Reproductive issues in sickle cell disease

Three cases illustrate the unique challenges ob/gyns face while caring for SCD patients at various life stages.

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Sickle cell disease (SCD) is a devastating blood disorder with particular implications for women. In the 1970s, the life expectancy for a person with SCD in the United States was approximately 10 years.[1] Now, the life expectancy is approximately 50 years.[1] Girls born with SCD in this century can expect to live to and through their childbearing years. Their blood disorder, however, presents unique challenges at every life stage that ob/gyns need to know how to manage.

Etiology of SCD

SCD is an autosomal-recessive disease characterized by presence of sickled red blood cells (RBCs). Sickled RBCs form in an individual who is homozygous for the sickle hemoglobin (HbS) gene (SS genotype) or is heterozygous for HbS and has another abnormal hemoglobin such as hemoglobin C (SC genotype), beta thalassemia (S-beta thal+ or S-beta thal^0 genotype), or some other rare hemoglobin. HbS has a single amino acid substitution of valine for a glutamic acid in the beta chain of the hemoglobin molecule, which prevents hemoglobin from forming neat tetramers. Instead the hemoglobin forms long, fibrous polymers that distort RBC membranes. These distorted RBCs are readily destroyed by the reticuloendothelial system. The normal life span of sickled RBCs is approximately 15 days compared to the 120 days of normal RBCs.[2] Consequently, individuals with SCD suffer from moderate to severe anemia. Table 1 lists the prevalence of various genotypes derived from California newborn screening data[2] and the severity of the various genotypes.[3] The SS genotype (which accounts for more than half of the affected individuals in the United States) and the S-beta thal^0 genotype generally result in a more severe phenotype described as "sickle cell anemia." The other genotypes do not usually result in severe disease.

Anemia is not the only mechanism of the disease. Lysed RBCs release free hemoglobin, which consumes nitric oxide and leads to endothelial damage and possibly thrombosis. Membrane receptors become rearranged on the distorted RBC surface, altering its adhesive properties. These altered RBCs interact with the endothelium, white blood cells, and platelets, and contribute to intravascular congestion, thrombosis, and downstream ischemia, resulting in both acute and chronic tissue damage.

Epidemiology of SCD

SCD affects approximately 1 million individuals worldwide, two-thirds of whom live in West Africa. Unfortunately, mortality for children with SCD in low-

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TABLE 1 Sickle cell genotypes identified through newborn screening in California[3]

Genotype	% of Newborns	Phenotype
SS	56%	Severe = sickle cell anemia
SC	29%	Not severe
S-beta thal^{+}	9%	Not severe
S-beta thal^{0}	5%	Severe = sickle cell anemia
SD, SE, SO	Rare	Varies

and middle-income countries is 50% to 90%. In the United States, approximately 100,000 Americans are affected with SCD, mostly individuals of African descent, but also Mediterranean, Middle Eastern, and Indian descent.[1] Forty years ago, 50% of children in the United States born with SCD also died before adulthood and 30% died before their fifth birthday,[3] but since the 1970s, newborn screening programs, institution of penicillin prophylaxis, vaccinations against encapsulated organisms, and disease-modifying therapy with hydroxyurea have led to a dramatic decline in childhood mortality. SCD is no longer a life-threatening disease of childhood, but now a chronic disease of adults.[3]

Consequences of SCD

SCD affects almost every organ and organ system, as shown in Table 2. Acute complications of the disease are listed in Table 3.[4-7] The cost of care, estimated from a study of Florida Medicaid claims from 2001-2005, averaged $1389 per month per patient.[8]

Of particular concern to ob/gyns are the maternal and fetal consequences of SCD. Pregnancy complications are summarized in Table 4. During normal pregnancy, there is a demand for increased erythropoiesis. Because women with SCD are already anemic, 30% to 40% require transfusion during pregnancy.[4,5,9] During normal pregnancy, women have an increased susceptibility to certain infections. The risk of infection is compounded in women with SCD. Compared to women without SCD, infectious morbidity is increased 2- to 13-fold. During normal pregnancy, women have an increase in glomerular filtration. Pregnancy has the potential to further impair renal function in women with sickle cell nephropathy. Normal pregnancy results in an increase in cardiac output. In a woman with SCD, the increased cardiopulmonary demands of pregnancy are potentially life-threatening, especially in women with SCD-induced pulmonary hypertension. Pregnancy results in an increased risk of thrombosis. In women with SCD who are already at high risk of VTE and stroke, pregnancy increases the risk of thrombosis 2- to 5-fold compared to women without the disease. Preeclampsia is increased 6- to 8-fold in women with SCD and maternal mortality is increased 6-fold, compared to women without SCD.[6,10] Fetal growth appears to start out normally, then lags after 25 weeks' gestation.[7] Fetal consequences of SCD include a 2-fold increased risk of preterm birth,[6] a 3-fold risk of small-for-gestational age,[6] and a 4-fold increased risk of stillbirth.[6]

