Objectives

- Definition of anemia
- Diagnosis of fetal anemia
  - Normal developmental hematopoiesis
- Etiology of fetal anemia
  - Decreased production
    - Congenital, acquired
  - Malfunction of hemoglobin production
    - Alpha thalassemia
  - Increased destruction
    - Blood loss, hemolytic anemia
- Treatment options
What does blood do?

- Transports gasses, nutrients, wastes, hormones, heat
- Regulates water balance, pH
- Protection from infection, and other alien invaders
The bloodmobile

- https://www.youtube.com/watch?v=Futnu_6NmQo&list=RDFutnu_6NmQo
What is blood?

- Red blood cells (flexible sacks of the protein hemoglobin which carry O2 and CO2)
- White blood cells (cells with different mechanisms to kill organisms)
- Platelets (make temporary walls to keep from bleeding)
- Plasma (salt water that carries everything else!)
Anemia

Definition:
- Decreased levels of red blood cells or
Anemia

Definition:
- Decreased levels of hemoglobin

Picture from http://medstat.med.utah.edu/WebPath/HEMEHTML/HEME008.html
Anemia

- The fetus uses red blood cells to carry oxygen in its circulation just as children do.
- When anemia is severe, the fetus can experience heart failure and death.
Diagnosis of fetal anemia

- Spectral analysis of amniotic fluid
- Cordocentesis
- Doppler ultrasound – check for velocity of blood flow in the brain
- Ultrasound of the heart can show signs of strain
Diagnosis of fetal anemia

- Spectral analysis of amniotic fluid
- Cordocentesis
- Doppler ultrasound – check for velocity of blood flow in the brain
- Ultrasound of the heart can show signs of strain
- Ultrasound can also show signs of tissue edema in severe anemia (hydrops fetalis)
Most common is blood loss (i.e. bleeding)

- Obstetrical causes
- Feto-maternal, feto-placental, feto-fetal transfusion
- Internal hemorrhage
- Iatrogenic
Etiology

- Increased red blood cell destruction
  - Intrinsic: Enzyme defects, membrane defects, hemoglobinopathies
  - Extrinsic: Immune mediated (anti Rh) Acquired hemolysis (infection such as malaria or parvovirus 19, drug exposure)
Etiology

- Decreased red blood cell production
  - Congenital hypoplastic marrow
  - Bone marrow suppression (particularly from parvovirus B19)
  - Nutritional anemia (maternal iron deficiency)
Thalassemia: non-immune intrinsic hemolytic anemia

Case study:
- 27 yo Asian woman has miscarried twice. Ultrasound shows signs of anemia, and early hydrops.
- Because of previous miscarriages and ethnicity, amniocentesis is done and shows a four gene deletion alpha thalassemia
Normal Hemoglobin

- 2 $\alpha$-like globin chains
- 2 b-like globin chains
- 4 heme rings
- 4 oxygen molecules
- Gas transport
- $O_2$, $CO_2$, NO
Human globin genes

α-like genes on chr 16

β-like genes on chr 11
Progression of Globin Synthesis
Disorders of hemoglobin

- Mutation in DNA
  - GENETIC DISEASES
- Leads to
  - defect in production of hemoglobin (thalassemias)
  - defect in hemoglobin function (hemoglobinopathy)
  - defect in hemoglobin stability
Disorders of hemoglobin

- Hemoglobin variants
  - Hemoglobin C, D, E, O<sub>Arab</sub>

- Defects in production of hemoglobin, or its subunits
  - α-thalassemia
  - β−thalassemia
  - Hemoglobin Lepore

- Disorders in the hemoglobin structure
  - Hemoglobin E
  - Hemoglobin S
  - Hemoglobin C

- Mixed disorders
  - SC, S<sub>β</sub><sup>0</sup>, S<sub>β</sub><sup>+</sup>, E<sub>β</sub><sup>0</sup>
Alpha Thalassemia

