMIM)
Thalassemia – genetic principles

• Heterozygote advantage – carriers of trait display resistance to malaria; prevalence in an ethnic group reflects past and present exposure of a population to malaria
  – Ethnic variation in allele frequencies

• Gene dosage – amount of gene present affects degree of symptoms
Thalassemia & Pregnancy

- Thalassemia trait not increased risk
- Autosomal recessive implications, Screening at risk ethnic groups (Asians, Mediterranean, Blacks)
- Thalassemia major (little to no $\beta$ chain production) - pregnancy is recommended if normal cardiac function, Hb > 10g/dL after hypertransfusion and iron chelation therapy (ACOG 2007)
  - During pregnancy Hb goal >10 g/dL; Deferoxamine stopped
  - Fetal testing (serial growth scans, weekly testing); CD for obstetric indications
- $\beta$-thalassemia minor – mild anemia; only ppx iron; fetal testing (ACOG 2007)
- Supportive therapy – Hct >21% (Hb >6g/dL); ideal Hct > 30%
Sickle cell anemia – Overview

- **Definition** – AR hemoglobin disease due βglobin chain (chromosome 11) missense mutation that substitutes valine for glutamic acid at amino acid 6 (β-globin glu6val mutation)
- **Incidence** – 1 in 700 (African), carrier rate ~1 in 10
- **Pathogenesis** – the glu6val mutation DECREASES the solubility and deformability of the βglobin chain so that after repeated cycles oxygenation and attendant sickling, the chains become permanently ‘sickled’ and occlude capillaries causing infarctions (painful crisis, acute chest syndrome, asplenia); irreversible sickled cells are removed by the spleen and the rate of removal of erythrocytes from the circulation exceeds the production capacity of the bone marrow and causes a hemolytic anemia
- **Diagnosis** – Peripheral smear; Hemoglobin electrophoresis identifying Hb SS (p100 Gehleter) – normal adult A (97.5%), A2 (2%), F (0.5%)
Hgb electrophoresis
Electric field
Sickle (glu6val) valine in place of glutamine
Glutamine has a more Negative charge thus it travels further than Valine (S) or lysine (C)
-A = glutamine has the most negative charge – thus it goes far on the gel
-S = glutamine to valine (middle charge b/n +/−)
-C = glutamine to lysine (more + charge thus it does not go as far on the gel)
-A2 (most positive charge, thus it does not go far on the gel)
Sickle Cell Disease and genetic principles

- Heterozygote advantage, plays role in ethnic variation in allele frequency
- Novel property mutation - sickle cell disease is an exception to the allelic heterogeneity rule in that one specific mutation is responsible for the unique ‘novel’ properties of sickle Hb; Hb C is less soluble than Hb A and tends to crystallize in red cells, decreasing the deformability in capillaries and this also creates mild hemolysis, but Hb C does not sickle or form the rod shaped polymers like Hb S
<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>HB SS</th>
<th>Hb AS</th>
</tr>
</thead>
<tbody>
<tr>
<td>African American</td>
<td>1/700</td>
<td>1/14</td>
</tr>
<tr>
<td>Asian Indian</td>
<td>0/1600</td>
<td>1/700</td>
</tr>
<tr>
<td>Hispanic</td>
<td>1/46,000</td>
<td>1/180</td>
</tr>
<tr>
<td>Middle Eastern</td>
<td>0/22,000</td>
<td>1/360</td>
</tr>
<tr>
<td>Native American</td>
<td>1/17,000</td>
<td>1/180</td>
</tr>
<tr>
<td>White</td>
<td>1/160,000</td>
<td>1/600</td>
</tr>
<tr>
<td>Asian</td>
<td>0/200,000</td>
<td>1/1300</td>
</tr>
</tbody>
</table>
Sickle cell disease & Pregnancy

- Increased risk of morbidity/mortality – depends on severity of anemia
  - Hb SS and to lesser extent Hb SC- Risks include infection, acute chest syndrome, pain crises, dehydration, severe anemia, cholecystitis, preterm birth, low-birth weight infants (<2500g), fetal growth restriction, hospitalization
  - Folic acid supplementation – 4mg/day
  - Painful crisis (tx with pain control, oxygen, IV hydration) – avoid cold temp, heavy exertion, dehydration, stress
  - Acute chest syndrome (fever, tachypnea, chest pain, hypoxia)
  - Autosomal recessive implications for offspring
  - Prophylactic or exchange transfusion – goal of Hct - >21% (ideal ~30%) – decreases risk of painful crises, severe anemia, not necessarily associated with improved pregnancy outcome, less crises, less anemia (ACOG 2007)
Screening in pregnancy (ACOG, 2007)

- CBC, hemoglobin electrophoresis, ferritin (<10 mcg/dL – iron deficiency)
- Individuals of African, Southeast Asian, and Mediterranean descent are at increased risk for being carriers of hemoglobinopathies and should be screened
- Carriers or affected patients – genetic counseling, prenatal diagnosis if mutations have been defined in the parents for thalassemia – DNA mutation analysis for sickle cell disease is available 2 carriers or affected patients
- MCV < 80fL, normal ferritin – screen with hemoglobin electrophoresis
Fig. 1. Specialized antepartum evaluation for hematologic assessment of patients of African, Southeast Asian, or Mediterranean descent. Patients of Southeast Asian or Mediterranean descent should undergo electrophoresis if their blood test results reveal anemia. Abbreviations: CBC = complete blood count; RBC = red blood cell; MCV = mean corpuscular volume; Hb = hemoglobin.
Conclusions

• Keep inheritance patterns and recurrence risk straight

• Use OMIM, GeneTest for review and options for prenatal diagnosis and counseling
Notes re: bactrim in pregnancy
CREOG – extra slides, notes from genetics -end
Fetal Anomalies

Adapted from Anomaly presentation – Dr. Anthony Vintzileos
– Winthrop U, New York

• Head-Face
• Neck
• Spine
• Chest
• Abdomen
• Urinary tract
• Genitalia
• Extremities
Head Anomalies

- Acrania (absence of skull bones)/ Anencephaly (no brain/NTD)
- Ventriculomegaly
- Agenesis of corpus callosum
- Dandy-Walker complexes
- Holoprosencephaly
- Hydranencephaly
- Porencephaly/Schizencephaly
- Arachnoid cyst(s)
- Encephalocele/meningocele
- AV malformation
- Misc
Acrania (absence of skull bones)/Anencephaly (no brain/NTD)

- Lethal
- Multifactorial (NTD), 5, 10, 15%
- Maternal diabetes
- AEDs
- DDX – acrania, microcephaly, large encephalocele
- Workup
  - R/O spina bifida (50%)
  - R/O ABS (5%)
Ventriculomegaly/Hydrocephalus

• **Def** – shrinkage /dangling of choroid plexus

• **Posterior horn** >10mm
  - Mild 10-12
  - Mod 12-15
  - Overt/severe >15mm

• **Cannot tell hydrocephalus on ultrasound**

Fetus.net
Ventriculomegaly

- Mild/moderate 10-15mm
- DDX – normal variant, large CPC
- Workup
  - R/O chrom abn – 10% (T21)
  - R/O infection (TORCH)
  - R/O other anomalies
- Prognosis – if isolated (10% abnl neurodevelopment), 90% normal

- Severe/overt >15mm
- DDX
  - Holoprosencephaly
  - Hydranencephaly
  - Encephalocele
  - Dandy-Walker
  - Arachnoid cyst
  - Porencephaly
  - Other
- Workup
  - R/O OSB (25-30%)
  - R/O other anomalies (50%) – intracranial, cardiac (FE), renal GI, TORCH
- Prognosis
  - If isolated or with OSB (1/3, 1/3, 1/3)
  - 1/3 severe MR,
  - 1/3 moderate MR,
  - 1/3 normal
Agenesis of corpus callosum

- Absent corpus callosum/cavum septi pellucidi
- Upward displacement of 3rd ventricle
- Distended interhemispheric fissure
- Separated lateral ventricles
- Irregular radiate gyri

© 1999 Gianluigi Pilo
corpus callosum

CSP

3v

3v
Need to finish Vintzileos review
Adapted from Dr. Anthony Vintzileos ppt
Case – AV canal & pleural effusion
Case –23-week scan (4CV)
Case – 23 weeks

• Summary –
  - AV canal with pleural effusions thought to be due to fetal cardiac disease
  - Recurrence of congenital heart disease vs. aneuploidy (association of trisomy 21 and AV canal)*
  - No karyotype as the patient did not want the amniocentesis
  - Monitoring?
Case – 26 weeks

• 26 weeks – Pediatric Cardiology consult
  – Confirmed AV canal, suspected bicuspid aortic valve
  – ? Fetal ascites, concern for hydrops fetalis

• Sent to L&D for confirmation (OK)
  – Fetal monitoring (wrong)
  – Corticosteroids initiated (wrong)
  – NOT AN EMERGENCY, especially in a patient with a mechanical heart valve that is fully anticoagulated

• Lesson learned
Case – 29 weeks Hydrops & Fetal Demise

- Fetal karyotype of stillbirth – aneuploidy, not recurrence of congenital heart disease
  - Mosaicism with translocation resulting in trisomy 21
    - mos47,XY,+2,add(21)(p11.2)
    - 45,XY,der(15;21), (q10;q10)
    - 46,XY,+21,der(21;21)(q10;q10)
- Maternal karyotype – 46,XX
- Paternal karyotype not available

- Now pregnant again and did not get her planned aortic valve replacement
Case – Current pregnancy

19-week scan
Case – Current pregnancy
19-week scan
Case – Current pregnancy
19-week scan
Sensitivity of Ultrasound in Detection of Congenital Cardiac Disease

• Incidence of congenital heart disease
  - General population
    • 5.6 /1000 births (~0.05-0.08%)
  - Family history + for congenital heart disease
    • Maternal – 8-14%
    • Sibling – 5%

