Sickle cell disease in pregnancy

Obstetric and anesthetic management perspectives

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ABSTRACT

Recent advances in the pathophysiology, clinical investigations, and management of sickle hemoglobinopathies enables all physicians to better manage these disease states and their sequelae. Patients with sickle cell disease (SCD) are living longer and are thus more likely to contract unrelated diseases that require surgery and anesthesia. Patients with SCD continue to be a challenge to all branches of medicine particularly in obstetrics, surgery and anesthesia; however, the armamentarium of new knowledge and practice places a different perspective on the care of this old disease. In general, the literature to date suggests that neither prophylactic transfusion of pregnant sicklers nor the selection of an anesthetic in labor have a major impact on patient outcome; however, perioperative management can greatly affect the consequences. A thorough knowledge of the impact of the disease on clinical status can determine how, when, and why to manage parturients with SCD.

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A tremendous amount of progress has been made toward finding a cure for sickle cell disease (SCD) since the enactment of the National Sickle Cell Anemia Control Act.[1-3] Today a cure is possible with a bone marrow transplant, which is available to only a limited number of individuals who meet the criteria for bone marrow transplantation. More recently, there have been 3 breakthroughs in the management of SCD, namely: preimplantation genetic diagnosis (PGD) and the selection of healthy zygotes for implantation, and cord blood transplant from an unrelated donor newborn.[4] The first case of this nature was carried out in 1998 at the Grady Memorial Hospital, Atlanta, Georgia, United States of America (USA), with promising results. A 12-year-old African child who underwent this procedure has not had any sickle cell crises for the past 3 years. The third advance has been in perfecting the process of harvesting cord blood stem cells, and reusing the harvested cells for treatment of other patients.[5,6]

Current management focuses on avoidance of hemoglobin S (Hb S) polymerization, decreasing the percentage of circulating Hb S, or increasing the percentage of Hb F. Until other cures become readily available, we must rely on these various modes of therapy for the management of patients with SCD.

We review the history of SCD and the implications of its pathophysiology in the obstetric and anesthetic management of parturients with steady-state disease. Important issues in the preoperative, intraoperative, and postoperative periods are discussed. Concerns of parturients with SCD are also addressed.

History. Sickle cell anemia was first described in 1910 by Dr. James Herrick.[7] There is good evidence to support the recognition of SCD in Africa centuries before its discovery by modern medicine. The fact that SCD is a disease of red blood cells was not apparent in traditional medical systems, where microscopy was not available. The

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inherited nature of the disease was known to traditional African medicine as a condition that ran in families, and it was linked to the myth of reincarnation and explained the existence of "repeater children." It is most probable that the "reincarnate" or "repeater" child had sickle cell anemia as this disease would explain all the clinical features and natural history of "reincarnation".[8] Practitioners of traditional medicine found it difficult to believe that the clinical manifestations of SCD, such as yellow sclera, frequent pain over the entire body, chronic leg ulcers, and mortality from overwhelming infections, could be part of the same disease.

Epidemiology. Sickle cell disease is a major health problem the world over. Individuals living in Southern Italy, Northern Greece, