Complications in pregnant women with sickle cell disease

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Pregnancy in women with sickle cell disease (SCD) is associated with increased maternal and fetal morbidity and mortality. Outcomes vary widely owing to methodological limitations of clinical studies, but overall, hypertensive disorders of pregnancy, venothromboembolism, poor fetal growth, and maternal and perinatal mortality are increased globally. Few therapeutic interventions have been explored other than prophylactic and selective transfusion therapy. Unfortunately, existing data are limited, and it remains unclear whether prophylactic use of chronic transfusions will improve pregnancy outcomes. Management of pregnant women with SCD is best accomplished with a multidisciplinary team that includes a sickle cell expert and an obstetrician familiar with high-risk pregnancies. Women with SCD should have individualized care plans that outline management of acute pain and guidelines for transfusion therapy. Neonates require close monitoring for neonatal abstinence syndrome and hemolytic disease of the newborn. Ideally all young women with SCD will have a "reproductive life plan" developed as a component of preconception counseling and health promotion. Research leading to improved pregnancy management focused on diminishing adverse maternal and neonatal outcomes is overdue. International collaborations should be considered to improve subject recruitment and foster timely completion of clinical trials. Additional therapeutic interventions outside of transfusion therapy should be explored.

Learning Objectives

- Describe the maternal/fetal morbidity and mortality associated with pregnancy in sickle cell disease
- Describe the impact of prophylactic and selective (on-demand) transfusion protocols in women with sickle cell disease
- Discuss the important components of managing pregnancy in women with sickle cell disease to optimize outcomes

Introduction

Despite advancements in health care over the last 4 decades, maternal and fetal morbidity and mortality remain high, with limited therapeutic interventions to improve pregnancy-related outcomes in women with sickle cell disease (SCD). Because of early diagnosis and improved pediatric care, more individuals with SCD are reaching reproductive age, thereby directing attention to improving reproductive health care and outcomes for pregnant women. Awareness of the need to seek medical care by a multidisciplinary team early in pregnancy and the need for reproductive counseling is necessary at the patient, provider, and community levels. A reproductive health plan for all patients with SCD as recommended by the National Heart, Lung, and Blood Institute's Sickle Cell Expert Panel 2014 should include education on the pregnancy outcomes and genetic risks. Similar to the general population, unplanned pregnancies in adolescents and young adults are not uncommon. Subsequently, pediatric care providers as well as adult care providers should be knowledgeable about pregnancy-related issues to better prepare their patients for pregnancy and possibly, improve pregnancy outcomes.

Maternal and fetal mortality rates are high in pregnant women with SCD regardless of geographic location. It is not surprising that, as maternal mortality has increased in the United States since 2010, it has not improved in women with SCD.[1] However, the majority of complications in the general US population leading to maternal mortality could have been avoided; however, similar data on maternal mortality in women with SCD are unknown. Information on causes of death in pregnant women with SCD is lacking. Whether there is variation in causes of death during pregnancy, during labor, and in the year after pregnancy has not been collected nationally.

Large gaps in knowledge remain about clinical risk features associated with pregnancy-related complications, complication prevention, and management. Published clinical studies have been limited by design and execution. Pregnant women with SCD are more likely to develop a host of complications, particularly hypertensive syndromes (such as preeclampsia), venothromboembolism (VTE), preterm labor, and fetal loss. Newborns are more likely to have growth problems and prematurity. Clinical application of prophylactic transfusion, aspirin therapy and systematic use of a multidisciplinary team following protocol-driven care have not been studied prospectively in randomized trials. Well-designed research studies are needed to promptly address these gaps in knowledge. Before these knowledge gaps are addressed, emphasis must be placed on educating patients and providers on pregnancy-related complications and management as well as the benefit of early prenatal protocol-driven care provided by a multidisciplinary team.[2]

Case report

The patient is a 19-year-old with SCD type SS who comes in for a routine pediatric hematology visit and reports that she is 10 weeks

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pregnant. She has a history of infrequent acute pain while receiving hydroxyurea therapy, which she elected to discontinue 5 months ago owing to concerns that she may become pregnant after unprotected sex. She reports a positive home pregnancy test 2 months ago, 3 months after discontinuing hydroxyurea. The patient is concerned, because her sister with SCD had a complicated pregnancy recently. During her pregnancy with twins, she had frequent acute pain episodes requiring hospitalization. Because of a known cerebral aneurysm, she had been scheduled for an elective Cesarean section, but because of preeclampsia-related complications, she delivered at 33 weeks. Her sister's delivery was complicated by a massive pulmonary embolus that required intensive care unit admission. Her babies had neonatal intensive care unit stays because of prematurity, neonatal abstinence syndrome (NAS), and hemolytic disease of the newborn.

