Sickle cell disease
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KEY POINTS

- Sickle cell disease is an autosomal recessive disease resulting from an alteration in the structure of hemoglobin producing hemoglobin S (HbS). It is characterized by chronic hemolytic anemia and vaso-occlusive events.
- Diagnosis is made by hemoglobin electrophoresis.
- Severe complications during pregnancy and adverse pregnancy outcomes are most commonly experienced by women with HbSS and HbS\(b^0\) genotypes.
- Complications may include pregnancy loss, fetal growth restriction, preterm birth, preeclampsia, placental abnormalities, anemia, painful crises, UTI and other infections, thromboembolic events, acute chest syndrome (ACS), alloimmunization, postpartum infections, and maternal mortality.
- Pneumococcal and influenza vaccines are important preventive interventions.
- Painful crises are managed with narcotic (preferably morphine) therapy and IV fluids. Antibiotics should be added if the woman is febrile, has an infection, or has ACS; oxygen should be added if the woman has low oxygen saturation.
- Prophylactic blood transfusions are not beneficial. Blood transfusions are indicated for symptomatic or orthostatic anemia, hemoglobin <6 g/dL or hematocrit <25%, acute stroke, ACS, or multiple organ failure.
- In the 10% of patients with sickle cell disease who develop ACS, a chest X-ray is necessary. Antibiotics (usually cefepime or erythromycin) aimed at infectious pathogen(s) in pulmonary tree, and bronchodilators are the mainstay of therapy.

HISTORIC NOTES

Sickle cell disease was first described in 1910 by Herrick. In 1949, Linus Pauling described the molecular structure of sickle cell hemoglobin. In 1956, Ingram and Hunt discovered the single amino acid change in sickle cell hemoglobin. In 1961, two and 1966, the sixth amino acid in the \(b\)-globin chain from glutamic acid to valine. As noted above, other forms of sickle cell disease result from co-inheritance of HbS with other abnormal \(b\)-globin chain variants.

DEFINITION

Sickle cell disease is an inherited disorder resulting from an alteration in the structure of hemoglobin producing HbS. It is characterized by hemolysis and vaso-occlusive events. Sickle cell disease is associated with a mild to moderate chronic anemia. The term sickle cell disease includes sickle cell anemia (HbSS), hemoglobin S combined with hemoglobin C (HbSC), hemoglobin S combined with \(\beta\)-thalassemia (HbS/\(\beta^+\) or HbS/\(\beta^0\)), and other double heterozygous conditions causing sickling and thus, clinical disease (e.g., hereditary persistence of fetal hemoglobin (HgS/HPHP), and hemoglobin E (HbE/HbE) (5). The clinical manifestations vary among these genotypes, with HbS/\(\beta^0\) usually with similar severe phenotype as HbSS; HbSC associated with intermediate disease; and very mild or symptom free for HbS/\(\beta^+\), HbSHPHP, and HbSE (1.6).

DIAGNOSIS

The diagnosis is made by hemoglobin electrophoresis, according to the definition above. In all 50 U.S. states, newborns are screened for sickle cell disease at birth.

EPIDEMIOLOGY/INCIDENCE

Sickle cell disease occurs in about 1 and 600 African-Americans. Sickle cell trait occurs in 1 and 12 African-Americans, resulting in the birth of approximately 1100 infants with sickle cell disease annually in the United States. HbSS accounts for 60% to 70% of sickle cell disease in the United States. The prevalence of sickle cell disease and patients with sickle cell trait is highest in West Africa (25% of the population have one mutation), Mediterranean, Saudi Arabia, India, South and Central America, and Southeast Asia (1.6).

GENETICS/INHERITANCE

Sickle cell disease is an autosomal recessive disorder characterized by a mutation of a single nucleotide of the \(\beta\)-globin gene on chromosome 11p, changing the sixth amino acid in the \(\beta\)-globin chain from glutamic acid to valine. As noted above, other forms of sickle cell disease result from co-inheritance of HbS with other abnormal \(\beta\)-globin chain variants, the most common forms being sickle hemoglobin C disease (HbSC) and two types of sickle \(\beta\)-thalassemia (HbS/\(\beta^+\) thalassemia and HbS/\(\beta^0\) thalassemia). Inheriting one HbS gene results in sickle cell trait. Inheriting two HbS genes results in sickle cell disease. Concordant with an autosomal recessive pattern of inheritance, if both parents carry one HbS gene, the fetus has a 25% chance of having sickle cell disease, 50% chance of having sickle cell trait, and 25% chance of being unaffected.

