Fetal Anemia
02/13/13

Anjulika Chawla, M.D.
Assistant Professor
Division of Pediatric Hematology/Oncology
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
What is blood?

- Red blood cells: flexible sacks of hemoglobin to carry gases
- 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!
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 (hemoglobin levels at 40-70% of normal), 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
- Ultrasound can also show signs of tissue edema in severe anemia (hydrops fetalis)
Etiology of fetal anemia

- 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: maternal antibodies to fetal red cell antigens
    - Acquired hemolysis (infection, drug exposure)
Etiology

- Decreased red blood cell production
  - Congenital hypoplastic marrow (chromosomal anomalies)
  - Bone marrow suppression (particularly from parvovirus B19)
  - Nutritional anemia
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 α-like globin chains
- 2 β-like globin chains
- 4 heme rings
- 4 oxygen molecules

Gas transport: O2, CO2, NO
Human globin genes

α-like genes on chr 16

β-like genes on chr 11
Progression of Globin Synthesis
**Human Hemoglobins**

<table>
<thead>
<tr>
<th>Zeta</th>
<th>Epsilon</th>
<th>$\zeta_2\varepsilon_2$</th>
<th>Hb Gower 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Epsilon</td>
<td>$\alpha_2\varepsilon_2$</td>
<td>Hb Gower 2</td>
</tr>
<tr>
<td>Zeta</td>
<td>Gamma</td>
<td>$\zeta_2\gamma_2$</td>
<td>Hb Portland</td>
</tr>
<tr>
<td>Alpha</td>
<td>Beta</td>
<td>$\alpha_2\beta_2$</td>
<td>Hb A</td>
</tr>
<tr>
<td>Alpha</td>
<td>Gamma</td>
<td>$\alpha_2\gamma_2$</td>
<td>Hgb F</td>
</tr>
<tr>
<td>Alpha</td>
<td>Delta</td>
<td>$\alpha_2\delta_2$</td>
<td>Hb A$_2$</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td>$\beta_4$</td>
<td>Hb H</td>
</tr>
<tr>
<td>Gamma</td>
<td></td>
<td>$\gamma_4$</td>
<td>H Barts</td>
</tr>
</tbody>
</table>
### Human Hemoglobins

<table>
<thead>
<tr>
<th>Zeta</th>
<th>Epsilon</th>
<th>$\zeta_2 \varepsilon_2$</th>
<th>Hb Gower 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha</td>
<td>Epsilon</td>
<td>$\alpha_2 \varepsilon_2$</td>
<td>Hb Gower 2</td>
</tr>
<tr>
<td>Zeta</td>
<td>Gamma</td>
<td>$\zeta_2 \gamma_2$</td>
<td>Hb Portland</td>
</tr>
<tr>
<td>Alpha</td>
<td>Beta</td>
<td>$\alpha_2 \beta_2$</td>
<td>Hb A</td>
</tr>
<tr>
<td>Alpha</td>
<td>Gamma</td>
<td>$\alpha_2 \gamma_2$</td>
<td>Hgb F</td>
</tr>
<tr>
<td>Alpha</td>
<td>Delta</td>
<td>$\alpha_2 \delta_2$</td>
<td>Hb A$_2$</td>
</tr>
<tr>
<td>Beta</td>
<td></td>
<td>$\beta_4$</td>
<td>Hb H</td>
</tr>
<tr>
<td>Gamma</td>
<td></td>
<td>$\gamma_4$</td>
<td>H Barts</td>
</tr>
</tbody>
</table>

**Embryonol**

Synthesis is in the yolk sac
Human Hemoglobins

- **Zeta** Epsilon $\zeta_2\varepsilon_2$ Hb Gower 1
- **Alpha** Epsilon $\alpha_2\varepsilon_2$ Hb Gower 2
- **Zeta** Gamma $\zeta_2\gamma_2$ Hb Portland
- **Alpha** Beta $\alpha_2\beta_2$ Hb A
- **Alpha** Gamma $\alpha_2\gamma_2$ **Hgb F**
- **Alpha** Delta $\alpha_2\delta_2$ Hb A$_2$
- **Beta** $\beta_4$ Hb H
- **Gamma** $\gamma_4$ H Barts