The patient is counseled on the complications of pregnancy, and her partner is screened for hemoglobinopathy trait status. She is referred to a high-risk obstetrician at a hospital with an adult hematology practice with expertise in SCD.

During her pregnancy, she has had several hospitalizations for acute pain management in the third trimester but no acute chest syndrome (ACS). She had red cell transfusions for anemia at 20 and 24 weeks gestation. She had spontaneous rupture of membranes at 37 weeks gestation and delivered a 3.2-kg healthy infant vaginally without complications. She had an acute pain episode requiring morphine and an acute exacerbation of anemia requiring transfusion postpartum. She returns 10 days later complaining of back pain and is found to have a hemoglobin of 2.8 g/dL with a new red cell antibody. She had not received C, E, Kell-matched blood at the outside hospital.

Background: potential pathophysiologic mechanisms impacting pregnancy in women with SCD

The physiologic impact of SCD on pregnancy outcomes is thought to be multifactorial, vary throughout pregnancy, and involve early organ system. However, the cardiovascular, respiratory, hematologic, and endocrine adaptations may be particularly challenging in a woman with SCD. Cardiovascular output increases in the first trimester, and total blood volume increases proportionately by increasing primarily plasma volume, which seems contracted in late pregnancy in women with SCD. This may be because of blunting of the renin-angiotensin axis.[3] For a woman with SCD, this may lead to cardiovascular stress and an exacerbation of anemia. Alterations in progesterone and an enlarging uterus lead to changes in pulmonary function. Oxygen consumption increases to meet the metabolic demands of the fetus. This is all in the background of a developing placenta, which may be impacted by red cell sickling, endothelial damage, vascular occlusion, and inflammation.[4]

The consequences of intraerythrocytic sickling, such as hemolysis and vascular endothelial dysfunction, combined with a background of chronic inflammation, hypoxia, and increased cellular adhesion support cellular dehydration, shear stress, and hyperviscosity. Because of these multiple mechanisms, many theorize that intravascular occlusion red cells, white cells, and platelets lead to tissue hypoxia and local environmental changes that further exacerbate intraerythrocytic sickling and endothelial dysfunction.

Anemia is known to impact fetal growth in the general population as well as in women with SCD. Vaso-occlusion and vasculopathy may impact placental health. The chronic inflammation seen in SCD may predispose women to preeclampsia, which may, in turn, limit fetal growth and increase the likelihood of preterm birth. The complications of SCD are both acute and chronic such that, when women with SCD become pregnant, the normal physiologic changes that occur are in a background of chronic organ damage, hemolysis, vascular damage, and inflammation.

Epidemiology of maternal and fetal outcomes

Maternal and fetal complications are increased in women with SCD (Table 1). Their rates vary widely in published reports owing to inherent clinical study limitations. Many studies are retrospective, case-control, or cross-sectional administrative database studies. Country of origin variation adds to the economic diversity, access to health care issues, and the absence of statistical analysis for confounding variables. Maternal and perinatal adverse outcomes in high-income countries are much lower compared with those in low-income countries when considering individual studies,[5] but when considering odds ratios for pooled adverse outcomes, both high- and low-income countries are similarly high.[6] Another salient discrepancy among studies is the use of controls or the selection of appropriate control groups for outcome comparison. Finally, study populations vary by the proportion of women with various SCD genotypes, prior disease severity, presence of comorbidities, maternal age, parity, and gestational age at study entry.

Some early studies report few adverse outcomes,[7] whereas more recent studies and meta-analyses report continued increased adverse events despite recent advancements in care. Obstetrical complications are broad, but hypertensive disorders (such as preeclampsia and eclampsia), poor fetal growth, preterm labor, delivery-requiring Cesarean section, and maternal/perinatal mortality seem to be consistently reported across both retrospective and prospective observational studies as well as cross-sectional clinical administrative databases. Maternal complications related to SCD include acute and chronic pain, ACS, acute stroke, and other complications similar to a prepregnancy state. VTE rates are higher in nonpregnant women with SCD, but this rate seems to increase further in pregnant women.

Hypertensive disorders of pregnancy

Hypertensive disorders of pregnancy, common in women with SCD, may be because of endothelial dysfunction/damage, inflammation, and placental infarction, although the exact cause is unknown. Preeclampsia rates are high (~12%) in some US populations of pregnant women with SCD[1] compared with 4% of pregnancies in the United States.[8,9] Pregnant women with SCD have a 2.42 relative risk (RR) of preeclampsia (95% confidence interval [95% CI], 1.75-3.39),[5] and concomitant HIV infection increases rates of severe preeclampsia in women with SCD from 2.7 per 100 to 6.6 per 100.[10] This increased risk is thought to be owing to increased persistent inflammation associated with HIV infection. Preeclampsia, the second most frequent cause of maternal mortality worldwide, is associated with severe maternal complications, such as eclampsia,[9] stroke, and organ failure, as well as fetal complications, such as intrauterine growth restriction (IUGR), low birth weight, and stillbirth.[11-13] Management of these complications often leads to early induction of labor, Cesarean section delivery, or preterm birth. Significant gaps exist in our understanding of preeclampsia and its relationship to SCD.

