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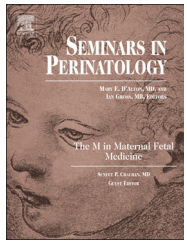

Sickle cell crisis and pregnancy

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ABSTRACT

Pregnant women with sickle cell disease appear to be more likely to experience antepartum, intrapartum, and postpartum complications when compared with unaffected women. Access to high-risk obstetric care, patient education, and close follow-up is important to minimize maternal morbidity and mortality. A high index of suspicion and good diagnostic acumen is necessary to obtain optimal results in the pregnant patient affected by sickle cell crisis.

1. Introduction

In the United States, sickle cell anemia affects about 70,000 people.[1] The disease is most prevalent in African Americans and occurs in about 1 of every 500 births. Patients with hemoglobin S-S (Hgb S-S), as well as with other variants such as hemoglobin S-C (Hgb S-C) and hemoglobin S-β thalassemia (Hgb S-β Thal), are said to have sickle cell disease. This disease is associated with abnormal sickling of the red blood cell resulting in microvascular occlusion (vasoocclusion) that is most often manifested clinically as an acute painful episode or crisis.

There is consistent evidence that anemia and vasoocclusive crises occur more often in pregnancy and are the most common maternal complications associated with sickle cell disease in pregnancy, occurring in over 50% of pregnant women with this hemoglobinopathy.[2–9] Painful crises are more common with advancing pregnancy and in the postpartum period.[3] Due to lack of randomized clinical trials, management of vasooclussive crises in pregnancy can be complex and is often based on retrospective findings and expert opinion. This was illustrated in a 2009 Cochrane systematic review, which confirmed the paucity of randomized trials that address the efficacy and safety of treatment approaches for painful sickle crisis during pregnancy.[10] It is difficult to provide standardized recommendations in regarding the treatment of a painful crisis in pregnancy as most cases have to be individualized after consideration of a wide range of variables. Figure 1 provides the reader with a good template that will provide appropriate initial steps regarding the management of these patients. The information provided in this figure is gleaned from information obtained from the American Congress of Obstetricians and Gynecologists, the National Institutes of Health, the American Pain Society's expert panel on treatment of pain, and incorporation of our own clinical experience.[11–13]

The standard approach to management of crisis consists of prompt evaluation for precipitating factors such as dehydration, hypoxia, or infection. Additional environmental triggers include cold temperatures, changes in weather, over exertion, and exposure to tobacco smoke. Treatment modalities include oral or intravenous fluid resuscitation, oxygen supplementation, and aggressive pain control using opioids and other analgesics. The use of non-steroidal anti-inflammatory drugs (NSAIDs) is generally avoided after 30 weeks of gestation because of an increased risk of premature narrowing or closure of the ductus arteriosus but can be considered during the second trimester of pregnancy or postpartum. There are also reports of successful pain control with epidural analgesia in the antepartum setting, especially if traditional interventions are not providing relief.[14]