Goldenberg 2004, Grandjean Eurofetus study
Detection rates of congenital heart disease:
- 28% (Grandjean 2002 - EUROFETUS)
- 43% (Crane 1994 - RADIUS)

Goldenber 2004, Grandjean Eurofetus study 2002

http://www.fetalecho.com/
- DeVore (2008)
4-Chamber View + Outflow Tracts

- Detection improved
  - From 50% up to 80% by some examiners

Nyberg 2003
Huff anomalies
THE GENETIC SONOGRAM

Darren Farley, MD

Created by Robert W. Huff, M.D., MFM fellowship mentor
Rationale

• Fetuses with chromosomal disorders typically have structural malformations

• For each chromosomal disorder, characteristic sonographic features have been described

• Finding a structural abnormality carries a risk of a chromosomal disorder

• The presence of subtle findings may indicate a chromosomal disorder
<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Midtrimester</th>
<th></th>
<th>Term Liveborn</th>
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<tr>
<td></td>
<td>DS</td>
<td>All Aneuploidies</td>
<td>DS</td>
<td>All Aneuploidies</td>
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<tr>
<td>33</td>
<td>1/417</td>
<td>1/208</td>
<td>1/625</td>
<td>1/345</td>
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<td>34</td>
<td>1/333</td>
<td>1/152</td>
<td>1/500</td>
<td>1/278</td>
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<td>35</td>
<td>1/250</td>
<td>1/132</td>
<td>1/384</td>
<td>1/204</td>
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<td>1/192</td>
<td>1/105</td>
<td>1/303</td>
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<td>1/227</td>
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<td>1/19</td>
<td>1/50</td>
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<td>1/25</td>
<td>1/15</td>
<td>1/38</td>
<td>1/24</td>
</tr>
<tr>
<td>45</td>
<td>1/19</td>
<td>1/12</td>
<td>1/30</td>
<td>1/19</td>
</tr>
</tbody>
</table>

Abbreviation: DS, Down syndrome.

Ultrasound Findings Associated with Chromosomal Defects

- Head
- Face
- Neck
- Chest
- Heart
- Abdomen
- Kidneys
- Extremities
- Hydrops
Head findings

- Hydrocephaly
- Holoprosencephaly
- Dandy-Walker Malformation
- Strawberry head shape
Hydrocephaly
Holoprosencephaly
Dandy-Walker malformation
Strawberry head shape
Strawberry head shape
Face findings

- Cleft lip with or without Cleft palate
- Single nostril
- Hypotelorism
Cleft Lip with or without Cleft Palate
Single nostril
Hypotelorism
Neck findings

• Cystic hygroma
Cystic hygroma
Cystic hygroma
Chest findings

- Diaphragmatic hernia
Diaphragmatic hernia
Heart findings

- A-V canal
- Congenital heart disease
A-V canal
Congenital heart disease
VSD
Abdominal findings

- Omphalocele
- Duodenal atresia
Omphalocele
Duodenal atresia
Kidney findings

• Polycystic kidneys
Polycystic kidneys
Extremity findings

- Club foot
- Rocker bottom foot
- Polydactyly
- Clenched fist
Club foot
Rocker bottom foot
Polydactyly
Polydactyly
Clenched fist
Fluid findings

- Hydramnios
- Hydrops fetalis
Hydramnios
Hydrops fetalis
Hydrops fetalis
<table>
<thead>
<tr>
<th>Structural Defect</th>
<th>Population Incidence</th>
<th>Aneuploidy Risk</th>
<th>Most Common Aneuploidy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cystic hygroma</td>
<td>1/120 EU–1/6,000 B</td>
<td>60–75%</td>
<td>45X (80%); 21,18,13,XXY</td>
</tr>
<tr>
<td>Hydrops</td>
<td>1/1,500–4,000 B</td>
<td>30–80%*</td>
<td>13,21,18,45X</td>
</tr>
<tr>
<td>Hydrocephalus</td>
<td>3–8/10,000 LB</td>
<td>3–8%</td>
<td>13,18, triploidy</td>
</tr>
<tr>
<td>Hydranencephaly</td>
<td>2/1,000 IA</td>
<td>Minimal</td>
<td>13,18,18p-</td>
</tr>
<tr>
<td>Holoprosencephaly</td>
<td>1/16,000 LB</td>
<td>40–60%</td>
<td>21,18,13,22,8,9</td>
</tr>
<tr>
<td>Cardiac defects</td>
<td>7–9/1,000 LB</td>
<td>5–30%</td>
<td>21</td>
</tr>
<tr>
<td>Complete atrioventricular canal</td>
<td>40–70%</td>
<td></td>
<td>21</td>
</tr>
<tr>
<td>Condition</td>
<td>Frequency Range</td>
<td>Risk Grade</td>
<td>Reference</td>
</tr>
<tr>
<td>---------------------------------</td>
<td>--------------------------</td>
<td>------------</td>
<td>------------</td>
</tr>
<tr>
<td>Diaphragmatic hernia</td>
<td>1/3,500–4,000 LB</td>
<td>20–25%</td>
<td>13,18,21,45X</td>
</tr>
<tr>
<td>Omphalocele</td>
<td>1/5,800 LB</td>
<td>30–40%</td>
<td>13,18</td>
</tr>
<tr>
<td>Gastroscisis</td>
<td>1/10,000–15,000 LB</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Duodenal atresia</td>
<td>1/10,000 LB</td>
<td>20–30%</td>
<td>21</td>
</tr>
<tr>
<td>Bowel obstruction</td>
<td>1/2,500–5,000 LB</td>
<td>Minimal</td>
<td></td>
</tr>
<tr>
<td>Bladder outlet obstruction</td>
<td>1–2/1,000 LB</td>
<td>20–25%</td>
<td>13,18</td>
</tr>
<tr>
<td>Prune belly syndrome</td>
<td>1/35,000–50,000 LB</td>
<td>Low</td>
<td>18,13,45X</td>
</tr>
<tr>
<td>Facial cleft</td>
<td>1/700 LB</td>
<td>1%</td>
<td>13,18, Deletions</td>
</tr>
<tr>
<td>Limb reduction</td>
<td>4–6/10,000 LB</td>
<td>8%</td>
<td>18</td>
</tr>
<tr>
<td>Club foot</td>
<td>1.2/1,000 LB</td>
<td>6%</td>
<td>18,13,4p-,18q-</td>
</tr>
<tr>
<td>Single umbilical artery</td>
<td>1%</td>
<td>Minimal</td>
<td></td>
</tr>
</tbody>
</table>
Typical Appearance of Different Chromosomal Problems

- Trisomy 21 – Down syndrome
- Trisomy 18 – Edwards syndrome
- Trisomy 13 – Patau syndrome
- 45, X – Turner syndrome
Trisomy 21 – Down syndrome

- Cardiovascular – A-V canal and VSD
- Central nervous system – mild ventriculomegaly
- Gastrointestinal – duodenal atresia
- Craniofacial – cystic hygroma
- Hydrops fetalis
Trisomy 18 – Edwards syndrome

• Head – strawberry shape, choroid plexus cysts, small cerebellum, ventriculomegaly
• Face – clefts, micrognathia
• Cardiovascular – septal and valvular defects
• G-I – omphalocele and diaphragmatic hernia
• Extremities – clenched fists, rocker bottom feet, club feet
• Kidneys – horseshoe kidney and hydrenephrosis
Trisomy 13 – Patau syndrome

- Head – holoprosencephaly, facial clefts, single nostril, hypotelorism and cyclopia
- Neural tube defects
- Cardiac – septal defects, Tetralogy of Fallot, hypoplastic left heart
- G-I – omphalocoele
- Kidneys – polycystic kidneys
- Extremities – polydactyly
45, X – Turner syndrome

- Neck – cystic hygromas
- Cardiovascular – coarctation
- General – hydrops fetalis
Next Step in Development of the Genetic Sonogram

• In the mid-1980s, Dr. Nicolaides described the “lemon” sign and the “banana” sign associated with spina bifida and showed how ultrasound could identify subtle markers for birth defects

• Subsequently, many investigators began to look for markers of chromosomal disorders

• The original studies were in women scheduled to have an amniocentesis
Lemon
Lemon sign and Banana sign
Subtle Findings in Women at High Risk for a Chromosomal Problem

- Head
- Heart
- Kidneys
- Intestines
- Extremities
Head

- Choroid plexus cysts
- Thickened nuchal fold
Choroid plexus cysts
Thickened nuchal fold
Heart

- Echogenic intracardiac focus
Echogenic intracardiac focus
Intestines

• Echogenic bowel
Echogenic bowel
Kidneys

• Pylectasis
Pylectasis
Extremities

- Short femur
- Short humerus
- Sandal toe
- Middle phalanx of 5th finger small or absent
Sandal toe
5\textsuperscript{th} Finger - normal
Development of the Genetic Sonogram

- Intended for use to reduce risk of a chromosomal defect in a woman at high risk because of age or abnormal serum screen
Rationale for a Genetic Sonogram

• Many women (30-50%) who are candidates for amniocentesis because of advanced maternal age or abnormal serum screening test do not want an invasive procedure because of the risk of pregnancy loss.

