Anomalies and Genetics Review
– CREOG Review

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Objectives

• Anomalies
• Genetics
• Fetal infections
• Sickle Cell Disease
• Twins
• Cover as much as we can
Epidemiology

• 2-3% general population anomaly rate
Anomalies - Definitions
• Malformation – programmed deformity; develops incorrectly; example - limb in sirenomelia was programmed to develop abnormally and thus intrinsically, genetically abnormal

• Dysmorphism – morphological and developmental abnormalities as seen in many syndromes of genetic or environmental origin
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 previable 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
Sequence

• 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)
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

- Neurofibromatosis
- Autosomal dominant polycystic kidney disease
- Huntington’s disease
- Waardenburg syndrome
- Achondroplasia
- Tuberous sclerosis
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
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
Polydactyly
Omphalocele
45, X – Turner syndrome

- Neck – cystic hygromas
- Cardiovascular – coarctation
- General – hydrops fetalis
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
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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<tbody>
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</table>
Autosomal Recessive Conditions

- Cystic fibrosis
- Sickle cell anemia
- Spinal muscular atrophy
- Congenital adrenal hyperplasia
- Phenylketonuria
- Autosomal recessive polycystic kidney disease
- Meckel-Gruber syndrome
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, t13, 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 (Def): shrinkage / dangling of choroid plexus
- Posterior horn: >10mm
  - Mild: 10-12
  - Moderate: 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\(^2\)

**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\(^1\).

**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%
• 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 omphaloceles 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 view (A) and on coronal section (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
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>
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</thead>
<tbody>
<tr>
<td><strong>Sonographic signs</strong></td>
<td>Normal liquor</td>
<td>Oligohydramnios</td>
</tr>
<tr>
<td></td>
<td>Diagnosis after 24 wk</td>
<td>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</td>
<td>Perinephric urinoma</td>
</tr>
<tr>
<td></td>
<td>Isolated</td>
<td>Associated abnormalities</td>
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<tr>
<td><strong>Urine biochemistry</strong></td>
<td>Sodium: $&lt;100$ mEq/L</td>
<td>Calcium: $&gt;100$ mEq/L</td>
</tr>
<tr>
<td></td>
<td>Chlorine: $&lt;90$ mEq/L</td>
<td>Chlorine: $&gt;90$ mEq/L</td>
</tr>
<tr>
<td></td>
<td>Osmolality: $&lt;210$ mOsm/L</td>
<td>Osmolality: $&gt;210$ mOsm/L</td>
</tr>
<tr>
<td></td>
<td>Calcium: $&lt;2$ mmol/L</td>
<td>Calcium: $&gt;2$ mmol/L</td>
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<tr>
<td></td>
<td>Phosphate: $&lt;2$ mmol/L</td>
<td>Phosphate: $&gt;2$ mmol/L</td>
</tr>
<tr>
<td></td>
<td>$\beta_2$-Microglobulins: $&lt;2$ mg/L</td>
<td>$\beta_2$-Microglobulins: $&gt;2$ mg/L</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 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 (klinefelters sd – XXY is all you need for klinefelters sd – can have 48XXYY, 49XXXY)
- 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
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
- 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.
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/P LAC034.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% 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
ACOG anomalies - end
High Yield Select Topics

• Added here 2015-2016
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); 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 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%)
- **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?