- A genetic defect which causes a reduction in the gene product
  - Decreased \( \alpha \) chains produced
  - Excess \( \gamma \) chains to dimerize (\( \gamma_4 \)) in the infant, and extra \( \beta \) chains (\( \beta_4 \)) in the adult
  - These “pseudohemoglobins” precipitate in the RBC, damaging the membrane and causing hemolysis
  - The ensuing anemia stimulates marrow to produce red cells that die early: ineffectual erythropoiesis.
  - Hemolysis and marrow expansion lead to multisystem disease
FIGURE 1. The human α-globin gene cluster and the deletions affecting it. The deletions are shown by the black bars. The hatched bars indicate where the boundary of the deletion is not defined. Med and SEA denote lesions that predominate in the Mediterranean or southeast Asian populations, respectively.

(C.Y.W. Kan, 1985)
Alpha thalassemia

Maternal

Paternal
Alpha thalassemia
Alpha thalassemia

Maternal

Paternal

HS-40

HS-40
Alpha thalassemia

Maternal

Paternal
Alpha thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Description</th>
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</thead>
<tbody>
<tr>
<td>$\alpha\alpha/\alpha\alpha$</td>
<td>Normal</td>
</tr>
<tr>
<td>$\alpha\alpha/\alpha-$</td>
<td>Mild microcytosis, NO anemia</td>
</tr>
<tr>
<td>$\alpha\alpha/-/-$</td>
<td>Mild microcytosis, mild anemia - no therapy required</td>
</tr>
<tr>
<td>$\alpha/-/\alpha-$</td>
<td>Hemoglobin H disease - sometimes requires transfusion therapy</td>
</tr>
<tr>
<td>$\alpha/-/-/-$</td>
<td>Hemoglobin Barts - Hydrops Fetalis unless transfused in utero</td>
</tr>
</tbody>
</table>
Natural History

- Growth retardation
  - Delayed puberty
- Pallor
- Varying icterus
- Skin Bronzing: gray-brown pigmentation
- Features of hypermetabolic state
- Hepatosplenomegaly
- Skull changes:
  - Frontal bossing
  - Maxillary hyperplasia
  - Radiating striations
Natural History

- Recurrent infections
- Complication due to bone deformation
- Bleeding tendency
- Increasing hypersplenism
- Gallstones
- Leg ulcers
- Extramedullary hematopoiesis
Treatment

- Genetic counseling
- Transfusion therapy
- Iron overload treatment
- Bone marrow transplant
Transfusion therapy

- Corrects anemia and ineffective erythropoiesis

Consequences:
- Risk of fetal loss with each invasive transfusion
- Time/effort/money
- Reaction, infection
- Iron overload
  - Liver deposition leads to cirrhosis
  - Endocrine
  - Cardiac deposition leads to failure
  - Iron chelation therapy
Endocrine disturbances - panhypopituitarism
- Impaired gonadotropins
- Hypogonadism
- IDDM
- Adrenal insufficiency
- Hypothyroidism
- Hypoparathyroidism

Cirrhotic liver failure

Cardiac failure due to myocardial iron overload
Iron chelation

- **Desferoxamine**
  - Very high affinity and specificity for iron
  - Removes it from both extra and intracellular spaces.
  - Mostly excreted through urine (iron mostly from RES), though some also fecally (iron mostly from liver) excreted.
  - Goal to keep ferritin <2500
  - Liver iron stores <15mg/gm
  - Many drawbacks
    - Side effects: Hearing loss, retinal damage, growth failure, local skin reaction hypersensitivity
    - Must be given continuous subcutaneously
    - Expensive

- **Deferasirox**
  - Oral iron chelator, similar profile otherwise to desferoxamine
Causes of death

- Congestive heart failure
- Arrhythmia
- Sepsis (postsplenectomy)
- Multiple organ failure due to hemochromocytosis
- Thrombosis
Bone Marrow Transplant

- Only curative option
- Upfront mortality about 5% with matched sibling donor
- Upfront mortality about 15% with unrelated matched donor
- Morbidity from immunosuppression, toxicity of chemotherapy/radiation, graft vs host disease