Recently, some have questioned the definition of elevated blood pressure in pregnant women with SCD, because patients with SCD have lower blood pressures at steady state compared with the general population.[14] Subsequently, pregnant women with SCD may

Table 1. Maternal and fetal complications in women with SCD

Complications
Maternal complications of pregnancy
Increased maternal mortality
Hypertension syndromes—preeclampsia and eclampsia
Venothromboembolism
Increased pain (acute, chronic, or recurrent acute) and other SCD-related complications, including infection, acute chest syndrome, acute exacerbation of anemia, and acute splenic sequestration
Worsening steady-state anemia
Proteinuria, worsening of renal disease
Hepatic dysfunction, worsening of hepatic disease
Fetal complications of pregnancy
Mortality
Prematurity
Growth problems—intrauterine growth restriction and small for gestational age

have blood pressures that are significantly higher compared with prepregnancy values but may be within the normal range for the general population. Therefore, early signs of preeclampsia may be missed in the SCD population.

There are no studies on the management of preeclampsia in women with SCD. Although transfusion therapy does not seem to change the outcomes, evaluation of other interventions has not been reported systematically. Aspirin therapy at dose of 100 mg and higher has been beneficial in preventing preterm preeclampsia but not term preeclampsia in the general population.[15] The US Preventive Service Task Force did not include SCD in the group of high-risk patients who should receive low-dose aspirin after 12 weeks of pregnancy. However, they did include women with a history of preeclampsia, chronic hypertension, multifetal gestation, kidney disease, and autoimmune disease.[16] Other moderate risk features, including first pregnancy, as well as family history are included by the American College of Obstetrics and Gynecology (ACOG).[17] In addition, the RCOG recommends aspirin daily starting at 12 weeks of pregnancy.[18] Therefore, women with SCD should be offered low-dose aspirin or 81 to 150 mg daily[17] starting at 12 weeks gestation and continuing throughout pregnancy.

VTE

The risk for VTE increases in the general population during pregnancy but also, in women with SCD.[19] It may be that the underlying pathophysiologic mechanisms of SCD leading to increased cellular adhesion and hyperviscosity exacerbate the hypercoagulable tendencies associated with pregnancy. Both deep vein thrombosis and pulmonary embolism occur with increased frequency.[20] These risks are throughout pregnancy, labor, and delivery as well as postpartum.

Fetal growth, prematurity, and perinatal mortality

Babies of mother with SCD are at increased risk for IUGR, low birth weight, small for gestational age (SGA), prematurity, and perinatal mortality. These findings are not influenced by geographic or economic factors, because data are similar in both low- and high-income countries.[6] Poor intrauterine growth is an indicator of placental insufficiency. In women with SCD, this may be owing to vascular occlusion and endothelial damage among many other factors. In addition, women with SCD have low body mass index compared with other women of child-bearing age, and they gain weight at slower rates during pregnancy. These factors may be causal to fetal growth problems, and poor fetal growth is associated with poor clinical outcomes. Babies who are SGA make up 28% to 45% of nonanomalous stillbirths.[21] Infants born SGA have higher rates of neurodevelopmental delay, poor school performance, metabolic disease, and obesity.[21] IUGR is reported at almost 5-fold higher rates in babies of women with SCD compared with those without SCD.[22] The risk of prematurity among babies of women with SCD is twice as likely compared with babies of women without SCD[6] and occurs in 31% to 36% of pregnancies. Women with SCD have babies who have low birth weights and meet criteria for SGA even when birth weights are corrected for prematurity and the effects of maternal ethnicity and parity.[23]

Perinatal mortality

Increased fetal and neonatal deaths occur, including perinatal deaths and stillbirth. These rates vary widely according to country and economic resources. In economically advanced countries, such as Canada and the United Kingdom, these rates are high at 1.6 per 1000 deliveries[24] and 2.9 per 1000 deliveries,[5] respectively, compared with the general population. In less resourced countries, the RR of stillbirth is up to 5-fold higher compared with the general population.