• \(1 = p + q\)
• \(1 = p^2 + 2pq + q^2\)
• \(p = \text{dominant allele}\)
• \(q = \text{recessive allele}\)

• \(\frac{1}{12} \times \frac{1}{12} \times \frac{1}{4} = 1 \text{ in } 576\)
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

(T/T Genetics in Medicine)
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
<table>
<thead>
<tr>
<th>Configuration</th>
<th>Placentas</th>
<th>Amnions</th>
<th>Chorions</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Twin peak</strong></td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>Lambda sign/twin peak</strong></td>
<td>2</td>
<td>2</td>
<td>2</td>
</tr>
<tr>
<td><strong>T sign</strong></td>
<td>1</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td><strong>T sign</strong></td>
<td>1</td>
<td>1</td>
<td>1</td>
</tr>
</tbody>
</table>

- **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

*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
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 anastamoses (Jain et al); not widely used

TTTS
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

![Graph showing the level of AFP (mg/ml) over gestation (weeks).]
AMNIOTIC FLUID AFP

![Graph showing the change in AFP over gestation](graph.png)
MATERNAL SERUM AFP
INTERPRETATION

![Graph showing maternal serum alpha-fetoprotein levels for unaffected pregnancies, open spina bifida, and anencephaly.](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
MSAFP & DOWN SYNDROME

[Diagram showing the distribution of maternal serum AFP in pregnancies with Down syndrome, unaffected pregnancies, and pregnancies with Spina bifida.]
<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>

www.Carolguze.com
### ACOG – Screening for Chromosomal Anomalies - 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>
</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 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>
<tr>
<td><strong>Stepwise sequential</strong></td>
<td></td>
</tr>
<tr>
<td>First-trimester test result:</td>
<td></td>
</tr>
<tr>
<td>Positive: diagnostic test offered</td>
<td></td>
</tr>
<tr>
<td>Negative: second-trimester test offered</td>
<td></td>
</tr>
<tr>
<td>Final: risk assessment incorporates first</td>
<td>95*</td>
</tr>
<tr>
<td>and second results</td>
<td></td>
</tr>
<tr>
<td><strong>Contingent sequential</strong></td>
<td></td>
</tr>
<tr>
<td>First-trimester test result:</td>
<td></td>
</tr>
<tr>
<td>Positive: diagnostic test offered</td>
<td></td>
</tr>
<tr>
<td>Negative: no further testing</td>
<td></td>
</tr>
<tr>
<td>Intermediate: second-trimester test offered</td>
<td></td>
</tr>
<tr>
<td>Final: risk assessment incorporates first</td>
<td>88–94%‡</td>
</tr>
<tr>
<td>and second results</td>
<td></td>
</tr>
</tbody>
</table>
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 Counsel 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>
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<td>AA</td>
<td>Aa</td>
</tr>
<tr>
<td>a</td>
<td>aA</td>
<td>aa</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 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 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.
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 (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
<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

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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 2. Cardiovascular Changes With 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>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>27</td>
<td>30</td>
<td>29</td>
<td>17</td>
</tr>
<tr>
<td>Secondary</td>
<td>25</td>
<td>56</td>
<td>15</td>
<td>33</td>
</tr>
<tr>
<td>Associated with congenital heart disease*</td>
<td>73</td>
<td>36</td>
<td>29</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)

![Graph showing aortic diameter measurements over time](image-url)

*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*
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
      - In 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?
(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>
<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 $<2\text{cm}^2$; aortic valve $<1.5\text{cm}^2$; peak left ventricular outflow tract gradient $>30\text{mmHg}$)
  - 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%

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.

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>6 (3–14)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mitral valve area less than 2 cm²</td>
<td></td>
<td></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.

• 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 1\text{st}/3\text{rd} 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 ≈ 0.7) + ASA 80–100 mg qd

• UFH (aPTT 2.5–3.5) or LMWH (pre-dose anti-Xa ≈ 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 ≈ 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 \( \approx 0.6 \)) 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 \( \approx 0.6 \))

- SC UFH (mid-interval aPTT 2.0–3.0) or LMWH (pre-dose anti-Xa \( \approx 0.6 \)) throughout pregnancy
• 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.\textsuperscript{3,5} 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.24 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

![Bar chart showing changes in cardiac output during labor and after delivery](image)

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>
<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></td>
<td>Palliated tetralogy of Fallot with severe pulmonic regurgitation and right ventricular dysfunction</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