Fetal

Synthesis is in the liver
# Human Hemoglobins

<table>
<thead>
<tr>
<th>Hemoglobin</th>
<th>Chain Composition</th>
<th>Formula</th>
<th>Names</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta</td>
<td>Epsilon</td>
<td>$\zeta_2 \varepsilon_2$</td>
<td>Hb Gower 1</td>
</tr>
<tr>
<td>Alpha</td>
<td>Epsilon</td>
<td>$\alpha_2 \varepsilon_2$</td>
<td>Hb Gower 2</td>
</tr>
<tr>
<td>Zeta</td>
<td>Gamma</td>
<td>$\zeta_2 \gamma_2$</td>
<td>Hb Portland</td>
</tr>
<tr>
<td>Alpha</td>
<td>Beta</td>
<td>$\alpha_2 \beta_2$</td>
<td>Hb A</td>
</tr>
<tr>
<td>Alpha</td>
<td>Gamma</td>
<td>$\alpha_2 \gamma_2$</td>
<td>Hgb F</td>
</tr>
<tr>
<td>Alpha</td>
<td>Delta</td>
<td>$\alpha_2 \delta_2$</td>
<td>Hb A$_2$</td>
</tr>
<tr>
<td>Beta</td>
<td>$\beta_4$</td>
<td></td>
<td>Hb H</td>
</tr>
<tr>
<td>Gamma</td>
<td>$\gamma_4$</td>
<td></td>
<td>H Barts</td>
</tr>
</tbody>
</table>

*Synthesis is in the bone marrow*
## Human Hemoglobin Isoelectric Points

<table>
<thead>
<tr>
<th>Isoelectric Point</th>
<th>Amino Acid Composition</th>
<th>Formula</th>
<th>Pathologic</th>
</tr>
</thead>
<tbody>
<tr>
<td>Zeta</td>
<td>Epsilon</td>
<td>$\zeta_2\varepsilon_2$</td>
<td>Hb Gower 1</td>
</tr>
<tr>
<td>Alpha</td>
<td>Epsilon</td>
<td>$\alpha_2\varepsilon_2$</td>
<td>Hb Gower 2</td>
</tr>
<tr>
<td>Zeta</td>
<td>Gamma</td>
<td>$\zeta_2\gamma_2$</td>
<td>Hb Portland</td>
</tr>
<tr>
<td>Alpha</td>
<td>Beta</td>
<td>$\alpha_2\beta_2$</td>
<td>Hb A</td>
</tr>
<tr>
<td>Alpha</td>
<td>Gamma</td>
<td>$\alpha_2\gamma_2$</td>
<td>Hgb F</td>
</tr>
<tr>
<td>Alpha</td>
<td>Delta</td>
<td>$\alpha_2\delta_2$</td>
<td>Hb A$_2$</td>
</tr>
<tr>
<td>Beta</td>
<td>Gamma</td>
<td>$\beta_4\gamma_4$</td>
<td>Hb H</td>
</tr>
<tr>
<td>Gamma</td>
<td></td>
<td>$\gamma_4$</td>
<td>H Barts</td>
</tr>
</tbody>
</table>
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\textsubscript{Arab}
- Defects in production of hemoglobin, or its subunits
  - \(\alpha\)-thalassemia
  - \(\beta\)-thalassemia
  - Hemoglobin Lepore
- Disorders in the hemoglobin structure
  - Hemoglobin E
  - Hemoglobin S
  - Hemoglobin C
- Mixed disorders
  - SC, \(S\beta^0\), \(S\beta^+\),\(E\beta^0\)
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.

(7, H. Kan., 1985)
Alpha thalassemia

Maternal

Paternal
### Alpha thalassemia

<table>
<thead>
<tr>
<th>Genotype</th>
<th>Description</th>
</tr>
</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>$\alpha-/\alpha-$</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
NBS and Genetic Counseling Effect on Beta Thalassemia

- In Sardinia, NBS and education begun in 1975
- Incidence of thalassemia major has declined from 1:250 live births to 1:4000, a 94% reduction!

Figure 36.6. Fall of the birth rate of babies with homozygous β thalassemia in Sardinia.
Transfusion therapy

- Corrects anemia and ineffective erythropoiesis

Consequences:
- Risk of fetal loss with each invasive transfusion
- Lifelong transfusions after birth
- Time/effort/money
- Risks of reaction, alloimmunization, infection
- Iron overload
  - Liver deposition leads to cirrhosis
  - Endocrine
  - Cardiac deposition leads to failure
  - Iron chelation therapy
Natural History with Txfn

- Endocrine disturbances – panhypopituitarism
  - Impaired gonadotropins
  - Hypogonadism
  - IDDM
  - Adrenal insufficiency
  - Hypothyroidism
  - Hypoparathyroidism
- Cirrhotic liver failure
- Cardiac failure due to myocardial iron overload
Iron chelation

- **Desferroxamine**
  - Chelates iron from the blood and tissues and excretes it in the urine and feces
  - Goal ferritin <2500 and 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 desferroxamine
  - Have to remember to take daily
  - Side effects include skin rashes, risk of renal failure, hearing loss
  - Still expensive!
Avoid Iron Overload

- Chelation
- Exchange transfusion: remove “bad blood” replace with “good blood”
- Erythrocyeptapheresis: remove “bad blood” replace with “good blood” really, really fast with a machine
Procedure: Erythrocytapheresis
Causes of death

- Congestive heart failure
- Arrythmia
- 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/radation, graft vs host disease