Diagnosis

Diagnosis of SCD within the first 3 months of life allows for early treatment. Since 2006, every state in the United States has had a newborn screening program for the disease. A study conducted in California found that overall mortality for children who were diagnosed after they presented with symptoms was 8%, compared to 1.8% after early identification of SCD through screening and accompanying education of providers.[3,11]

Treatment

Treatment for SCD consists of preventing complications, managing pain, modifying the disease, or attempting a cure. Prevention of complications includes prophylactic penicillin for children to prevent sepsis and meningitis from encapsulated bacteria, and vaccinations against *Streptococcus pneumoniae* (pneumococcus) and *Haemophilus influenza*.[3] Individuals with SCD are particularly vulnerable to these encapsulated bacteria due to functional or surgical asplenia. Chil-

TABLE 2 Organs and organ systems affected by SCD

- Eyes
- Brain
- Heart
- Lungs
- Kidneys
- Liver
- Spleen → "autosplectomy"
- Bones
- Placenta

TABLE 3 SCD Acute complications

- Vaso-occlusive (pain) crises
- Acute chest syndrome (which most closely resembles pneumonia) and the most common cause of death in SCD
- Stroke (11% by age 20, 24% by age 25)
- Splenic sequestration
- Acute renal failure
- Acute cholecystitis
- VTE (10%-25% by age 30 to 40)

Abbreviation: VTE = venous thromboembolism

dren with SCD are also particularly vulnerable to stroke. Children with abnormal transcranial Doppler velocities are prescribed long-term transfusion therapy, which has been shown to dramatically reduce incidence of stroke.[12]

Managing the acute and chronic pain of SCD is challenging. The mainstay of pain management has been opioids, but nonsteroidal anti-inflammatory drugs (NSAIDs) have also been used. Particularly for management of chronic pain, amitriptyline, gabapentin, selective serotonin reuptake inhibitors (SSRIs), selective norepinephrine reuptake inhibitors (SNRIs), and complementary therapies have also been helpful. Disease-modifying therapy includes hydroxyurea, which raises fetal hemoglobin levels and reduces incidence of vaso-occlusive crises and episodes of acute chest syndrome. Hydroxyurea has been found to cause birth defects in animals, but has not been found to increase risk of birth defects in humans.[13] Nonetheless, hydroxyurea has generally been avoided during pregnancy. L-glutamine has recently been approved for prevention of vaso-occlusive crises, but there is little experience with this medication.[13] Other disease-modifying therapies are currently in development, but have not been approved for use.[10]

Cures of SCD have been accomplished with hematopoietic stem cell transplantation (HSCT) and now with gene therapy.[14] For HSCT, the donor may be related (e.g. a sibling) or unrelated. Related donors can be human leukocyte antigen (HLA) histocompatibility-matched (typically at 8/8 HLA loci) or haploidentical (matched at half of HLA loci). Originally only matched donors were considered, but now successful transplants have occurred with haploidentical donors as well. In preparation for HSCT, recipients receive chemotherapy or radiation. HCST offers a cure, but can result in death, graft rejection, graft versus host disease, and sterility.[3,13] After HSCT, a high proportion of young women do become amenorrheic and are presumed infertile. Gene therapy for SCD[15] is still experimental but there are three clinical trials underway. Subjects receive their own genetically modified hematopoietic stem cells. In preparation, however, they still require gonadotoxic chemotherapy with the same potential risks to fertility as those with HSCT.

CASE 1 Menstruation and contraception in young women with SCD

Typical case: A 16-year-old gravida 0 with SCD is referred by her pediatric hematologist because of heavy, painful periods since she started having periods 1 year ago. She reports that the menstrual pain is distinct from the pain of vaso-occlusive crises. Her disease is otherwise adequately managed. She has no history of stroke or venous thromboembolism (VTE). Her Hb is 9 g/dL. A transabdominal ultrasound of the pelvis was normal.