PATHOPHYSIOLOGY

In most individuals without hemoglobinopathy, 96% to 97% of hemoglobin in humans is Hemoglobin A (which consists of two \(\alpha\)- and two \(\beta\)-chains), with small portions of Hemoglobin A2 (two \(\alpha\)- and two \(\delta\)-chains), and at times Hemoglobin F (two \(\alpha\)- and two \(\gamma\)-chains). Hemoglobin provides the oxygen carrying capacity of erythrocytes. HbS occurs because of a point
mutation in which valine, a hydrophilic amino acid, is substituted for glutamic acid, a hydrophobic amino acid in the β-globin gene. This allows the sickle hemoglobin to polymerize when it is deoxygenated, triggering a cascade of repeated injury to the red-cell membrane. As a consequence, these cells become very rigid, assume a characteristic sickle shape, hemolysate, and are unable to pass through small capillaries, leading to vessel occlusion and ischemia. This tissue ischemia leads to acute and chronic pain as well as to end-organ damage. As vaso-occlusion can occur in any vessel, this is a systemic disease that can affect any organ. The life span of a sickle cell is about 10 to 20 days compared to the 120 days life span of a normal red blood cell. This chronic hemolysis contributes to the anemia (1,6,7). Dehydration, infection, decrease in oxygen tension, and acidosis, are common triggers of cell sickling and sickle cell crisis. Sickle cell crisis describes several independent acute conditions occurring in patients with sickle cell disease (vaso-occlusive crisis, aplastic crisis, hemolytic crisis).

**SYMPTOMS**

1. **Chronic hemolytic anemia**
   - Fatigue, pallor, shortness of breath
   - Aplastic crisis presents with severe anemia and reticulocytopenia. It is the most common hematologic crisis during pregnancy

2. **Acute vaso-occlusive episodes**
   - Pain involving the chest, lower back, abdomen, head, and bones/extremities
   - Dactylitis (inflammation of fingers and/or toes) often the first symptom of sickle cell disease
   - Exacerbated by cold, infection, stress, dehydration, alcohol, and fatigue

3. **Infections**
   - Urinary tract infections, pneumonia, osteomyelitis, endocarditis
   - Organisms include *Streptococcus pneumoniae, Hemophilus influenza, Staphylococcus, gram-negative organisms, Salmonella,* and mycoplasma

4. **Cardiac**
   - Systolic murmur, cardiomegaly, high output failure

5. **Pulmonary**
   - ACS presents with chest pain, dyspnea, tachypnea, fever, cough, leukocytosis, and pulmonary infiltrates. It is usually a result of infection, vaso-occlusion, or bone marrow embolization

6. **Gastrointestinal**
   - Right upper quadrant syndrome presents with abdominal pain, fever, hepatomegaly, hyperbilirubinemia, and increased liver function tests. Splenomegaly is common

7. **Renal**
   - Hematuria, papillary necrosis, nephrotic syndrome, renal infarction, pyelonephritis, hyposthenuria, and renal medullary carcinoma

8. **Neurologic**
   -Transient ischemic attacks, cerebrovascular accidents, seizures, coma, hemiparesis, hemianesthesia, visual field changes, and cranial nerve palsy
   - Moyamoya disease is a progressive occlusive process of the cerebral vasculature that results in the formation of collateral vessels with the appearance of “puffs of smoke” (Moyamoya in Japanese) on angiography

9. **Skeletal**
   - Avascular necrosis most often occurs in the humeral and femoral heads and is characterized by pain

**COMPLICATIONS**

Pregnancy in women with sickle cell disease is complicated not only by the maternal condition characterized by years of chronic organ damage but also by the physiologic changes and adaptations of pregnancy that can often compound or exacerbate underlying organ damage. However, the majority of these women can achieve a successful pregnancy: the majority tends to deliver beyond 28 weeks’ gestation with a >80% live birth rate, although 50% will require transfusion or medically indicated hospitalization and 75% will have a pain crisis during the pregnancy (8).