• Often they will accept less than 100% accuracy for 100% safety (ultrasound).
Genetic Sonogram

- Nyberg’s scoring system for predicting the likelihood of Down syndrome is based on the woman’s *a priori* risk multiplied by a likelihood ratio for specific sonographic findings.
- Negative findings for all markers reduces the risk of Down syndrome by a factor of 60%.
Nyberg’s Genetic Sonogram

<table>
<thead>
<tr>
<th>Marker</th>
<th>Likelihood ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural anomaly</td>
<td>25</td>
</tr>
<tr>
<td>Nuchal thickening</td>
<td>18.6</td>
</tr>
<tr>
<td>Echogenic bowel</td>
<td>5.5</td>
</tr>
<tr>
<td>Short humerus</td>
<td>2.5</td>
</tr>
<tr>
<td>Short femur</td>
<td>2.2</td>
</tr>
<tr>
<td>Echogenic intracardiac focus</td>
<td>2</td>
</tr>
<tr>
<td>Renal pylectasis</td>
<td>1.6</td>
</tr>
<tr>
<td>NORMAL SCAN</td>
<td>0.4</td>
</tr>
</tbody>
</table>
Benacerraf’s Genetic Sonogram

- Dr. Benacerraf, who was very instrumental in starting the whole process of describing markers for chromosomal problems, devised a scoring system to reduce the risk of Down syndrome in a patient who is at high risk because of age or serum screen results.
Benacerraf’s Genetic Sonogram

• In her scheme, 2 points qualifies for an amniocentesis
• Women get 1 point for maternal age 35-39 at delivery and 2 points for age 40 or more at delivery
• 2 points are also awarded for a structural malformation or for a thickened nuchal fold
# Benacerraf’s Genetic Sonogram

<table>
<thead>
<tr>
<th>Marker</th>
<th>Points</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structural malformation</td>
<td>2</td>
</tr>
<tr>
<td>Thickened nuchal fold</td>
<td>2</td>
</tr>
<tr>
<td>Short femur</td>
<td>1</td>
</tr>
<tr>
<td>Short humerus</td>
<td>1</td>
</tr>
<tr>
<td>E.I.F.</td>
<td>1</td>
</tr>
<tr>
<td>Hyperechoic bowel</td>
<td>1</td>
</tr>
<tr>
<td>Pylectasis</td>
<td>1</td>
</tr>
</tbody>
</table>
Benacerraf’s Genetic Sonogram

- Under Dr. Benacerraf’s scheme, a woman of 35-39 years old could avoid an amniocentesis if her scan has none of the markers present.

- The finding of a thickened nuchal fold or of a structural anomaly would prompt an amniocentesis at any age.
Problems with the Genetic Sonogram

- Finding a marker for chromosomal disorder in a “low risk” woman has an unknown significance and can terrify her*

Problems with the Genetic Sonogram

- A meta-analysis showed that ultrasound screening for Down syndrome is not a sensitive technique except for nuchal thickening.*

Conclusions

• Fetuses with chromosomal abnormalities frequently have structural malformations and/or a thickened nuchal fold

• Women at high risk for a chromosomal problem because of age or serum screen may have their risk reduced if none of the markers is present
Conclusions cont.

• The presence of a single marker for Down syndrome or another chromosomal problem in a woman at low risk need not mandate invasive testing, but it does mandate discussion in a supportive atmosphere.
Huff genetics
Genetic Counseling and Prenatal Diagnosis

Darren Farley, MD
Created by Robert W. Huff, M.D., MFM fellowship mentor
Genetic Counseling and Prenatal Diagnosis

Learning Objectives:

1. Identify people who may benefit from genetic counseling
2. Describe the process of genetic counseling
3. List common techniques for prenatal diagnosis
4. Describe the indications, timing, accuracy, limitations and risks of each procedure
5. Identify the diagnostic tests which can be performed with each technique
Genetic Counseling
Genetic Counseling-Indications

- Genetic reasons
  A. Chromosomal
  B. Single gene disorders
  C. Polygenic/multifactorial
- Exposures
- Poor pregnancy outcome
- Abnormal screening tests
# Genetic Questionnaire

## Prenatal Genetic Screen

<p>| | | | |</p>
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Name</strong></td>
<td><strong>Patient #</strong></td>
<td><strong>Date</strong></td>
<td></td>
</tr>
</tbody>
</table>

1. Will you be 35 years or older when the baby is due?  
   - Yes  
   - No

2. Have you, the baby’s father, or anyone in either of your families ever had any of the following disorders?  
   - Down syndrome (mongolism)  
   - Other chromosomal abnormality  
   - Neural tube defect, i.e., spina bifida (meningomyelocele or open spine), anencephaly  
   - Hemophilia  
   - Muscular dystrophy  
   - Cystic fibrosis  
   - If yes, indicate the relationship of the affected person to you or to the baby’s father  
   - Yes  
   - No

3. Do you or the baby’s father have a birth defect?  
   - Yes  
   - No  
   - If yes, who has the defect and what is it?  

4. In any previous marriages, have you or the baby’s father had a child born, dead or alive, with a birth defect not listed in question 2 above?  
   - Yes  
   - No

5. Do you or the baby’s father have any close relatives with mental retardation?  
   - Yes  
   - No

6. Do you, the baby’s father, or a close relative in either of your families have...  
   - Yes  
   - No
### Genetic Questionnaire

<table>
<thead>
<tr>
<th>Question</th>
<th>Yes</th>
<th>No</th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Do you, the baby's father, or a close relative in either of your families have a birth defect, any familiar disorder, or a chromosomal abnormality not listed above?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>7. In any previous marriage, have you or the baby's father had a stillborn child or three or more first-trimester spontaneous pregnancy losses?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>8. If you or the baby's father are of Jewish ancestry, have either of you been screened for Tay-Sachs disease?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>9. If you or the baby's father are black, have either of you been screened for sickle cell trait?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>10. If you or the baby's father are of Italian, Greek, or Mediterranean background, have either of you been tested for β-thalassemia?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>11. If you or the baby's father are of Philippine or Southeast Asian ancestry, have either of you been tested for α-thalassemia?</td>
<td>Yes</td>
<td>No</td>
</tr>
<tr>
<td>12. Excluding iron and vitamins, have you taken any medications or recreational drugs since becoming pregnant or since your last menstrual cycle? (Include nonprescription drugs). If yes, give name of medication and time taken during pregnancy.</td>
<td>Yes</td>
<td>No</td>
</tr>
</tbody>
</table>

Table 1. Prenatal genetic screen. Questionnaire for identifying couples having increased risk for offspring with genetic disorders. Any persons replying “YES” to a question should be offered appropriate counseling. If the patient declines further counseling or testing, this should be noted in the chart. Given that genetics is a field in a state of flux, alterations or updates to this form will be required periodically. From *Genetics in Obstetrics and Gynecology* by Simpson & Golbus.
Chromosomal Disorders

- Previous child or one of the parents with a chromosomal disorder
- Advanced Maternal Age - 35 or more at the time of delivery
Maternal Age and Risk of Chromosomal Disorder

Table 2. Maternal Age and Chromosomal Abnormalities (Livebirths)\(^a\)

<table>
<thead>
<tr>
<th>Maternal Age</th>
<th>Risk for Down syndrome</th>
<th>Total Risk for Chromosomal Abnormalities</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>1/1,667</td>
<td>1/526(^b)</td>
</tr>
<tr>
<td>21</td>
<td>1/1,667</td>
<td>1/526(^b)</td>
</tr>
<tr>
<td>22</td>
<td>1/1,429</td>
<td>1/500(^b)</td>
</tr>
<tr>
<td>23</td>
<td>1/1,429</td>
<td>1/500(^b)</td>
</tr>
<tr>
<td>24</td>
<td>1/1,250</td>
<td>1/476(^b)</td>
</tr>
<tr>
<td>25</td>
<td>1/1,250</td>
<td>1/476(^b)</td>
</tr>
<tr>
<td>26</td>
<td>1/1,176</td>
<td>1/476(^b)</td>
</tr>
<tr>
<td>27</td>
<td>1/1,111</td>
<td>1/455(^b)</td>
</tr>
<tr>
<td>28</td>
<td>1/1,053</td>
<td>1/435(^b)</td>
</tr>
<tr>
<td>29</td>
<td>1/1,000</td>
<td>1/384(^b)</td>
</tr>
<tr>
<td>30</td>
<td>1/952</td>
<td>1/385(^b)</td>
</tr>
<tr>
<td>31</td>
<td>1/909</td>
<td>1/322(^b)</td>
</tr>
<tr>
<td>32</td>
<td>1/769</td>
<td>1/317(^b)</td>
</tr>
<tr>
<td>33</td>
<td>1/625</td>
<td>1/260</td>
</tr>
<tr>
<td>34</td>
<td>1/500</td>
<td>1/224</td>
</tr>
</tbody>
</table>
Maternal Age and Risk of a Chromosomal Disorder

<table>
<thead>
<tr>
<th>Age</th>
<th>Risk Prevalence</th>
<th>Risk Prevalence</th>
</tr>
</thead>
<tbody>
<tr>
<td>33</td>
<td>1/625</td>
<td>1/260</td>
</tr>
<tr>
<td>34</td>
<td>1/500</td>
<td>1/204</td>
</tr>
<tr>
<td>35</td>
<td>1/385</td>
<td>1/164</td>
</tr>
<tr>
<td>36</td>
<td>1/294</td>
<td>1/130</td>
</tr>
<tr>
<td>37</td>
<td>1/227</td>
<td>1/103</td>
</tr>
<tr>
<td>38</td>
<td>1/175</td>
<td>1/82</td>
</tr>
<tr>
<td>39</td>
<td>1/137</td>
<td>1/65</td>
</tr>
<tr>
<td>40</td>
<td>1/106</td>
<td>1/51</td>
</tr>
<tr>
<td>41</td>
<td>1/82</td>
<td>1/40</td>
</tr>
<tr>
<td>42</td>
<td>1/64</td>
<td>1/32</td>
</tr>
<tr>
<td>43</td>
<td>1/50</td>
<td>1/25</td>
</tr>
<tr>
<td>44</td>
<td>1/38</td>
<td>1/20</td>
</tr>
<tr>
<td>45</td>
<td>1/30</td>
<td>1/15</td>
</tr>
<tr>
<td>46</td>
<td>1/23</td>
<td>1/12</td>
</tr>
<tr>
<td>47</td>
<td>1/18</td>
<td>1/10</td>
</tr>
<tr>
<td>48</td>
<td>1/14</td>
<td>7</td>
</tr>
<tr>
<td>49</td>
<td>1/11</td>
<td></td>
</tr>
</tbody>
</table>

*a* Because sample size for some intervals is relatively small, confidence limits are sometimes relatively large. Nonetheless, these figures are suitable for genetic counseling.