Maternal mortality

The risk of maternal mortality is high in women with SCD, with RR rates as high as 18.5 (95% CI, 8.63-39.72) compared with women without SCD. In those with SS, maternal mortality estimates include an RR of 5.98 (95% CI, 1.94-18.44).[5] The rates of maternal mortality in the US general population are followed by the CDC. Rates have increased from 7.2 deaths per 100 000 live births in 1987 to 17.2 deaths per 100 000 live births in 2015. There are disparities, with African-American women having the highest rates of maternal deaths at 42.8 per 100 000 live births. This emphasizes the need for appropriate control groups in studies of maternal mortality in US women with SCD who are predominantly of African descent. Maternal mortality in the Canadian population of pregnant women with SCD is 1.6 per 1000 deliveries. Although analysis of several US cohorts suggests low numbers of maternal deaths, US national data are limited. Reports on the cause of death in pregnant women with SCD are not well described. Some women die of SCD-related causes, such as ACS, both antenatally and postnatally[25] as well as stroke, hemorrhage, and pulmonary embolus.[26]

Risk factors for adverse outcomes

Women with SCD, type SS are more likely than women with SC to have preeclampsia, premature labor, and newborns who are SGA. In addition, red cell transfusions are required more frequently in women with SS compared with women with SC.[11] Twin pregnancy is associated with severe outcomes in several published reports.[27,28] In addition, low steady-state hemoglobin, high white blood cell counts, and high platelet counts have been associated with more severe outcomes.[29-31] However, these potential risk factors have not been studied in large prospective cohorts.

Management of pregnant women with SCD

After a woman with SCD has a confirmed positive pregnancy test, then facilitating referral to a knowledgeable multidisciplinary team to manage her high-risk pregnancy is primary, because studies suggest that health care by a multidisciplinary team throughout pregnancy improves outcomes. Establishing prenatal care early in pregnancy may reduce adverse outcomes, since women with SCD are less likely to receive prenatal care than their American counterparts.[32] Even when women are unsure about carrying a pregnancy to term, management must focus on prompt obstetrical care to optimize outcomes for both the mother and the fetus until final decisions are made about pregnancy continuation. An SCD expert and an obstetrician familiar

Table 2. Management recommendations for pregnant women with SCD

Trimester
First trimester/initial visit
General recommendations
Identify and establish a communication plan with members of multidisciplinary team, including a specialist in SCD and high-risk obstetrical care
Establish frequency of routine visits throughout pregnancy
Test for and treat iron deficiency
Start folic acid supplementation—5 mg daily
Discuss need for penicillin prophylaxis, particularly in women with a past history of pneumococcal sepsis
Vaccinate for encapsulated organisms and hepatitis B if not administered previously; administer influenza vaccine
Discuss low-dose aspirin therapy—consider starting aspirin 75-81 mg daily at 12 wk gestation; for patients with prior preeclampsia, renal disease, or hypertension, discuss higher doses of daily aspirin
Discuss VTE prophylaxis—compression stocking use daily and low-molecular weight heparin prophylaxis during hospitalizations; for patients with permanent venous catheters, discuss daily low-molecular weight heparin
Close monitoring for hypertension—establish baseline blood pressure and monitor blood pressure frequently
Regular monitoring of fetal growth by ultrasound
Routine screening for bacteriuria
Establish steady-state values
Pulse oximetry
Blood pressure
Hemoglobin phenotype/genotype
Hemoglobin and reticulocyte count ranges
Red cell antigen phenotype or genotype
Red cell antibodies—both present and transient
End-organ damage assessment
Echocardiogram
Urine protein assessment
Pulmonary function tests
Ophthalmologic examination
Evaluation for iron overload
Screen for red cell alloimmunization
Medication evaluation
Discontinue hydroxyurea, warfarin, angiotensin-converting enzyme inhibitors, and angiotensin receptor blockers; chelation therapies; and consider substitute therapies; chelation therapies
Genetic counseling and patient education
Hemoglobin electrophoresis on patient's partner/father of child
In-person meeting to discuss test results and educate on potential outcomes of pregnancy for mother and child, including both positive and negative events
Develop plans for pain management, end-organ damage and blood pressure monitoring, red cell transfusions, and fetal monitoring
Pain management
Analgesics to be used according to trimesters
Identification of hospital team to manage pain and hospital unit location
Monitoring of fetus during inpatient stays
Use of anticoagulation for VTE prophylaxis
End-organ damage and blood pressure monitoring
Urinalysis, glomerular filtration rate, and proteinuria assessments monthly
Establish, document, and communicate systolic and diastolic steady-state ranges for patient before pregnancy
Blood pressure monitoring during pregnancy every 2-4 wk
Red cell transfusions
Establish hemoglobin goals at steady state and during inpatient admissions
Monitor complete blood count and reticulocyte count every 2-3 mo
Establish indications for intermittent red cell transfusions
Establish indications for chronic/prophylactic transfusions
Communicate appropriate red cell antigen matching—at minimum ABO, D, C, E, Kell; consider further extended antigen matching based on red cell alloimmunization and history of delayed hemolytic transfusion reactions
Establish posttransfusion hemoglobin and hemoglobin S percentage goals
Fetal monitoring
Fetal ultrasound at 7-9 wk; recommend every 4 wk through 24 wk and then, every 2 wk to monitor fetal growth
Biophysical profile during inpatient stays
Second trimester
Revise first trimester management plans if necessary
Develop a plan for delivery, including plan for Cesarean section
Educate mother and her support system about complications that may occur during and after delivery as well as possible need for neonatal intensive care unit stay for infant
Communicate plans to members of multidisciplinary team
Revise frequency of routine visits
Test for and treat iron deficiency
Third trimester
Include neonatologist in discussions about fetal growth, plans for delivery, mother's alloimmunization status, and use of opioids throughout pregnancy
Revise first/second trimester management plan if necessary
Revise plan for delivery, including plan for Cesarean section and whether transfusion before delivery is required
Discuss pain management postpartum and need for initiating/restarting prepregnancy disease-modifying therapies; plans may need modification according to whether the patient plans to breastfeed
Develop plan for VTE prophylaxis postdelivery
Develop plan for screening infant for neonatal abstinence and hemolytic disease of the newborn
Communicate plans to members of multidisciplinary team
Revise frequency of routine visits
Test for and treat iron deficiency