Several complications have been reported: effects of sickle cell disease on pregnancy—Table 15.1 (8-12); effects of pregnancy on sickle cell disease—Table 15.2 (8,11,12).

| Table 15.1 Complications: Effects of Sickle Cell Disease on Pregnancy |
|---|---|---|
| Complication | HBSS | HBSC | HBS¹ |
| Pregnancy loss (mostly first trimester) | 7–36% (8–10) | 9% (10) |
| Fetal death | No increase (8,9) | No increase (8,9) |
| Fetal growth restriction (FGR) | 45% (9) | 21% (9) |
| Small for gestational age (SGA) | 21% (11) | 15% (11) |
| Acute anemia | 4% (11) | 3% |
| Urinary tract infections | 20–50% (8,9,11) | 19–26% (9,11) |
| Preterm birth | 45% (9,11) | 22% (9) |
| Preeclampsia | 10% (9,12) | 3% |
| Aplomunization ² | 62% (9) | 26% ² | 2.8(9) |
| Antepartum admissions ² | 1.4 (12) |

% is reported if available in the source study.

²Preeclampsia and acute anemia episodes are risk factors for SGA. High hemoglobin F levels are protective for fetal growth (11).

³There is no difference in the rate of painful episodes before, during and after pregnancies (11).

⁴The mean gestational age at delivery is 34 to 37 weeks (9,11).

²Any woman with sickle cell disease is at increased risk for Rh and other antibodies if she has had blood transfusions in the past.

Because of all the above complications, in particular painful crises, and increased incidences of infections in general, women with sickle cell disease in pregnancy are at increased risk for hospitalization.

¹More likely to have postpartum infections secondary to endometritis or pyelonephritis. The effect is listed as Odds Ratio compared to the African-American population. No increase risk for postpartum hemorrhage (8,9).
**PREGNANCY MANAGEMENT**

**Principles**
Multidisciplinary team approach, involving hematologist, blood bank, primary care, obstetrician, and any other involved health care workers (e.g., pulmonologist, cardiologist, pain and drug dependency services, and social services).

**Workup**

*For diagnosis: Hemoglobin electrophoresis*

*For a crisis: Hemoglobin, hemoglobin electrophoresis, urine culture, and culture of any other possible infectious source; blood gas if hypoxia is present*

**Preventive Care**

Pneumococcal and influenza vaccines; avoid triggers (especially infections), optimize hemoglobin status by educating on good nutrition and prescribe vitamins/folic acid/iron as needed, establish plan for home medication regimen, and educate on analgesia safety in pregnancy.

**Preconception**
Patients are no longer counseled to avoid pregnancy. Counseling should consist of a review of the effects of sickle cell disease on pregnancy, highlighting an increased risk for hospital admissions, pain crises, infections, severe anemia, maternal mortality, and others (Tables 15.1 and 15.2) (8–12). The discussion should also entail the effects of sickle cell disease on the fetus, which are early pregnancy loss, growth restriction, and perinatal mortality, as well as a risk for inherited hemoglobinopathies. Preventive care should be emphasized. Try to optimize hemoglobin status by prescribing up to 4 mg folic acid and a prenatal vitamin (4,13). Discuss medication use during pregnancy and change/stop teratogenic medications (ACE inhibitors, iron chelators, and possibly hydroxyurea) and vaccinate as needed.

**Prenatal Care**

1. Initial visit: medical (assess for chronic organ damage, especially pulmonary hypertension, renal disease, and congestive heart failure), obstetrical, transfusion, and social history; nutritional assessment; discuss precipitating factors for painful crises and prior successful pain management. Counseling regarding risks (Tables 15.1 and 15.2). Advice on the need for adequate hydration and fluid intake. Preventive care.

2. Initial laboratory studies: CBC, reticulocyte count, Hb electrophoresis, serum iron studies, bilirubin, liver function tests, hepatitis A, B, and C, HIV, BUN, creatinine, antibody screen, rubella antibody titer, VDRL, tuberculosis skin test, Pap smear as appropriate, chlamydia and gonorrhea cultures.

3. Test the father of the baby (CBC, hemoglobin electrophoresis). Offer genetic counseling if father is positive for HbS. If father is positive for HbS, direct DNA analysis is available by polymerase chain reaction via chorionic villous sampling or amniocentesis. Interestingly, the vast majority of women at risk of an affected fetus decline prenatal diagnosis.

4. Serial urine cultures every four to eight weeks.

5. CBC every trimester.

6. Folate supplementation up to 4 mg daily plus prenatal vitamin (4,13). Ferrous sulfate 325 mg only if iron deficient (avoid iron overload).

7. Pneumococcal and influenza vaccines.

8. Consider first-trimester ultrasound for exact dating, which might be helpful in the evaluation of suspected growth restriction later during pregnancy. Ultrasound at 18 to 20 weeks for a detailed anatomy scan, and then growth scans starting at 28 to 32 weeks as clinically indicated.

9. For patients with multiple red cell alloantibodies and an anticipated need for a blood transfusion, consider to have phenotypically matched units of PRBC identified.

10. Rescreen for red cell alloantibodies in third trimester (14).

**THERAPY**

1. **Painful crisis** (diagnosis made by history, often no physical or laboratory finding).
   - **Narcotics:** Morphine is the preferred agent. Consider using a patient-controlled analgesia (PCA) system for severe pain. Oral controlled-release morphine is as effective as intravenous morphine in nonpregnant adults. Ask women regarding which narcotic or pain management works best for them, and implement as appropriate. After 28 to 32 weeks, avoid NSAIDs, which are safe and effective earlier in pregnancy. Prescribe stool softeners with narcotic use (15).
   - **Intravenous fluids:** Effective in nonpregnant adults. Adequate fluid intake is 60 mL/kg/24 hr in adults (15). Consider 150 cc/hr. Monitor fluid balance.
   - **Antibiotics:** Broad-spectrum antibiotics should be used if patient is febrile (T > 38°C), or if there is evidence of infection. Add a macrolide (e.g., erythromycin) if chest symptoms are present (15).
   - **Oxygen:** Use only for ACS or if O₂ saturation is less than patient’s known state or <95% (4) (such treatment is ineffective in nonpregnant patients and may be so in pregnant women as well) (15).
   - **Labor and delivery:** There is no need to alter general recommendations for labor and delivery in women in sickle cell crisis. A crisis is not an indication for cesarean delivery or other special intervention. Close monitoring of mother and fetus for adequate oxygenation is paramount. Pain during labor can be managed with narcotics, regional anesthesia, or local anesthesia via pudendal block (19). Pediatricians should be aware of any chronic narcotic use in pregnancy, as such is a risk for neonatal withdrawal.
2. Anemia

- **Transfusions:** There is limited evidence to assess the efficacy of prophylactic blood transfusions for pregnant women with sickle cell disease. Compared to transfusion only for Hb < 6 g/dL, transfusion (or exchange transfusion) with two units of red cells every week for three weeks, or until hemoglobin level is 10 to 11 g/dL or HbS < 35%, is associated with no significant difference in perinatal outcome (16). Prophylactic transfusions decreased the number of painful crisis (14% vs. 50%). Disadvantages of prophylactic transfusion include increase in costs, number of hospitalizations, and risk of alloimmunization (16). Therefore, prophylactic blood transfusions are not indicated universally for pregnant women with sickle cell disease.

  Indications for transfusions are: any woman who is symptomatic or orthostatic from anemia, and/or with a hemoglobin of < 6 g/dL or hematocrit < 25%, or with acute stroke or chest syndrome or multiple organ failure.

  Sickle cell crisis is not an absolute indication to transfusion. Persistent crises are an indication to transfusion to avoid recurrence. If blood transfusion is indicated, it should always be leukodepleted and matched for Rh and Kell antigens.

  - **Iron, folic acid, and multivitamins:** Only prescribe iron if patient is deficient (avoid iron overload).
  - **Hydroxyurea** (hydroxycarbamide): Decreases number and severity of painful crisis and improves survival in nonpregnant adults and children (17). However, there are insufficient clinical data and trials to make a firm recommendation on its use, efficacy, and teratogenicity during pregnancy (18).

**ALLOIMMUNIZATION**

If the antibody screen is positive, follow recommendations in chapter 52. The antigen status of the father of the pregnancy should be tested, as he often does not carry the offending antigen, with the maternal antibody usually acquired by prior transfusions. Bilirubin level (Delta OD450) in amniotic fluid of women with sickle cell disease is unreliable for detecting fetal anemia, as maternal hemolysis and hyperbilirubinemia increase fetal and AF bilirubin levels. Fetal anemia may be assessed by middle cerebral artery Doppler (see chap. 52).

**ANTENATAL TESTING**

There are no prospective studies on the use of antepartum testing in sickle cell disease women (10). Fetal monitoring can be started at 32 weeks with weekly non-stress test/amniotic fluid indexes, especially if fetus is growth restricted (6).

**DELIVERY**

It is safe for patients to deliver vaginally. Inductions and cesarean sections should be reserved for obstetrical indications (4).

There is one case report of a sickle cell crisis triggered by induction of labor with a prostaglandin (19). Some recommend prophylactic transfusion before a cesarean delivery to avoid precipitating a crisis because of blood loss in patients with hemoglobin 7 to 8 g/dL or less (20).

**ANESTHESIA**

There are no contraindications to anesthesia (IV, regional, or general) (4).

**POSTPARTUM**

During the postpartum period, early ambulation and adequate hydration is encouraged. Compression boots and incentive spirometry should be used during bedrest. Anemia should be assessed and transfusion only if indicated (see above). Breast-feeding is encouraged. Low-dose oral contraceptives, Depoprovera injections, and intrauterine devices are all safe in pregnancy (21).

**ACUTE CHEST SYNDROME**

**Definition**

New pulmonary infiltrate of at least one complete lung segment with alveolar consolidation and excluding atelectasis; and presence of chest pain, temp T >38.5°C, tachypnea, wheezing, or cough. Hypoxia, decreasing hemoglobin levels, and progressive pneumonia are frequent. Mostly associated with pulmonary fat embolism and pulmonary infection, with 3% to 10% chance of death, related to pulmonary embolism and pneumonia.

**Incidence**

Acute chest syndrome develops in about 10% of women with sickle cell disease.

**Pathophysiology**

Cause of ACS remains mainly unknown. Infection leading to sickle crisis, anemia, hypoxia, and vaso-occlusion with ischemic damage are the most common associations.

**Symptoms**

Chest pain, pain in arms and legs, dypnea, fever, etc.

**Complications**

ACS is one of the most common causes of death (3–10%) among those with sickle cell disease. Neurologic complications, probably secondary to CNS hypoxia, occur in about 20% of patients. Pulmonary embolism and infarction can also occur.

**Workup**

For ACS, chest X-ray; sputum culture, nasopharyngeal sample and/or bronchoscopy washings culture (*Chlamydia pneumoniae* and *Mycoplasma pneumoniae* are most common pathogens).

**Therapy**

Antibiotics (usually cephalosporin and erythromycin) aimed at infectious pathogen(s) in pulmonary tree, and bronchodilators (even if no evidence of reactive airway disease). Blood transfusions (especially in hypoxic and/or anemic women), oxygen (15% need mechanical ventilation), and pain control as needed (22).
SICKLE CELL TRAIT
Pregnant women with sickle cell trait should be screened with a hemoglobin electrophoresis if this has not been done before, and testing of the father and genetic counseling should be offered. They are at increased risk of urinary tract infections, and therefore should have a urine culture at first prenatal visit and in every trimester, with asymptomatic bacteriuria adequately treated.

HbSC DISEASE
HbC is due to a single nucleotide substitution (A for G) in the 6th codon of the β-globin gene (making it a Hb C gene) in chromosome 11, leading to substitution of lysine for glutamic acid on the β-globin chain, resulting in β' globin. Of African-Americans, 1% are carriers (trait). Diagnosis is by electrophoresis. No disease with trait only.

HbS-βthal
Diagnosis by hemoglobin electrophoresis: HbS > HbA; elevated HbF. Prognosis and management are as for HbSS.

HEMOGLOBIN E
Prevalent in Southeast Asia. No increase in morbidity and mortality, except possible slight decrease in birth weight and increase in abruption.

REFERENCES