*b* 47,XXX excluded for ages 20-32 years (data not available). From Obstetrics: Normal and Problem Pregnancies by Gabbe, Niebel & Simpson
Single Gene Disorders

• Autosomal Dominant
• Autosomal Recessive
• X-linked
Autosomal Dominant

- Males and females equally affected
- Affected person has an affected parent
- Many are structural
- Many are new mutations
- Penetrance and expressivity are important
- Age of onset is important
- 50% recurrence risk
Pedigree Symbols

- Male
- Female
- Sex not indicated
- Deceased
- Affected
- Heterozygous
- General Characteristics of Disease
- Heterozygous female carrier of X-linked trait
- Maternal
- Affection/Marriage

- Pregnant
- 23rd week, see comments
- Fetal
- Birth in Chronic Disease of Birth
- Monosomy Tethyl
- Down syndrome
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
- Zygous Tertiary
Autosomal Dominant Pedigree
Autosomal Dominant Conditions

- Neurofibromatosis
- Autosomal dominant polycystic kidney disease
- Huntington’s disease
- Waardenburg syndrome
- Achondroplasia
- Tuberous sclerosis
Autosomal Recessive

- Males and females equally affected
- Carrier parents are usually normal
- Most are biochemical disorders
- Most are usually the first case in the family
- Consanguinity
- 25% recurrence risk
Autosomal Recessive Pedigree
Autosomal Recessive Conditions

- Cystic fibrosis
- Sickle cell anemia
- Congenital adrenal hyperplasia
- Phenylketonuria
- Autosomal recessive polycystic kidney disease
- Meckel-Gruber syndrome
X-linked

- Males affected
- Some carrier females mildly affected
- Affected males related through carrier females
- No male to male transmission
- 50% recurrence risk in males
X-linked Pedigree
X-linked Conditions

- Duchenne muscular dystrophy
- Hemophilia
- Fragile X
Polygenic/multifactorial

- More than one gene involved and possibly environmental factors
- Many are surgically treatable
- Threshold risk
- 2-5% recurrence risk
- Sex of proband may influence recurrence
Polygenic/multifactorial Conditions

• Neural tube defects
• Congenital heart disease
• Cleft lip with or without cleft palate (males)
• Cleft palate (females)
• Club foot
Exposures

- Radiation
- Prescription drugs
- Street drugs
- Chemicals
- Infections
Poor Pregnancy Outcome

- Repetitive abortions
- Stillbirth or neonatal death
- History of birth defects
Screening Tests

Dictionary definition of Screening.

2. Examination of a group of usually asymptomatic individuals to detect those with a high probability of having a given disease.
Recommendations by ACOG and ACMG

- Women over 35 years of age should be offered diagnostic testing for chromosomal problems in the fetus and screening for neural tube defects and cystic fibrosis.

- Women under age 35 should be offered screening tests for neural tube defects, cystic fibrosis and chromosomal problems in the fetus.
Genetic Counseling

• Most physicians should be able to provide the basics
• Provide practical information about the risk of developing or transmitting an inherited disorder or birth defect
• Provides information in a non-directive way so people can make their own informed decision
PRENATAL DIAGNOSIS
PRENATAL DIAGNOSIS

Goal is to identify fetal problems prior to birth to assist in planning the remainder of the pregnancy.
Prenatal Diagnosis Techniques

- Ultrasound
- Amniocentesis – standard and early
- Chorionic Villus Sampling (CVS)
- Fetal Blood Sampling, also called Cordocentesis or Percutaneous Umbilical Blood Sampling (PUBS)
- Fetal Cell Isolation from Maternal Blood
- Free Fetal DNA and RNA in Maternal Blood
ULTRASOUND

- For Screening
- For Diagnosis
Ultrasound Uses

- Measure structures
- Identify normal and abnormal anatomy
- Guide procedures such as:
  - Amniocentesis
  - CVS
  - Fetal blood sampling
Ultrasound-Indications

- Suspected twins
- Suspected abnormal pregnancy-pelvic mass, ectopic, molar, IUFD
- Too much or too little amniotic fluid
- Evaluate fetal anomaly
- Evaluate placental location
- Adjunct to procedures-amnio, cerclage, external version
- Biophysical evaluation of fetus
- Determine fetal presentation
- Evaluate gestational age-too large, too small
Ultrasound-first trimester

Transvaginal Scan

1. Identify gestational sac and its location
2. Identify embryo and crown-rump length (nuchal translucency)
3. Record fetal number
4. Document fetal heart activity
5. Evaluate uterus and adnexal area
Ultrasound – first trimester
Ultrasound Basic Scan - second and third trimesters

- Identify fetal number, life and presentation
- Estimate fetal age - measure several structures
- Estimate amniotic fluid volume
- Locate the placenta
- Evaluate uterus and adnexal areas
- Survey fetal anatomy
Basic Scan-fetal anatomy

- Cerebral ventricles
- Four chamber heart and thorax
- Spine
- Stomach
- Renal region
- Abdominal wall
- Urinary Bladder
Basic Scan - what should you see?

- Anencephaly
- Hydrocephaly
- Ascites
- Hydronephrosis
- Hydrothorax
- Omphalocele
- Gastroschisis
Basic Scan - hydrocephaly
Basic Scan - ascites
Basic Scan - omphalocele
Basic Scan—what do you miss?

- Cleft palate
- Ambiguous genitalia
- Transposition of great vessels
- Agenesis of corpus callosum
- Hemivertebrae
Ultrasound - factors affecting fetal visualization positively

- Equipment - no longer an important factor
- Time taken for the scan
- Training, skill and knowledge of the person doing the scan
Ultrasound - factors affecting fetal visualization negatively

- Maternal factors - obesity, scars and edema
- Gestational age of pregnancy (22-24 weeks is best)
- Fetal factors - position and oligohydramnios
- Organ system being evaluated
- Time of appearance of anomalies
Amniocentesis

- History
- Early amniocentesis
- Technique
Amniocentesis
Amniocentesis - history

- First study
  NICHD Study
  9 centers
  July 1, 1971 – June 30, 1973

J.A.M.A., 1976
NICHD STUDY

- Designed a registry to be “representative of the national experience”

- Goal - 1000 subjects and 1000 controls

- Designed to discover a doubling of adverse events in the study group
NICHD STUDY

- 1,040 Patients
- 992 Controls (24% not matched)
- 29% had ultrasound to locate the placenta
  (4 sets of twins scanned and only 1 set diagnosed)
NICHD STUDY

- Fetal loss rate 3.5% for study group
- Fetal loss rate 3.2% for control group
• Ultrasound for placental location
• Size of the needle used, unless larger than 18 ga
• Participating institution or other setting
• Bloody fluid or volume removed
NICHD STUDY losses were related to

- Needle insertions
  1 insertion - 2.9% loss
  2 insertions - 4.3% loss - not statistically different
  3 insertions or more - 8.1% loss rate - statistically different
- Brownish fluid at the time of amniocentesis
NICHD STUDY complications within one week

- Vaginal bleeding --------- 12
- Amniotic fluid leakage---- 11
- Labor pains-------------- 3
- Spontaneous abortion---- 2
- Amnionitis--------------- 1
NICHD STUDY accuracy – 99.4%

- 1 Error in metabolic diagnosis
- 3 Errors in sex diagnosis
- 2 Trisomy 21 after diagnosis of normal
- Total – 6 errors in 1,040 patients
Amniocentesis-technique

- Prep abdomen
- Sterile technique
- Ultrasound guidance
- Not over 2 insertions
Amniocentesis
Early Amniocentesis

• Definition—originally less than 15 weeks, later came to be less than 13 weeks (first trimester)
• Difficulties—few cells for growth and tenting membranes
• Safety—relatively large amounts of fluid removed
Early Amniocentesis

- Study on early amniocentesis was stopped because of a high complication rate
- 4.4% leaked amniotic fluid
- Many who leaked developed talipes equinovarus
- Seldom used presently
CEMAT
Canadian Early vs Midtrimester Amnio Trial

• Early amnio is 11 to 12 6/7 weeks and Midtrimester is 15 to 16 6/7 weeks
• 4374 women randomized
• 22 ga needle used for both
• 10 ml fluid removed for EA and 20ml for MA
• Fetal loss 2.6% for EA and 0.8% for MA
• 28 culture failures for EA vs 1 for MA
CEMAT

- 3.5% of EA patients leaked fluid vs 1.6%
- 3/4 occurred within 1 day of the procedure and lasted 3 days
- There were 9 fetal losses in the early leakage group -- 8 after EA, 1 after MA
- Talipes -- 0.05% after MA
  -- 1.0% after EA without leak
  -- 9.8% after EA with a leak
Amniocentesis-indications

• Advanced Maternal Age
• History of chromosomal disorders
• Abnormal screening test
• Abnormal ultrasound examination
• Risk of a Mendelian disorder
Amniocentesis-studies

- Karyotype
- Fluorescent *in situ* hybridization (FISH)
- Alpha fetoprotein
- Enzyme analysis
- Molecular analysis (PCR)
KARYOTYPE

Figure 2–5. A human male karyotype with Giemsa banding (G banding). The chromosomes are individually labeled, and the seven groups A to G are indicated. Photomicrograph courtesy of R. G. Worton.
Amniocentesis - risks

• Spotting
• Needle stick of the fetus
• Infection
• Leakage of amniotic fluid
• Pregnancy loss
Amniocentesis-accuracy and limitations

- Virtually 100 % accurate
- Cannot detect all possible problems
Amniocentesis-problems

- Failure to obtain fluid
- Maternal cell contamination
- Inability to grow cells
- Unexpected findings-47,XYY; de novo rearrangements; mosaicism
Ambiguous Results