with high-risk pregnancy care are key members of the health care team.[2] Other specialists to consider include a neonatologist, an anesthesiologist, a transfusion medicine specialist, and a pain management expert. An individualized plan to monitor SCD-related complications, need for transfusion therapy, the fetus for growth abnormalities, and blood pressure for development of preeclampsia is strongly recommended (Table 2).

Comorbidities/chronic therapies

Pregnant women with SCD require close monitoring to insure maternal and fetal health. Many medical issues must be addressed during pregnancy, delivery, and postpartum. For women with chronic organ damage from SCD, end-organ evaluations should be included throughout the pregnancy (Table 3).

Close monitoring of blood pressure changes is required to identify early signs of pregnancy-induced hypertension or preeclampsia. The

Table 3. Screening for chronic disease complications

Screening
Pulmonary hypertension and prolonged QTc—echocardiogram, electrocardiogram
Proteinuria and high blood pressure—urinalysis, renal function tests, urine creatinine/protein, serum creatinine, assess glomerular filtration rate, consider renal ultrasound
Hepatopathy/gallbladder disease—liver size, aspartate aminotransferase, alanine aminotransferase, bilirubin levels, abdominal ultrasound
Splenomegaly/hypersplenism—physical examination and splenic ultrasound if necessary, complete blood count
Retinopathy—dilated ophthalmologic examination
Strokes, aneurysms, moyamoya—brain magnetic resonance imaging/MRA
AVN—imaging with plain films, magnetic resonance imaging
Chronic lung disease/asthma—pulmonary function tests
Iron overload—serial serum ferritins, imaging for hepatic iron
Red cell alloimmunization—red cell antibody testing; blood bank communication for transient red cell antibodies at all institutions where patient has received blood in the past

AVN, avascular necrosis; MRA, magnetic resonance angiogram.

care team should establish prepregnancy blood pressures to ensure that blood pressure elevations are not missed, because low prepregnancy blood pressures are common in women with SCD. Women with renal disease, pulmonary hypertension, stroke, VTE, asthma, and transfusional iron overload may be receiving long-term therapies that require either discontinuation or close monitoring during pregnancy. Medications to manage renal disease, particularly proteinuria, and hypertension, such as angiotensin-converting enzyme inhibitors and angiotensin receptor blockers, should be discontinued, and other medication options should be discussed with the obstetrics and renal teams. In addition, other medications with known acceptable risks during pregnancy may be substituted if indicated. Controlling chronic renal disease in pregnant women can be challenging and often requires input from a nephrologist, because distinguishing the signs of preeclampsia from worsening chronic kidney disease may be difficult. Establishing protocols for blood pressure monitoring and medication adjustments should be made in early pregnancy.

Women with SCD may be receiving disease-modifying therapies at the time of pregnancy. Current recommendations are to stop hydroxyurea before or at the time of pregnancy. Fetal risks associated with L-glutamine are unknown. Prior chronic transfusion therapy may be continued during pregnancy; however, pretransfusion and posttransfusion hemoglobin and hemoglobin S levels should be discussed with a multidisciplinary team (additional discussion of transfusions is given below). Chelation therapy should be discontinued until discussions with obstetrics and sickle cell experts, who can design an individualized plan for management of iron overload during pregnancy if necessary.

Folic acid supplementation should be continued or instituted throughout pregnancy. Recommended doses are 4 to 5 mg.[33] When drugs are needed, such as antifolate antimalarials, infectious disease specialists should be consulted. Screening for iron deficiency is required throughout pregnancy.

VTE monitoring and prevention are recommended throughout pregnancy. Women should use graduated compression stockings and receive low-molecular weight heparin for VTE prophylaxis when hospitalized. Women with SCD and central venous catheters should consider daily receive low-molecular weight heparin as long as catheters are in place.