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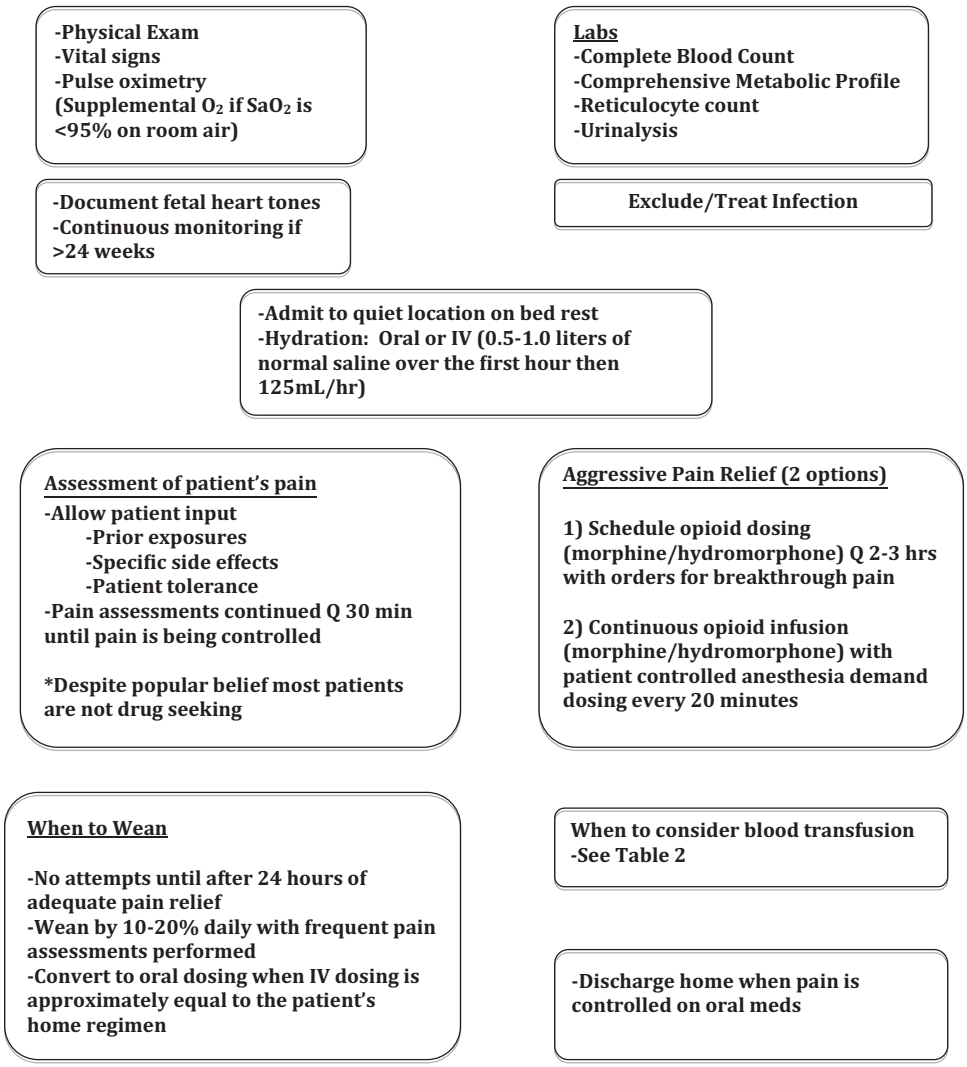

Fig. 1 – Management of the pregnant patient who presents with painful sickle crisis.

2. Antepartum

During the prenatal period when the patient is remote from term, hospitalization where bed rest, analgesia, and hydration can be carried out is optimal. Because of the risk of fetal loss, health assessment via biophysical profile and/or fetal heart rate monitoring is carried out during crisis treatment if gestational age is sufficient to consider intervention for fetal distress. Administration of corticosteroids for fetal benefit should be considered in those patients with crisis who are at a viable gestational age due to the associated increased risks of preterm labor, preterm premature rupture of membranes, fetal distress, and preeclampsia.

Initial medical assessment should focus on detection of the following medical complications that require immediate intervention: infection, dehydration, acute chest syndrome (fever, tachypnea, chest pain, hypoxia, and radiologic chest infiltrates), severe anemia (Hgb $<$ 5.0–6.0 g/dL), cholecystitis, splenomegaly, hepatomegaly, abdominal crisis (abdominal pain, distension, and rigidity), and neurologic events (cerebral infarct, cerebral hemorrhage, transient ischemic attack, and seizure). Vigorous rehydration is useful, particularly in crisis patients who are febrile.[15] In the absence of cardiopulmonary disease; infusion of a liter of Ringer's lactate or isotonic saline during the first 2-h period with continuing replacement at 125 mL/h is undertaken. Careful monitoring of intake and output is essential, but invasive hemodynamic monitoring and urinary catheterization are usually avoided because of the risk of infection. The administration of alkali during the hydration process has not been found to be helpful.[16] In regard to analgesia, opiates are superior to non-steroidal agents in the presence of severe pain. The initial dosing for opiates and/or other adjuvant therapies should involve careful consideration of the patient's input regarding what treatment regimens have been useful in the past, what their tolerance level may be, and what medications the patient typically takes at home (Table 1). The clinician should not withhold treatment in patients presenting with crisis due to concerns for "drug seeking," as the harmful behavior of a few patients should not alter the care of those patients who really require opiate intervention. The majority of reports demonstrate no evidence of teratogenicity with regard to opiate use in pregnancy, but long-term exposure to opiates can result

Table 1 – Pain management options for sickle cell crisis.

Medication	Oral	Parenteral	Side effects	Teratogenicity	Cost[a]
Morphine	10–30 mg every 3–4 h	5–10 mg every 2–4 h	Sedation, constipation, pruritus, and respiratory depression	No human reports of birth defects. NAS	$0.65/30 mg dose
Hydromorphone	7.5 mg every 3–4 h	1.5 mg every 3–4 h	Sedation, constipation, pruritus, and respiratory depression	No human reports of birth defects. NAS	$0.80/4 mg dose
Codeine	15–60 mg every 3–6 h	NA	Sedation, constipation, pruritus, and respiratory depression	Reports in human pregnancies inconsistent. NAS	$1.00/30 mg dose
Ibuprofen[b]	600–800 mg every 6–8 h	NA	Dyspepsia, GI bleeding, nausea, and tinnitus	Inconsistent reports suggest increased risk for miscarriage. Concerns for premature ductal closure.	$0.10/600 mg dose
Ketorolac[b]	10 mg every 4–6 h	30 mg every 6–8 h	Headache, nausea, abdominal pain, dyspepsia, and GI bleeding	Concerns for premature ductal closure	$2.50/30 mg dose
Acetaminophen	300–1000 mg every 4–6 h	NA	Nausea, rash, headache, and hepatotoxicity	Considered safe although some inconsistent reports of association with childhood asthma or cryptorchidism	$0.06/500 mg tablet