• Usually establish 2-3 cultures
• 1 abnormal cell in 1 culture = artefact
  – level 1 mosaicism or pseudo mosaicism
• 2 or more abnormal cells in 1 culture = could be artefact or real
  – level 2 mosaicism, 20% chance real mosaicism
• Abnormal cells in 2 or more cultures = true mosaicism
  – level 3 mosaicism
  – To resolve need to repeat amniocentesis or do FBS
Chorionic Villus Sampling

• CVS developed in the 1980s to allow for earlier diagnosis and pregnancy termination if desired
• Generally performed at 10-12 weeks of pregnancy
CVS-history

- Blind aspiration --- 1975
- Endoscopic biopsy --- 1982
- Ultrasound directed transcervical aspiration --- 1983
- Ultrasound directed transabdominal aspiration --- 1988
CVS
CVS-advantages

• Earlier Diagnosis-First trimester
  More time to prepare for birth
  Earlier and safer termination, if desired
  Fetal therapy (adrenal hyperplasia)

• Quicker results-Direct prep
CVS-questions, safety and accuracy

- Failure to obtain a specimen (1-2%)
- Infection (transcervical)
- Maternal cell contamination
- Mosaicism
- Pregnancy losses
CVS studies

• Canadian trial
• United States trial
• CVS registry of the first 100,000 patients voluntarily submitted
EARLY AMNIO vs CVS -- DENMARK

- Baseline ultrasound at 10 weeks
- 1160 pregnant women randomized to CVS at 10-12 weeks or early amnio at 11-13 wks
- 20 ga needle used for amnio, filter also used
- Approximately 25 ml of fluid filtered for cells
- Double needle used for CVS (all abdominal) 18 ga and 21 ga
EARLY AMNIO vs CVS -- DENMARK

- Study stopped early because of high incidence of talipes equinovarus in the early amnio group -- 9 vs 0
- This was strongly associated with amniotic fluid leakage (4.4% leaked)
- Fetal loss rates were not different, but ...
- 13 CVS patients required another sample vs 1 in the early amnio group and 4 CVS patients had an amnio because of difficulty
CVS-indications and studies

- Very similar to those for amniocentesis except no amniotic fluid studies can be done such as alpha fetoprotein
CVS-risks

- Limb reduction defects when done before 10 weeks
- Greater pregnancy loss rate – 1-2 %
Fetal Blood Sampling

- Also called funipuncture, cordocentesis and percutaneous blood sampling (PUBS)
- Developed in late 1970s with fetoscope, but the loss rate was 5%
- Refined in the late 1980s with ultrasound guidance
PUBS-technique

- A needle is inserted transabdominally, with ultrasound guidance into the umbilical cord. The site where the cord attaches to the placenta is preferred.
- Alternate sites include a “free loop” of cord, the umbilicus, the intrahepatic vein, and even the heart has been used.
PUBS-timing and studies

- Generally only after 20 weeks of pregnancy
- Any study that can be done on blood can be done on fetal blood—rapid karyotype, anemia evaluation, platelet counts, detecting fetal infection and checking for immune deficiency syndromes
- Provide access for fetal transfusion
• **MUST** confirm the blood is fetal!!
• Generally confirm by measuring the Mean Corpuscular Volume (MCV)
• Fetal erythrocytes measure 120-160 fl
• Maternal, measure 80-95 fl
PUBS-difficulties and risks

- Inability to obtain blood
- Bleeding
- Hematoma
- Infection
- Fetal bradycardia
- Loss rate around 1% - higher before 20 weeks or with IUGR (thin cord)
Fetal Cells in Maternal Blood

- Advantage—could be done early in pregnancy with no risk to the mother or to the pregnancy
Fetal Cell Isolation from Maternal Blood

- Fetal cells known to be in maternal blood from the first trimester on
- Very few in number
- Attempts to isolate them have been fraught with difficulty - always 5 years away
Fetal Cells in Maternal Blood

- Erythroblasts, nucleated red cells have been among the best candidates for isolation
- **BUT** it has not been possible to obtain cell division on fetal cells from maternal blood so studies have been limited to PCR amplification of fetal DNA and FISH studies of chromosomes in the interphase nucleus.
Fetal Cells in Maternal Blood

- NIFTY study from NIH started in 1987
- To date it has not been better than a “single marker” to detect fetal aneuploidy
- Lancet – 2003 says it is difficult and not clinically practical
Comparative Genomic Hybridization (CGH)

- Compares reference DNA with DNA from the person being tested to look for deletions or duplications which are too small to be seen on a karyotype.
- Usually used for persons with unexplained dysmorphic features, retardation, birth defects developmental delay, autism, seizures or any suspicion of genomic imbalance.
Too much or too little genetic material can cause differences in growth and development. Oligo Array is a diagnostic procedure that looks for the presence of too much or too little genetic material and is more sensitive than traditional chromosome analysis.

Deletion: Too little genetic material

Duplication: Too much genetic material
What Can Oligo Arrays Detect?

- Too few or too many chromosomes
- Deletions ranging from very large to very small
- Duplications ranging from very large to very small
- The exact boundaries of deletions and duplications
- Specific genes that may be involved in a disorder

What Can Oligo Arrays Not Detect?

- Changes that do not result in a gain or loss of genomic material
Typical Pattern of Negative Microarray Result

Normal amount of DNA (2 copies) appears as “yellow” dots on array

Hundreds of spots are graphically lined up to depict one whole chromosome

Normal results seen as even signals around baseline
Typical Pattern of a Genomic Deletion

Probes in deleted region appear as "green" dots on array
Typical Pattern of a Genomic Duplication

Probes in duplicated region appear as “red” dots on array

Normal  Duplication

3 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies
2 copies

Duplication seen as “jump” in signal intensity
Microdeletion on the short arm of chromosome 7 associated with a known genetic disorder
Mapping the fetus genome

Since the human genome was mapped, technology has advanced so rapidly that in a few decades pregnant women may know in the first trimester whether their baby will have inherited metabolic conditions, diseases, or disorders such as mental retardation, partial blindness, an endocrine disorder, a rare blood disease, or even a predisposition to diabetes, endometriosis, or cancer later in life.

"I think where this technology is heading is to a point where we can comprehensively sequence the fetus’s entire genome early in pregnancy," said Aleksandar Rajkovic, MD, PhD, associate professor of ob-gyn at Baylor College of Medicine in Houston and a member of ACOG’s Committee on Genetics. "Technologies are emerging that may change the landscape of what obstetricians diagnose and when we diagnose it."

Although sequencing of the entire fetal genome in utero may still be some years away, today there are DNA microarray technologies that experts believe will soon replace conventional karyotyping. Using DNA microarrays and the concept of comparative genomic hybridization—called CGH—genetic mutations can be revealed by overlapping an individual’s DNA pattern with a normal DNA pattern. Current research has used the technology to determine potential genetic causes for a child’s mental retardation after he is born, but such technology will likely not be limited to pediatrics.

"I’ve no doubt it will be applied to prenatal care," said Deborah A. Driscoll, MD, professor and chair of the department of ob-gyn at the University of Pennsylvania in Philadelphia.

"I think where this technology is heading is to a point where we can comprehensively sequence the fetus’s entire genome early in pregnancy."

Anthony R. Gregg, MD, director of maternal-fetal medicine and medical director of genetics at the University of South Carolina and chair of ACOG’s Committee on Genetics, provided an analogy to explain the leap forward that CGH technology provides: "Imagine you have a bookshelf with a set of encyclopedias on it. A karyotype offers a bird's eye view of those books from 30 to 40 feet away. You can determine if a book is missing or if there is an extra book that doesn’t belong. Now, imagine that bird’s eye view becoming fine enough that you can read actual sections and paragraphs in one of the books—that’s what CGH offers, according to Dr. Gregg.

However, Dr. Gregg said, two things need to happen before DNA microarrays are ready for "prime time" in prenatal screening. First, researchers need to catalog the links between ultrasound findings and conditions tested for on the microarray. Second, the cost of implementing the technology must be reduced before CGH can be considered an appropriate screening tool.

Parsing the ethical issues

As the technology develops, the medical field—and society as a whole—will likely debate the surrounding ethical issues. Some of these questions are the same ones that have been debated with newborn screening: Do you screen for disorders and conditions that have no cure? Do you screen all patients for new diseases? How many diseases will patients be tested for?

"So many genes have been identified; the question is Where do we draw the line?" Dr. Driscoll said.
CGH for Prenatal Diagnosis

• Currently studies are underway to use array CGH to analyze samples from amniocentesis or CVS as a possible first line test for chromosomal abnormalities

• Balanced translocations and inversions cannot be detected because there is no change in the copy number
Free Fetal DNA (ffDNA) in the Maternal Blood

• Shorter fragments than maternal free DNA found as early as 32 days post conception

• Increases with gestational age – 3% of free DNA is fetal in first trimester – 6% in third trimester

• Cleared in 2 hours

• Sources – placental apoptosis, fetal cells in maternal circulation
ffDNA uses

- Isoimmune disorders – currently in use in Europe for this – fetal Rh status
- Aneuploidy screening and diagnosis
- Autosomal dominant disorders on the paternal side
- Risk assessment of autosomal recessive disorders
ccffDNA – RhD status

- It is thought that universal RhD determination is cheaper than antepartum RhIG for Rh negative women who might be carrying an Rh negative fetus – We will see

- This test was supposed to be available in the USA in March 2009 but now they say in 2010
Free Fetal mRNA

- 2000 - mRNA from Y chromosome detected in plasma of women carrying a male fetus
- 2003 – placenta the major source of fetal mRNA in maternal plasma
- 2007 – a placental specific mRNA from a gene on chromosome 21 identified – PLAC4
Free Fetal mRNA