Delay in menarche is not uncommon in girls with SCD. Several studies have reported on delayed menarche among girls with the disease.[16] A longitudinal cohort study of girls from infancy to young adulthood in Jamaica found that compared to controls, girls with SC genotype had a delay in mean age at menarche of 0.5 years and girls with SS genotype had a delay in mean age at menarche of 2.4.[17] This patient's ability to distinguish menstrual pain from the pain with vaso-occlusive crises is also not uncommon. Women with SCD do report distinct differences in the pain of menstruation compared to the pain with vaso-occlusive crises.[18]

Management of primary dysmenorrhea includes hormonal contraceptives and NSAIDs. In SCD, NSAIDs may increase vascular, bleeding, and renal risks, which may be compounded in patients with end-organ co-morbidities. For patients with SCD without a contraindication, however, NSAIDs are acceptable.[12] Hormonal therapy can reduce blood loss and pain with periods (a potential benefit in SCD), but combined hormonal contraceptives increase risk of VTE and stroke[19] (a potential hazard in SCD). Depot medroxyprogesterone acetate (DMPA) injections have also been shown to increase risk of VTE,[16] but other progestin-only contraceptives do not.[16] In women with SCD, a systematic review of four studies showed no increased risk of VTE among those who used

hormonal contraceptives, but there were only 118 total subjects.[20] Obviously, no combined hormonal contraceptives should be prescribed to a young woman with a history of stroke or VTE. Common sense further dictates progestin-only contraceptives be prescribed to a woman with SCD over combined hormonal contraceptives whenever possible.

Anticipation of HSCT

The first published case[14] of a young woman referred for HSCT describes a scenario that has become more frequent. This patient was a 19-year-old young gravida 0 with SS genotype. She had a history of multiple episodes of vaso-occlusive pain crises and acute chest syndrome. Fortunately, her sister was an HLA match. She was referred to a reproductive endocrinologist who counseled her and her family regarding the options for cryopreservation of:

- embryos (created with donor sperm), which allows for preimplantation genetic testing (PGT)
- oocytes, and
- ovarian tissue – still experimental, but the only option for prepubescent girls.

A low-dose ovarian stimulation protocol was used. Enoxaparin 30 mg subcutaneous every 12 hours was administered during stimulation and held 24 hours before egg retrieval. Eight mature oocytes were vitrified (rapidly cooled to prevent formation of crystals). No reports exist about whether this patient has pursued a pregnancy successfully, but thousands of women without SCD have had successful pregnancies after oocyte preservation.[21] Also, while ovarian tissue preservation is considered experimental, more than 87 subsequent pregnancies have been reported, including two in women with SCD (one using her own ovarian tissue and another using her sister's).[3]

CASE 2 Preconception counseling

A typical case: A 28-year-old gravida 0 with SCD with SS genotype is referred by her hematologist because she will be married soon and is planning a pregnancy. She is currently taking hydroxyurea. Her partner does not think he has sickle trait or beta thalassemia minor, but he is not certain.

This patient's partner should be referred for testing. If he has abnormal Hb, the couple should be referred for genetic counseling and they should be aware of the option of PGT with in vitro fertilization. A type and screen should be reviewed or obtained. If antibodies are present that are known to cause hemolytic disease, the partner should be tested for the corresponding antigen(s). The patient should be counseled regarding the maternal and fetal risks of SCD in pregnancy. Although the risk of maternal mortality is increased, the absolute risk of maternal mortality is about 1%,[22] which does not discourage most women and their families from pursuing a pregnancy. The patient's medications should be reviewed and before a prenatal vitamin is prescribed, her ferritin should be checked. If the level is elevated, which is very likely if the patient has received transfusions, she should receive a prenatal vitamin WITHOUT iron (such as prenatal gummies). In addition, the American College of Obstetricians and Gynecologists recommends 4 mg of folate per day for women with SCD.[23] With respect to hydroxyurea, the patient should have a consultation with a maternal-fetal medicine specialist. After consultation

TABLE 4 SCD pregnancy complications

Complications	Risks compared to those without SCD
Maternal	
Severe anemia with need for transfusion	
Infection	2- to 13-fold
Thrombosis	2- to 5-fold
Preeclampsia	6- to 8-fold
Mortality	6-fold
Fetal	
Alloimmunization	Depends on maternal RBC antibody and paternal RBC antigen status
Preterm birth	2-fold
Small-for-gestational-age at delivery	3-fold
Stillbirth	4-fold
Neonatal	
Neonatal abstinence syndrome	Depends on fetal exposure to opioids
Sickle cell disease	Depends on paternal sickle/thalassemia status

Abbreviations: RBC = red blood cell; SCD = sickle cell disease

with that specialist and a hematologist regarding risks and benefits, some patients may elect to continue hydroxyurea during pregnancy or at least until conception, stop for the duration of pregnancy, or stop it temporarily and restart it after the first trimester.