An individualized transfusion plan (Table 4) should be developed early in pregnancy outlining indications for acute and long-term transfusion therapy.[34,35] These plans should address transfusion indications, transfusion goals, methods, and posttransfusion monitoring. Many women with SCD have received acute or chronic transfusion therapy; therefore, communication with blood banks where past transfusions have been received is necessary to insure transfusion with the safest red cell unit. Transient red cell antibodies are common in patients with SCD, and therefore, testing at the time of pregnancy may miss red cell alloimmunization. In patients with red cell alloimmunization or a history of delayed hemolytic transfusion reaction, the decision on when and how to transfuse requires careful decision making between the SCD and obstetrical teams. C, E, Kell-matched units are preferred to minimize red cell alloimmunization risk. If a history of multiple red cell antibodies exists, then further extended antigen matched units may be warranted. When a patient has a history of severe delayed hemolytic transfusion reactions requires transfusion, then plans must be made as to whether IVIG or other therapies will be indicated before or at the time of transfusion.

Genetic counseling and counseling regarding potential neonatal complications

All pregnant women with SCD should be offered prenatal counseling, including hemoglobinopathy testing for their partner. The genotype of the mother should be established if not known previously. This is very important for informative prenatal counseling. For example, women with SCD, type SS and α-thalassemia trait may be confused with women with sickle β0-thalassemia. The risk for thalassemia syndromes as well as sickle syndromes will be important for these couples. Partners of pregnant women with SCD should be screened for hemoglobinopathy traits. Testing of the partner should include a complete blood count and hemoglobin electrophoresis quantification. Solubility testing is not appropriate for genetic counseling, and therefore, it is not recommended. Solubility testing may miss other abnormal hemoglobin that, when paired with sickle hemoglobin, can cause SCD. Couples at risk for having a child with a hemoglobinopathy require prenatal counseling to review the risk, the natural history of the disease, and current treatments. Prenatal genetic diagnostic testing should be offered, including chorionic villus sampling and amniocentesis, after the risks associated with testing are discussed.[33,36,37]

Expectant mothers should be prepared for possible outcomes in their children because of their SCD and its treatment. NAS occurs in newborns when mothers have been exposed to opioids; however, intermittent exposure may result in lower rates.[38] Because of the stigma associated with NAS, pregnant women with SCD who have been exposed to opioids should understand that, although rare, their newborn may experience withdrawal. Hemolytic disease of the newborn is not uncommon in women who have red cell alloantibodies. Because this can occur in 37% to 47% of individuals with SCD exposed to donor red cells, families and providers should monitor newborns for signs of hemolysis.

Management of disease-related complications

Acute SCD-related complications continue to occur during pregnancy. Acute pain episodes, ACS, acute splenic sequestration, stroke, and exacerbation are managed similarly to as they would be in nonpregnant patients with important exceptions. Fetal as well as maternal health must be considered. The use of noninflammatory

Table 4. Transfusion protocol for pregnant women with SCD

Transfusion protocol
Before transfusion
Establish indication (see below)
Select best method for transfusion—simple or exchange transfusion; exchange transfusion should be considered for acute stroke, severe ACS, or major surgery
Establish posttransfusion hemoglobin and hemoglobin S (sickle hemoglobin) goals—for most SCD-related complications, posttransfusion hemoglobin should be 10 g/dL but not above 12 g/dL in patients with SS; hemoglobin S for SCD-related complications should be <50%
Obtain red cell antigen genotype or phenotype before transfusion if not obtained previously
Consider quantitative hemoglobin S posttransfusion as well as pretransfusion—this may help with monitoring for delayed hemolytic transfusion reactions
Type and crossmatch; then, select E-, C-, K-matched units in addition to ABO, D matched; honor transient and present red cell antibodies; for patients with a history of severe delayed hemolytic transfusion reactions or multiple red cell antibodies, consider extended antigen matching for Kidd, Duffy, MNS, and other blood groups
Transfuse leuko-reduced irradiated units, because the patient may be a candidate for stem cell transplant
Cytomegalovirus-negative units are recommended during pregnancy (RCOG)
HbS-negative units are recommended to allow for best monitoring of posttransfusion HbS goals
Consider quantitative hemoglobin S posttransfusion as well as pretransfusion—this may help with monitoring for delayed hemolytic transfusion reactions
Indications for transfusion during pregnancy
Acute or simple transfusion
Acute complications of SCD, such as stroke, ACS, acute splenic sequestration
Acute exacerbation of anemia with illness—decrease in hemoglobin 2 g/dL; this may be owing to ACS, infection, acute splenic sequestration, or multiorgan system failure
Acute exacerbation of steady-state anemia—may be because of iron deficiency, renal disease, increase hemolysis
Chronic transfusions
Established chronic transfusion protocol at time of pregnancy
Twin pregnancy
Recurrent severe SCD-related complications during the pregnancy; for example, if exchange transfusion is required during pregnancy or >1 simple transfusion, then strongly consider continuing a chronic transfusion protocol for the remainder of the pregnancy
In particular circumstances—consider in patients for ACS prevention, acute recurrent pain prevention and past pregnancies with known severe complications