- Lo developed a test using single nucleotide polymorphisms (SNP) present in the coding region of PLAC4
- If the fetus is heterozygous for this SNP, the ratio would be 1:1 if it is euploid and 1:2 or 2:1 if there is trisomy 21
- The sensitivity is 90% and the specificity is 96.5% - the most accurate single marker for NIPD of trisomy 21
Non invasive Aneuploidy Testing

• Currently, it is planned to be available in 2010

• It will use markers on messenger RNA which are unique to the fetus – it is estimated to detect 90% of Down Syndrome – so I think it will be a screening test, not a diagnostic test
Prenatal Diagnosis

Many options now available:

- CVS
- First trimester screening
- Amniocentesis – standard, FISH, CGH
- Mid trimester screening
- Ultrasound screening
- ffNucleic acid screening
- A host of other screening and testing is possible
Prenatal Diagnosis

OPPOSING TRENDS PRESENTLY

1. Earlier prenatal diagnosis with CVS
2. Later prenatal diagnosis after biochemical and/or ultrasound screening
3. Replacing prenatal diagnosis with biochemical and/or ultrasound screening
Maternal screening Huff
Maternal Screening

MSAFP, MULTIPLE MARKER SCREENING

and

FIRST TRIMESTER
OBJECTIVES

• Review biology of alpha-fetoprotein
• History of AF-AFP and MS-AFP testing
• Setting the normal range
• Evaluation of abnormal results
• The folate story
• History of low values of MSAFP
• Maternal serum screening for chromosomal problems
• First trimester screening
ALPHA-FETOPROTEIN

- Structurally and functionally related to albumin
- Produced by the fetal yolk sac, G-I tract and liver
- Peak fetal serum concentration at end of first trimester
ALPHA-FETOPROTEIN

• AFP LEAVES THE FETUS IN FETAL URINE AND BY DIFFUSION ACROSS MEMBRANES

• AF-AFP ENTERS MATERNAL CIRCULATION BY DIFFUSION ACROSS PLACENTA (2/3) AND AMNION (1/3)
FETAL SERUM AFP

![Graph showing AFP levels across gestation weeks](A)
AMNIOTIC FLUID AFP
MATERNAL SERUM AFP
AMNIOTIC FLUID AFP

- NOTED TO BE ELEVATED IN PREGNANCIES WITH OPEN NEURAL TUBE DEFECTS
- IN LATE 1960s AND EARLY 1970s (PRE ULTRASOUND) AMNIO WAS DONE IN PATIENTS WITH HIGH RISK OF OPEN NTD TO LOOK FOR ELEVATED AF-AFP
MATERNAL SERUM AFP

• THE TEST WAS ORIGINALLY DESIGNED TO LOOK FOR HIGH VALUES IN PREGNANCIES WITH NEURAL TUBE DEFECTS

• IT WAS DEVELOPED IN THE UNITED KINGDOM WHICH HAS AREAS WITH A HIGH INCIDENCE OF NEURAL TUBE DEFECTS
SCREENING TESTS

- ADMINISTERED TO A LOW RISK POPULATION IN ORDER TO FIND INDIVIDUALS AT HIGHER RISK OF A CONDITION
- SCREENING TESTS DO NOT DIAGNOSE ANY CONDITION, THEY SELECT CANDIDATES FOR A DIAGNOSTIC TEST
- THEY HAVE FALSE POSITIVE AND FALSE NEGATIVE RESULTS
NEURAL TUBE DEFECTS

- INCIDENCE IN THE UNITED STATES IS APPROXIMATELY 1 : 1000 PREGNANCIES
- INCIDENCE IN THE UNITED KINGDOM IS UP TO 1 : 100 PREGNANCIES
- OTHER GEOGRAPHIC AREAS HAVE A HIGH INCIDENCE, ALSO
NEURAL TUBE DEFECTS

• MOST CASES HAVE NO KNOWN RISK FACTOR – POLYGENIC/MULTIFACTORIAL

• SOME GENETIC CAUSES SUCH AS TRISOMY 13 AND MECKEL-GRUBER SYNDROME

• SOME TERATOGENIC CAUSES SUCH AS ANTICONVULSANTS AND MATERNAL DIABETES
OPEN NTD RISK

- BASELINE 1/1000
- MATERNAL DIABETES 10/1000
- ANTICONVULSANT USE 10/1000
- PREVIOUS PREGNANCY 30/1000
INTERPRETATION of MSAFP RESULTS

NOT REPORTED IN ABSOLUTE NUMBERS BUT RATHER AS MULTIPLES OF THE MEDIAN OF UNAFFECTED PREGNANCIES
INTERPRETATION

FOR PROPER INTERPRETATION
YOU MUST KNOW:

1. GESTATIONAL AGE
2. MATERNAL WEIGHT
3. MATERNAL RACE
4. MATERNAL DIABETIC STATUS
DEFINING NORMAL

• AN MSAFP VALUE OF 1.0 MULTIPLES OF THE MEDIAN (MOM) IS NORMAL

• THE RANGE OF NORMAL IS GENERALLY UP TO 2.49 MOM

• SOME LABS USE OTHER VALUES, SUCH AS 2.39 MOM OR 2.0 MOM
INTERPRETATION

![Graph showing maternal serum alpha-fetoprotein level for unaffected and affected pregnancies.](image)

**Maternal serum alpha-fetoprotein level (Multiples of the median)**

- **Unaffected**
- **Open spina bifida**
- **Anencephaly**
CAUSES OF ELEVATED MSAFP VALUES

- NEURAL TUBE DEFECT
- MULTIPLE GESTATION
- WRONG DATES
- ABDOMINAL WALL DEFECT
- PLACENTAL PROBLEMS
- FETAL-MATERNAL BLEED
- IUFD
- FETAL RENAL PROBLEMS
- MATERNAL TUMORS
- SACROCOCCYGEAL TERATOMA
EVALUATION

ULTRASOUND

ABNORMAL
  - WRONG DATES
  - MULTIPLE GESTATION
  - FETAL ANOMALIES
  - PLACENTAL PROBLEMS

NORMAL
  - DECISION ABOUT AMNIO
    - NO AMNIO
    - AMNIO DONE
      - NORMAL
      - ABNORMAL
ANENCEPHALY
HEAD FINDINGS - LEMON AND BANANA
HEAD FINDINGS - HYDROCEPHALY
SPINAL DEFECT
GASTROSTOMY
OMPHALOCELE
ACCURACY OF MSAFP SCREENING

- OVERALL, SENSITIVITY IS AROUND 90% FOR DETECTION OF NEURAL TUBE DEFECTS
- UNFORTUNATELY, THE POSITIVE PREDICTIVE VALUE OF AN ELEVATED MSAFP IS ONLY 2-6% FOR AN OPEN NTD - THE FETUS MAY BE AT INCREASED RISK FOR OTHER CONDITIONS
NTDs
SECONDARY PREVENTION

• FOLIC ACID IN A DOSE OF 4mg /DAY HAS BEEN SHOWN TO REDUCE THE RISK OF RECURRENT NTD

• THERAPY MUST BE STARTED SEVERAL MONTHS PRIOR TO PREGNANCY AND CONTINUED FOR THE FIRST FEW MONTHS OF PREGNANCY

MRC VITAMIN STUDY RESEARCH GROUP. LANCET 338:131,1991
NTDs
PRIMARY PREVENTION

• MULTIVITAMINS WITH 0.4 mg OF FOLATE HAVE BEEN SHOWN TO REDUCE THE RISK OF THE FIRST OCCURRENCE OF NTDs*

• THE PUBLIC HEALTH SERVICE RECOMMENDS THAT ALL WOMEN OF CHILDBEARING AGE TAKE A MULTIVITAMIN WITH 0.4 mg OF FOLATE DAILY

LOW VALUES OF MSAFP
THE ASSOCIATION
WITH
CHROMOSOMAL DISORDERS
MSAFP & DOWN SYNDROME
OTHER MARKERS

- ELEVATED SERUM CHORIONIC GONADOTROPIN
- DECREASED SERUM LEVELS OF UNCONJUGATED ESTRIOL
- INHIBIN CURRENTLY USED IN MANY TESTING SCHEMES
MULTIPLE MARKER SCREENING

- TRIPLE TEST DEVELOPED IN THE U.K.
- COMBINES THE RESULTS OF
  1. MSAFP
  2. hCG
  3. uE3

(Quad Test uses Inhibin also)

IN A COMPUTER PROGRAM INCLUDING THE WOMAN’S AGE AND ESTIMATES A RISK FOR FETAL DOWN SYNDROME
(GENERALLY, 1:270 IS THE RISK USED)
EVALUATION OF ABNORMAL MMS

• ULTRASOUND TO CONFIRM GESTATIONAL AGE
• OFFER AMNIOCENTESIS
• ANOTHER OPTION IS A TARGETED ULTRASOUND SCAN WHICH CAN LEAD TO THE DETECTION OF HALF OF THE PREGNANCIES WITH DOWN SYNDROME AND OVER 90% OF THE PREGNANCIES WITH TRISOMY 18
RECOMMENDATIONS FOR MMS

• ALL PREGNANT WOMEN UNDER 35 YEARS OLD SHOULD BE OFFERED MULTIPLE MARKER SCREENING AFTER DISCUSSION OF THE PROCESS

• PREGNANT WOMEN AGE 35 OR MORE SHOULD BE INFORMED ABOUT AMNIOCENTESIS AS WELL AS MULTIPLE MARKER SCREENING

• AMNIOCENTESIS IS A DIAGNOSTIC TEST AND MMS IS A SCREENING TEST
DETECTION RATES

- Using maternal age of 35 and amniocentesis, approximately 20% of pregnancies with Down Syndrome are detected (5% amnio).
- Using MMS leads to the detection of 60% of Down Syndrome pregnancies with an amniocentesis rate of 5%.
- MMS leads to the detection of up to 60% of pregnancies with Trisomy 18.
DETECTION RATES FOR MMS

• AT MATERNAL AGE 40 THE DETECTION RATE IS 90%, BUT THE AMNIOCENTESIS RATE IS 40%

• AT AGE 35-40 THE DETECTION RATE IS AROUND 75%

• FOR THESE REASONS, MMS IS NOT RECOMMENDED AS “ROUTINE” FOR WOMEN WITH AN AGE OF 35 AT THE DUE DATE
SUMMARY

• MULTIPLE MARKER SCREENING IS NOW THE “STANDARD OF CARE” IN THE UNITED STATES.