CASE 3 Pregnancy

A typical case: A 32-year-old gravida 3 para 1011 (one term pregnancy and one miscarriage) with SCD (SS genotype) at 36 weeks' gestation has worsening fetal growth restriction (FGR), which is now at the fourth percentile. Amniotic fluid volume is low normal and the umbilical artery Doppler S/D ratio is normal. The patient has been hospitalized almost monthly since conception for vaso-occlusive crises and was recently discharged from the medical intensive care unit after an admission for acute chest syndrome. She has received multiple transfusions in the past. Her antibody screen was positive for anti-C antibodies in this pregnancy, but her titer never exceeded 4. She took hydroxyurea in the past but stopped prior to her first pregnancy. The patient's family history is significant for a sister who also had SCD with SS genotype and died in the second trimester of her first pregnancy. Her partner's sickle cell status is unknown. The patient's current medications include prenatal gummies, low-dose aspirin for preeclampsia prevention, and oxycodone for pain. Her only complaint is near constant, severe pain in her bones. Her vital signs are normal, and her exam is unremarkable. Her Hb is 7.6 g/dL, hemoglobin 22%, creatinine 0.6, and lactate dehydrogenase is normal.

Once pregnancy is established, a patient with SCD should be cared for with the help of specialists in maternal-fetal medicine and hematology who have expertise in SCD. In early pregnancy, this patient's partner should have been offered testing. If he had abnormal Hb, the couple should have been referred for genetic counseling and made aware of the options for prenatal diagnosis. He also could have been tested for the C red cell antigen. Anti-C antibodies are a rare but documented cause of hemolytic disease of the newborn.[24] If the partner were negative, the fetus would not have been at any risk for alloimmunization.

Because of the increased risk of preeclampsia, low-dose aspirin was started at 12 weeks' gestation. Because of the increased risk of infection, monthly urine cultures were ordered. The patient's hemoglobin was monitored. A Hb of 8 g/dL was targeted and a Hb of > 7 g/dL was maintained for most of the pregnancy. There is no good-quality evidence that a strategy of prophylactic blood transfusion does or does not benefit the mother or fetus when compared to selective transfusion.[25] Whatever the transfusion strategy, the benefits of transfusion need to be balanced against the risks of alloimmunization and delayed hemolytic transfusion reactions, which can be life-threatening.[26]

Because of the high risk of FGR, fetal growth was monitored with serial ultrasounds.[23] Our practice is to start at 24 to 28 weeks' gestation. Due to the increased risk of stillbirth, a plan for fetal surveillance was also in place. Our practice is to start antepartum testing at 32 weeks' gestation. If all is going well, we plan to deliver women with sickle cell anemia (SS and S-beta thal^0 genotypes) at 37 weeks' gestation and women with other genotypes at 39 weeks. For the patient on opioid medication, the nursery needs to be prepared for neonatal withdrawal syndrome. During hospitalization, there should be a plan for VTE prophylaxis. It is our practice to prescribe prophylactic doses of low-molecular-weight heparin for 6 weeks postpartum.

Case 3 continued

This patient was transfused with 2 units of RBCs prior to induction of labor. She delivered a 2400-g infant vaginally. Postpartum, she received thromboprophylaxis with enoxaparin. She planned to use a long-acting reversible contraceptive and restart hydroxyurea postpartum.

Menopause

For a variety of reasons, women with SCD may be at risk of early menopause or even premature ovarian failure, but there are essentially no data about menopause in these patients.[13] With a life expectancy of 50 years, however, women with SCD will need the help of gynecologists to manage menopausal symptoms.

Conclusion

Increasing therapeutic options for women with SCD and a longer life span are changing how ob/gyns care for women with SCD. For more information please visit the website for the Foundation for Women and Girls with Blood Disorders at www.FWGBD.org. ■

DISCLOSURE The author reports no potential conflicts of interest with regard to this article.

FOR REFERENCES VISIT
contemporaryobgyn.net/SickleCellDisease