drugs for pain management requires discussion with the obstetrics team, because many of these agents are contraindicated in early and late pregnancy. However, nonsteroidal anti-inflammatory agents can be used between 12 and 28 weeks of gestation.[18] Acute complication management may exacerbate other pregnancy-related issues, such as hypertension, gestational diabetes, and preterm labor. Therefore, an individualized care plan should outline pain management (see below); recommendations for monitoring fetal health in the inpatient and outpatient settings; a transfusion plan focused on indication, product selection, and method; and a schedule for screening for obstetric complications, particularly hypertension, diabetes, maternal weight, and fetal growth. Because patients are at risk for stillbirth, pregnant women should be educated on symptoms that could indicate poor fetal health and plans for assessment. Monitoring for VTE is required in all hospitalized expectant mothers. This should include a good physical examination to look for signs and symptoms associated with DVT and PE. Doppler studies are recommended in patients with concerning symptoms and physical examinations.

Acute and chronic pain

Controversy exists as to whether acute pain episodes increase for an individual during pregnancy. Estimates from a prospective cohort study did not show a change in the rate of acute pain episodes before, during, and after pregnancy (CSSCD). Acute pain and ACS occur more frequently in those with the SS genotype compared with those with SC.[5] Acute pain episodes often develop during pregnancy, occurring in 50%,[1] as well as during labor and delivery, with 1 study reporting that 28.5% of women develop pain crises at the time of delivery.[24] Each woman requires an individualized pain plan detailing the use of opioids and nonopioid agents in the inpatient and outpatient settings according to gestational age and complication risk postpartum. Although opioids should not be withheld, pregnant women should be counseled that frequent opioid use in pregnancy has been associated with NAS. In addition, because of concerns regarding anti-inflammatory drug use in early and late pregnancy, the obstetrical team should provide guidance. Epidural anesthesia has been used particularly for acute pain episodes around labor and delivery.

Data on rates of ACS around pain admissions are lacking, but measures to prevent ACS during hospitalization, such as incentive spirometry use and frequent ambulation, should be considered. In women who develop ACS, evaluation for pulmonary embolus should be considered. Adequate oxygenation should be maintained with supplemental oxygen therapy. Pregnant women who are hospitalized for acute pain management should be closely monitored for ACS and VTE, and thromboprophylaxis should be initiated. Fetal monitoring results must be interpreted cautiously during pain episodes where opioids are used, because this may impact nonstress testing.[26]

For women with chronic pain who are receiving daily opioids before their pregnancy for pain management, opioids should be continued. It is unclear whether tapering opioids throughout the pregnancy lowers the likelihood of NAS.

Other SCD-related complications

Acute exacerbation of anemia occurs in pregnant women with all sickle cell genotypes. Women with SS are more likely to receive a transfusion than those with SC. Women with SCD and prior stroke require close monitoring for recurrent stroke, both infarctive and hemorrhagic, throughout pregnancy, including postpartum. Severe or persistent headache is a sign of hemorrhagic stroke. All women with SCD should be evaluated for stroke, particularly if hypertensive. In patients with severe ACS, stroke, or severe acute exacerbation of anemia, transfusion therapy should be instituted.

Special topics

Prophylactic and selective (on-demand) chronic transfusion therapy

The role of transfusion therapy in pregnancy is unclear, because data are lacking, and clinical studies are limited by methodological problems. Because many are searching for therapies to insure positive outcomes in pregnancy, guidelines have been developed, but efforts have not been made to address the lack of evidence. Guidelines and meta-analyses support continuation of prepregnancy chronic transfusion therapy.[18] In addition, they recommend selective

transfusions for particular indications or "on-demand" transfusion (ODT) therapy.[18,19,39] This encompasses using transfusions to treat acute complications that occur during pregnancy. Many broaden this and ODT to include instituting chronic transfusion therapy to prevent severe complication recurrence. However, the use of chronic transfusion therapy prophylactically throughout pregnancy is controversial.[40,41]

Meta-analyses designed to compare studies on groups of women treated with ODT with groups of women treated with prophylactic therapies are fraught with small sample sizes and methodological limitations.[39] Most studies are retrospective without consistent inclusion criteria, outcome variables, or transfusion protocols/goals. For prophylactic transfusions, the transfusions are initiated at various times during pregnancy, many after 20 weeks gestation. Not all studies collect data on the adverse impact of transfusion therapy, such as red cell alloimmunization, delayed hemolytic transfusion reactions, and hemolytic disease of the newborn. It is not surprising that few conclusions have been reached other than that prophylactic transfusions may decrease acute pain in pregnant women with SCD. However, because of limited data and inconsistencies between studies, no conclusions can be drawn on the impact of transfusions on obstetrical outcomes, such as preeclampsia and fetal growth. A recent study reports on the potential benefit of nocturnal oxygen supplementation to decrease the need for red cell transfusions.[42] Large randomized, controlled trials are needed to better address this issue.