NAS: neonatal abstinence syndrome.
[a] Data on cost obtained from drugstore.com and does not necessarily reflect inpatient costs.
[b] Can consider occasional use in the second trimester as an adjuvant to opiate treatment (not first line).

in neonatal abstinence syndrome shortly after birth. To our knowledge, there is no true definition for long-term or chronic use of opioids but some observational investigations use 90 days as meeting criteria for this definition.

As soon as the painful crisis begins to regress, non-narcotic agents should be considered. It is important to recognize that assessment of fetal well-being during a pain episode may be complicated by the use of opiates to treat sickle cell crisis pain, which transiently affects non-stress testing and biophysical profile scores.[17] Caution must be used when interpreting the results of these tests during an acute pain episode, as any observed negative effects are only transient and often times will not warrant delivery intervention unless ominous findings are observed (e.g. terminal bradycardia).[18]

Although the utility of oxygen therapy is unproven in randomized trials, it is often employed during crisis. Oxygen is administered at 3–6 L/min by tight facemask or nasal cannula. Arterial blood gas assessment is recommended if hypoxemia is suspected. Because infection is present in up to one-third of patients with vasoocclusive crisis and since it may be associated with maternal death occurring in sickle cell crisis, attempts to detect occult infection are undertaken immediately. If an infection is suspected, then broad-spectrum antibiotic therapy is begun after appropriate cultures are obtained. The initial empiric antibiotic of choice is ceftriaxone due to these patients' susceptibility to infection with encapsulated organisms (i.e. Streptococcus, Meningococcus, and Haemophilus). If meningitis is suspected then vancomycin is the preferred antibiotic. For those patients with cephalosporin allergies, clindamycin should be initiated.

3. Blood transfusion

There are two types of blood transfusion that have been designated in the care of sickle cell patients: therapeutic and prophylactic. In pregnant patients with sickle cell disease, prophylactic refers to a transfusion given for primary or secondary prevention of adverse events such as pain crisis, stroke, and other potential morbidities. Controversy exists regarding the role of prophylactic blood transfusion in the management of sickle cell disease in pregnancy.[19–23] It appears from the available evidence that the reduction in morbidity and mortality of sickle cell disease in pregnancy may be attributable to improvements in general management of pregnancy rather than the effects of prophylactic transfusion.[11] The only randomized trial to date that has evaluated the utility of prophylactic transfusions demonstrated a significant decrease in painful crises during pregnancy but did not demonstrate improved pregnancy outcomes overall.[20] However, there are some experts that believe selective use of prophylactic transfusion may be beneficial in pregnant

Table 2 – Indications for therapeutic blood transfusion.

Consult hematology and consider a simple vs. an exchange transfusion if patient presents with any of the following
Hemodynamic instability
Acute chest syndrome
Acute stroke
High-output cardiac failure
Multi-organ failure
Symptomatic anemia (dyspnea, marked fatigue)
Severe, refractory pain crisis (>10 days)
Persistence of preeclampsia sequelae despite delivery
Reticulocytopenia (common after Parvovirus B19 infection; can occur with any infection)

Acute chest syndrome (fever, tachypnea, chest pain, hypoxia, and radiologic chest infiltrates).
High-output cardiac failure (characterized by an elevated resting cardiac index beyond the normal range of 2.5–4.0 L/min/m^2).

women with sickle cell disease who are at highest risk of complications, such as those with previous perinatal mortality or severe anemia.[24,25]

In contrast, therapeutic transfusions are indicated in patients who have particularly severe disease manifestations or for symptomatic patients who are unresponsive to conservative management (Table 2).[26–28] Pregnancies impacted by acute symptomatic or severe anemia (Hgb < 5.0–6.0 g/dL), intrapartum complications including hemorrhage and septicemia, refractory painful crisis (relapse <1 week, no improvement >10 days), and those women with reticulocytopenia (e.g. those affected by Parvovirus B19 infection) often benefit from intervention with a blood transfusion.[12,18,29] Additional indications in pregnant and postpartum women include anemic women who are scheduled to have a cesarean delivery and preeclamptic patients that continue to have signs and symptoms of preeclampsia despite delivery.[30]