• MMS SHOULD BE OFFERED TO ALL PREGNANT WOMEN UNDER AGE 35

• WOMEN OVER AGE 35 SHOULD BE OFFERED AN AMNIOCENTESIS

• WOMEN OVER 35 MAY ELECT TO HAVE MMS TO HELP DECIDE ABOUT AN AMNIOCENTESIS
SUMMARY

- USE OF THE MSAFP PART OF MMS CAN LEAD TO THE DETECTION OF 90% OF PREGNANCIES WITH NTDs AS WELL AS OTHER ANOMALIES
- USE OF MMS CAN LEAD TO AN OVERALL DETECTION RATE OF 60% FOR DOWN SYNDROME AND TRISOMY 18
First Trimester Screening
Nuchal Translucency History

- 1992 - Nicolaides reported that fetuses with increased nuchal translucency were at risk for fetal Down Syndrome
- When scanned at 11–14 weeks (CRL between 45 and 84 mm) fetuses with an increased nuchal translucency have a chromosomal abnormality in 1/3 of cases and 3/4 of these are trisomy 21 or 18
Nuchal Translucency
Nuchal Translucency
Nuchal Translucency: Results of NT alone

• 1998 Nicolaides reported on first 100,000 pregnancies screened with NT done by FMF trained sonographers

• Risk based on maternal age and NT – overall, 4.4% of normal pregnancies had an increased NT and 71.8% of FDS pregnancies did

• With a 5% screen positive rate, 77% of FDS pregnancies are detected (95% CI: 72-82%)
First Trimester Serum Markers: Free $\beta$-hCG

- Maternal free $\beta$-hCG normally decreases after 10 weeks gestation – in trisomy 21 pregnancies, the levels are higher and the difference increases with increasing gestational age

- At 10-14 weeks, the median value in trisomy 21 pregnancies was 2.15 MoM (95% CI: 1.94-2.33)

- With a 5% screen positive rate, about 35% of Down Syndrome pregnancies can be detected and by including maternal age, about 45% can be identified
First Trimester Serum Markers: PAPP-A

• Pregnancy Associated Plasma Protein-A levels normally increase in pregnancy – in trisomy 21 pregnancies, the levels are lower but the difference decreases with increasing gestation

• At 10-14 weeks, the median value of PAPP-A was 0.51 MoM (95% CI: 0.44-0.56)

• With a 5% screen positive rate, 40% of trisomy 21 pregnancies were identified and with maternal age combined, the detection was raised to 50%
Serum Markers: Both $\beta$-hCG and PAPP-A

By combining free $\beta$-hCG and PAPP-A with maternal age in a mathematical model, the estimated detection rate of trisomy 21 is about 60% in the first trimester with a 5% screen positive rate.
Theoretical Combination: NT, Maternal Age, PAPP-A and free β-hCG

- The theoretical detection rate for this combination is 90% with a screen positive rate of 5%
- If the screen positive rate was lowered to 1%, the detection rate would be 70%
FASTER – NEJM, November 2005

- Supported by NIH
- Study involved 15 centers in the United States from October 1999 through December 2002; 38,167 patients in the study and 117 had a fetus with Down Syndrome
- Compared first trimester screening with second trimester screening (current standard of care) and with screening in both trimesters
FASTER – Conclusions (MA incl.)

<table>
<thead>
<tr>
<th>Trimester</th>
<th>1%FP</th>
<th>5%FP</th>
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<tbody>
<tr>
<td><strong>SECOND TRIMESTER</strong></td>
<td></td>
<td></td>
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<tr>
<td>Triple test</td>
<td>45%</td>
<td>69%</td>
</tr>
<tr>
<td>Quad test</td>
<td>60%</td>
<td>81%</td>
</tr>
<tr>
<td><strong>FIRST TRIMESTER</strong></td>
<td></td>
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<tr>
<td>Nuchal translucency alone</td>
<td>54%</td>
<td>68%</td>
</tr>
<tr>
<td>PAPP-A and free β-hCG</td>
<td>46%</td>
<td>67%</td>
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<tr>
<td>Combined NT + serum</td>
<td>72%</td>
<td>85%</td>
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**FASTER – Conclusions cont.**

<table>
<thead>
<tr>
<th>Testing Type</th>
<th>1% FP</th>
<th>5% FP</th>
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<tbody>
<tr>
<td>Serum integrated</td>
<td>70%</td>
<td>86%</td>
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<tr>
<td>PAPP-A + Quad test</td>
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<td></td>
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<tr>
<td>Fully integrated</td>
<td>87%</td>
<td>95%</td>
</tr>
<tr>
<td>PAPP-A + NT + Quad test</td>
<td></td>
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</table>

**FIRST AND SECOND TRIMESTER TESTING**
Down Syndrome Screening-ACOG, January 2006

- Evidence supports first trimester Down Syndrome Screening
- Requirements:
  1. Training and quality control for NT measurements
  2. Quality control for lab
  3. Access to CVS
  4. Appropriate counseling of patients about their options
Down Syndrome Screening—What to Do?

• Now, the prospect of nuchal translucency screening at 11-14 weeks of gestation combined with serum screening and possibly nasal bone screening and tricuspid regurgitation screening promises to provide 95% detection of fetal Down Syndrome with a screen positive rate of 5%.

• When we can detect fetal aneuploidy by testing maternal blood, all these screening tests may become obsolete.
Down Syndrome Screening and Testing – personal thoughts

- Women at “high risk” for a chromosomal problem and who want testing should have it – don’t fool around with screening.

- Screening should be offered to all “low risk” women and they should be counseled about the types of testing available and the fact that 1:20 will have a positive test result.

- “High risk” women may elect to have screening tests done as long as they realize that screening tests can be falsely positive or negative.
Down Syndrome Screening and Testing – personal thoughts

• Many patients who are “high risk” because of age or serum screen results decide not to have an amniocentesis for fear of losing a normal pregnancy and/or because they say they would not abort a pregnancy with Down Syndrome – in this case, a targeted ultrasound may be helpful to identify markers of a chromosomal disorder.
Down Syndrome Screening and Testing – personal thoughts

• First trimester testing should be the Combined Test: NT, PAPP-A and free β-hCG – if this testing is used, MSAFP should be tested in the second trimester and a targeted scan should be done at 20 weeks

• In the mid trimester, the Quad test should be done between 15 and 20 weeks
Left over slides from Repr/Genetics talk to Dr. Moore in MFM fellowship
## COMMON MS-AFP PATTERNS (PAPPA, HCG, inhibin**)

<table>
<thead>
<tr>
<th>AFP</th>
<th>hCG</th>
<th>uE3</th>
<th>Condition</th>
</tr>
</thead>
<tbody>
<tr>
<td>lo</td>
<td>hi</td>
<td>lo</td>
<td>Down syndrome, dates less advanced, Turner syndrome with cystic hygroma</td>
</tr>
<tr>
<td>lo</td>
<td>lo</td>
<td>lo</td>
<td>trisomy 18</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>nl</td>
<td>open spina bifida, abdominal wall defects, fetal death</td>
</tr>
<tr>
<td>hi</td>
<td>nl</td>
<td>lo</td>
<td>anencephaly</td>
</tr>
<tr>
<td>hi</td>
<td>lo</td>
<td>hi</td>
<td>dates more advanced</td>
</tr>
<tr>
<td>nl</td>
<td>nl</td>
<td>very low</td>
<td>fetal death, X-linked ichthyosis (placental sulfatase deficiency), congenital adrenal adrenal hyperplasia, Smith Lemli Opitz Syndrome</td>
</tr>
<tr>
<td>Screening Test</td>
<td>Detection Rate (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>----------------------------------------------------</td>
<td>--------------------</td>
<td></td>
<td></td>
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<tr>
<td><strong>First Trimester</strong></td>
<td></td>
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<tr>
<td>NT measurement</td>
<td>64–70*</td>
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<tr>
<td>NT measurement, PAPP-A, free or total β-hCG†</td>
<td>82–87*</td>
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<tr>
<td><strong>Second trimester</strong></td>
<td></td>
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<tr>
<td>Triple screen (MSAFP, hCG, unconjugated estriol)</td>
<td>69*</td>
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<tr>
<td>Quadruple screen (MSAFP, hCG, unconjugated estriol, inhibin A)</td>
<td>81*</td>
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</tr>
<tr>
<td>Screening Test</td>
<td>Detection Rate (%)</td>
<td></td>
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<tr>
<td>---------------------------------------------------</td>
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<td></td>
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<tr>
<td><strong>First Plus Second Trimester</strong></td>
<td></td>
<td></td>
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<tr>
<td>Integrated (NT, PAPP-A, quad screen)</td>
<td>94–96*</td>
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<tr>
<td>Serum integrated (PAPP-A, quad screen)</td>
<td>85–88*</td>
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<tr>
<td>Stepwise sequential</td>
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<tr>
<td>First-trimester test result:</td>
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<td></td>
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<tr>
<td>Positive: diagnostic test offered</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Negative: second-trimester test offered</td>
<td>95*</td>
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<td></td>
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<tr>
<td>Final: risk assessment incorporates first and second results</td>
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<tr>
<td>Contingent sequential</td>
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<td>First-trimester test result:</td>
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<tr>
<td>Positive: diagnostic test offered</td>
<td></td>
<td></td>
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<tr>
<td>Negative: no further testing</td>
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<tr>
<td>Intermediate: second-trimester test offered</td>
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<tr>
<td>Final: risk assessment incorporates first and second results</td>
<td>88–94%‡</td>
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</tbody>
</table>
References


• Genetics in Primary Care and Clinical Medicine, 1st Edition. Editors: Seashore MR, Wappner RS. Copyright 1996.