Red cell transfusion for acute complications, such as ACS, symptomatic exacerbation of anemia, and stroke, is indicated as is the continuation of antenatal chronic transfusion therapy, although the use of transfusion to prevent complications is controversial.

Although many are interested in transfusion to prevent adverse outcomes, one must balance the risks associated with broad use of red cell transfusions. These risks include acute transfusion reactions, transfusion-transmitted infection, and transfusional iron overload. Red cell alloimmunization and delayed hemolytic transfusion reactions are particularly concerning for patients with SCD, because red cell alloimmunization is common and has significant clinical consequences, including difficulty finding compatible red cell units and delayed hemolytic transfusion reactions. In addition, severe exacerbation of anemia may impact the health of the fetus, and red cell alloimmunization may lead to hemolytic disease of the newborn.

Reproductive health promotion and preconception counseling

Reproductive health promotion and preconception counseling should be offered to all adolescents and young adults with SCD as well as women with SCD postpartum. A reproductive life plan should be discussed, documented, and communicated to the health care team.[36] For women who wish to become pregnant, offer preconception counseling, and for those who do not wish to become pregnant, offer contraception counseling. This is particularly important, because the impact of long-term therapies on reproductive health and pregnancy outcomes is not well known. Hydroxyurea, L-glutamine, and chronic transfusion therapy may support fertility by decreasing circulating sickle erythrocytes, thereby decreasing chronic/recurrent acute infarction and limiting organ dysfunction. However, there are potential risks with pharmacologic therapies during pregnancy. The teratogenic effects of pharmacologic L-glutamine are not known. Animal data suggest that hydroxyurea is a potential teratogen; therefore, recommendations are to stop hydroxyurea use before conception and avoid its use during pregnancy and breastfeeding. However, these recommendations have been made in the setting of limited human studies. There are ongoing studies of hydroxyurea excretion in breast milk (R. Ware, personal communication). Finally, untreated transfusional iron overload can cause endocrine dysfunction and secondary infertility in other chronically transfused populations.

Reproductive health and genetic counseling should be offered by a multidisciplinary team familiar with the medical, societal, and psychologic impact of living with SCD. Myths need to be addressed, such as that all women with SCD are infertile as well as that pregnancy in women with SCD is universally fatal. These extremes play out in a background of stigma associated with SCD and various cultures that may not welcome open discussions about sexuality and reproductive health. Young women with SCD should understand that fertility is likely to be normal, that pregnancy is possible, and that complication risk is high for both mother and child. Contraception is advised to prevent unplanned pregnancy. For women planning to become pregnant, disease management before conception should include discussions of when to suspend HU use and early pregnancy management by a multidisciplinary team, including high-risk obstetric and sickle cell experts. Preconception counseling should include partner testing (see prior discussion on genetic counseling). For couples at risk of having a child with a hemoglobinopathy, preimplantation genetic testing with in vitro fertilization should be discussed as well as prenatal/preconception genetic testing.[33] Reproductive planning and contraception counseling should be a consistent feature of a comprehensive SCD visit in pediatric- as well as adult-focused care. Preconception counseling must include discussion of pregnancy risks and emphasize the need for early prenatal care.

Future directions and clinical research needs

Pregnant women with SCD are at increased risk for adverse outcomes. However, limited information exists about risk factors for maternal death, pregnancy-related hypertension disorders, VTE, premature labor, or increased SCD-related complications in pregnancy. The impact on the fetus is profound, including prematurity, growth problems (such as IUGR and SGA), stillbirth, neonatal abstinence, and HDN. Therapeutic interventions to change these adverse outcomes that have been applied in the general population have not been systematically explored in SCD. Transfusion therapy and hydroxyurea therapy are disease modifying and decrease acute disease progression and acute recurrences, but the lack of well-designed studies limits their use in pregnant women. Few methods for collecting data on pregnancies or tracking adverse events have been applied. Published guidelines by the ACOG (2007)[33] and the RCOG[18] provide recommendations for the health care of pregnant women with SCD. However, the use of these guidelines varies, and recommendation adherence has not been tracked. Knowledge gaps are vast, and few well-designed prospective studies have been funded. Issues that are likely to occur in this population, such as postpartum depression and anxiety disorders, have not been addressed. Advocates for women's health and the SCD community should adopt a platform to reduce these health disparities and improve research interests and funding.

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