By limiting transfusion to situations in which it is clinically indicated, patients are not subjected to the increased risk for blood-borne infections, hyperviscosity syndrome, volume overload, iron overload, and alloimmunization. There is no consensus regarding the exact hematocrit value below which transfusion should be considered. However, when a transfusion is clinically indicated in the patient with sickle cell disease, the objective is to lower the percentage of Hgb S to approximately 40% while simultaneously raising the total hemoglobin concentration to about 10 g/dL.[11]

Once the decision to perform a transfusion arises, the choice between a simple or exchange transfusion should be based on the urgency of the situation and the availability of resources. Exchange transfusion, also known as erythrocytapheresis, allows the Hgb S-containing cells and irreversibly sickled cells to be removed by extracorporeal, differential centrifugation. It affords the simultaneous return of the patient's own plasma, leukocytes, platelets, and clotting factors along with donor's leukocyte-reduced Hgb A-containing red cells via venous access in the other arm. This type of transfusion utilizes a cell separator that allows for automated continuous erythrocytapheresis but can also be performed manually. The automated process allows for maintenance of isovolemia at all times and allows the provider to monitor the patient's hematologic indices such as hemoglobin levels and hematocrit. This process typically involves the exchange of six units of donor packed red cells, and there is generally a rapid resolution of crisis symptomatology and ongoing sickling.[31] Most of the complications associated with transfusions are related to the risk of the blood products. Blood products given to these patients should be cytomegalovirus-negative, leukocyte-depleted red cell units that are phenotypically matched for at least the C, D, E, and Kell blood groups.

Careful crossmatching to minimize minor blood incompatibilities and alloimmunization is critical in avoiding problems later including post-transfusion hemolytic crises.

4. Intrapartum

The occurrence of vasoocclusive crises during labor offers additional challenges to the provider. Obviously, with painful uterine contractions, the diagnosis of a vasoocclusive crisis may be more difficult. During labor, patients should remain in the lateral recumbent position and receive oxygen by tight-fitting facemask. Careful monitoring of maternal and fetal vital signs is essential. When a sickle cell crisis has been diagnosed during labor and late decelerations appear, our anecdotal experience suggests that infusion of blood products is associated with resolution of suspected fetal hypoxemia. Maternal blood gas assessment, if necessary, is carried out, but invasive hemodynamic monitoring is avoided unless other concomitant disease processes are present (e.g. complicated by severe preeclampsia, cardio-respiratory failure). Urinary catheters, as well as intrauterine catheters, should be used with caution because of their association with infection.

No consensus exists concerning the anesthetic care of parturients with sickle cell disease.[32–34] The use of general anesthesia can result in a significant increase in postpartum sickling complications.[35] Therefore, if cesarean delivery is indicated, regional anesthesia is preferred unless an obstetric emergency arises. Additionally, the use of intermittent intravenous opioids often yields little to no pain relief for laboring patients and therefore we typically recommend regional anesthesia, especially if labor is confounded by the concomitant presence of a vasoocclusive crisis. Avoidance of hypothermia and hypoxia during labor and delivery is critical. Persons skilled at neonatal resuscitation should be present at delivery. Consultation with anesthesia and neonatology during labor is important. The use of oxytocic agents for induction/augmentation or prostaglandins for cervical ripening or for postpartum hemorrhage is not contraindicated.

5. Postpartum

The same concepts of management applied during the antepartum period are also prudent after delivery. Sickle cell crises in the postpartum period can be decreased if measures are taken to avoid hypovolemia, infection, and acidosis. Because urinary tract infection and endometritis are more common in these patients, early detection and treatment are important in order to deter the onset of a vasoocclusive event. There is also an increased risk of pulmonary edema and thromboembolic disease in these patients.[36] Because of this risk, it is important that sequential compression devices and/or prophylactic anticoagulation is utilized for gravidas with sickle cell disease who are admitted for any reason during pregnancy or postpartum. Additionally, these authors believe that maintenance of isovolemia and higher Hgb A levels (>20%) decrease the risk of vasoocclusive crises in the postpartum period.

6. Summary

Overall, pregnant women with sickle cell disease appear to be more likely to experience antepartum, intrapartum, and postpartum complications when compared with unaffected women. Access to high-risk obstetric care, patient education, and close follow-up is important to minimize maternal morbidity and mortality. A high index of suspicion and good diagnostic acumen is necessary to obtain optimal results in the pregnant patient affected by sickle cell crisis.

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