References

• **ACOG Committee Opinion #238.** Genetic Screening for Hemoglobinopathies. July 2000.


References


References


Testing Algorithm for IHH Diagnosis

AM Testosterone (T)

- Normal/high
  - Measure LH
    - LH high: Consider androgen sensitivity
    - LH normal: Excludes Hypogonadism

- Low
  - Repeat T
    - Normal T
      - Measure LH/FSH
        - LH, FSH low/normal: Prolactin, Anterior pituitary testing, Ferritin, MRI pituitary
        - LH/FSH high: See evaluation for Primary Hypogonadism
    - Low T
      - See evaluation for Primary Hypogonadism

Pallais, OMIM - hypothalamic hypogonadism
Since aldosterone is the major hormone promoting potassium excretion, hyperkalemia (and hyponatremia b/c Na/HCO3 is exchanged in the distal tubule when K is secreted, so if K is not excreted, then more Na is lost) Uptodate. Rabolink, 1990
SRY in sex reversal (46,XX males; 46,XY females)

- Different deletions of the pseudoautosomal region and of the sex-specific region of the Y chromosome in sex reversed individuals were used to map the precise location of this gene.
  - X and Y chromosomes exchange in meiosis I within the Xp/Yp pseudoautosomal region (THIS IS WHAT NORMALLY HAPPENS); but if genetic recombination occurs outside of the pseudoautosomal region this can lead to XX males (1 in 20000, phenotypic males with 46,XX who possess some Y chromosomal sequences translocated to the short arm of the X) or XY females (1 in 20000, phenotypic females with 46,XY, but they have lost the testis determining region of the Y chromosome).
  - SRY gene – (Sex determining Region on Y)- lies near the pseudoautosomal boundry on the Y chromosome, and is present in 46,XX males, but is deleted or mutated in a proportion of female 46,XY patients thus strongly implicating the SRY in male sex determination.
  - SRY is expressed briefly early in development in cells of the germiinal ridge just before differentiation of the testis; SRY encodes a DNA binding protein that is likely to be a transcription factor; SRY is equivalent to the TDF on the Y chromosome; other genes are implicated in the sex-determination pathway b/c presence or absence of SRY does not explain all cases of abnormal sex determination.
Y chromosome – Fig 6-12 (Nussbaum) – etiological factors of XX male or XY female phenotypes by aberrant exchange b/n X and Y linked sequences. X and Y chromosomes normal recombine within the Xp/Yp pseudoautosomal segment in male meiosis. If recombination occurs below the pseudoautosomal boundary, between the X-specific and Y-specific portions of the chromosomes, sequences responsible for male sexual differentiations (including the SRY gene) may be translocated from the Y to the X. Fertilization by a sperm containing such an X chromosome leads to an XX male. In contrast, fertilization by a sperm containing a Y chromosome that has lost SRY will lead to an XY female. SRY, TDF region
Hyperaerated lungs, pulmonary blebs
http://www.eradimaging.com/images/krames/105629.jpg

http://www.mountnittany.org/assets/images/krames/105629.jpg

CYSTIC FIBROSIS
Left over slides from Repr/Genetics talk to Dr. Moore in MFM fellowship
Perinatal infections

• Related anomalies
CMV – most common congenital infection

- Primary infection – 40% fetal infection rate
  - <20 weeks, infection rate less, more severe infection,
  - >20 weeks, esp >28 weeks, infection rate higher, less severe infection
- 90/10 rule of primary infection
  - 90% asymptomatic at birth, 10% with symptoms at 2 yo (hearing loss, chorioretinitis
  - 10% symptomatic at birth (30% mortality rate), 90% of these will have long term complications;
- Nonprimary recurrent infection 10-15% risk of long term complications, usually not symptomatic at birth
CMV sonogram findings

- IUGR
- Microcephaly
- Intracranial calcifications
- Ventriculomegaly
- Echogenic bowel

- Complications
- Chorioretinitis
- Hearing loss
- Thrombocytopenia
- Hyperbilirubinemia
- Hepatitis

- Therapy – CMV IVIG, Gancyclovir
Toxoplasmosis

- Protozoan that affects humans via ingestion of contaminated meat or cat feces
- 0.8/10,000 US; 10/10,000 France
- 400-4000 estimate new cases of congenital toxoplasmosis each year
- 50% of US women with evidence of prior exposure

- 40% risk of congenital infection – risk is greatest in 3rd trimester; severity of infection is worse in first trimester
- Rate of infection at 13 wks - 6%, at 36 weeks 72%;
- if infection <20 weeks, 11% of newborns had congenital infection
- If infection >20 weeks, 45% had congenital infection
Toxoplasmosis

- Disseminated rash, hepatosplenomegaly, chorioretinitis, uveitis, seizures, MR

- Diagnosis: Serologic testing performed by standardized reference lab (send if + to lab Palo Alto California), toxoplasmosis PCR in amniotic fluid

- Sonogram findings: IUGR, ascites, ventriculomegaly, periventricular calcifications

- Treatment: Spiramycin to reduce risk and severity of congenital infection, confirmed by PCR in amniotic fluid or by reference lab

- Spiramycin to prevent infection; treatment if primary maternal infection; reduces risk of congenital infection; does not treat active infection

- If fetal infection diagnosed (sono findings, + PCR) treatment is with pyrimethamine, sulfadiazine, folinic acid

- Controversial if + maternal infection and neg PCR late in pregnancy as whether to give other medications in addition to spiramycin
Toxoplasmosis

• Which of the following is true about fetal rates of toxoplasmosis infection related to fetal age at the time of maternal infection?
  • *A- Risk of fetal infection increases with advancing fetal age
  • B- Risk of fetal infection decreases with advancing fetal age
  • C- Severity of fetal infection is much greater in late pregnancy
  • D-Risk and severity of fetal infection are not dependent on gestational age
• Williams OB
Varicella

- Diagnosis – disseminated, pruritic, vesicular rash often associated with fever; varicella pneumonia (admission, IV ACV, respiratory support)
  - Anti-VZV IgM antibodies
- Congenital varicella – very rare (<1% in first trimester, <2% in second trimester)
  - Ultrasound findings – IUGR, microcephaly, ventriculomegaly, echogenic foci in liver, limb anomalies
  - Highest rate of infection at term
  - Chorioretinitis, microophthalmia, skin or bone defects
- Neonatal varicella – maternal varicella 5 days before to 2 days after delivery; disseminated mucocutaneous lesions, visceral infection, pneumonia, encephalitis
- Treatment – within 72-96 hours of exposure
  - VZIG (not in US)
  - Acyclovir 800mg po 5x/d x 7 days or valacyclovir 1000mg po TID x7 days
  - Respiratory support (oxygen, ABG, pH, CO2 in pregnancy)
  - No varicella vaccination in pregnancy
  - No evidence that tocolysis at term works
- VariZIG - Canada
- Varicella zoster – Treatment with acyclovir
  - No increased risk of fetal infection
Varicella
Rubella

- Rubella – fetal infection rate
  - 1st trimester infection increased rate of infection – 80-90%
  - 13-20 weeks - 54% infection rate
  - Late 2nd – early 3rd trimester – 25% infection rate, then increases late in 3rd trim
- Most common defect – Sensorineural deafness, second is heart defects, PDA, pulmonary artery stenosis
Classic findings of fetal rubella syndrome: renal disorders, hypospadias, cryptorchidism, meningocele, glaucoma, patent ductus arteriosus, and peripheral pulmonary stenosis.
Parvovirus

The risk for congenital infection from an infected mother is between 10% to 20% and is highest in the first and second trimesters.

Pathophys - Aplastic anemia, High output cardiac failure, Myocardial damage from virus, Decreased oncotic pressure (anemia)
Listeriosis

- Gram + rod
- Risks of IUFD, PTL, fetal infection
- Early onset – sepsis, IUFD
- Late onset – meningitis, hydrocephalus, MR
- Hematogenous infection, leads to placental abscesses, fetal sepsis, IUFD
- Avoid unpasteurized cheeses, meats (uncooked hot dogs)
- Tx Ampicillin

Placental villitis is shown here with a small microabscess containing mostly neutrophils in a case of congenital infection with Listeria monocytogenes. Listeriosis is generally not life-threatening to the mother, but is potentially a cause for fetal demise. http://library.med.utah.edu/WebPath/PLACHTML/PLAC034.html
Lyme Disease

- Lyme:
- Borrelia burgdorferi
- Erythema chronicum migrans (60-80%)
- Erythema is later followed by meningitis or Bell’s palsy and peripheral radiculopathies
- 5-10% of patients will have cardiac disease-AV block
- Late infection associated with arthritis
- Associated with poor pregnancy outcome—but no pattern of teratogenesis (rash, syndactaly, IUG)
- May treat with amox 500 qid x 14-30 days
- Ceftriaxone 2gm IV daily for 14 days crosses blood brain barrier well
Syphilis

- *Syphilis*
- Incubate 10-90 days
- Primary lesion disappears in 2-6 weeks
- Secondary, or bacteremic stage lasts 2-6 weeks
- Early latent – may again get lesions, bacteremia up to 4 yrs
- Late latent— not infectious sexually
- Tertiary develops in 33% of patients
- Primary or secondary has 50% transmission, with 50% death rate
- Early latent 40% transmission and 20% death rate
- Late-10% transmission
- Early signs— rash, hepatosplenomegaly, snuffles, chorioretinitis
- Late— Hutchinson’s teeth, saber shins, saddle nose, cardiac
- After treatment VDRL should become negligible in 12 months. Do titers every 3 months for 1 year
- 2.4 mill units benzathine X 1 for primary and secondary or latent < 1 yr, otherwise repeat X 3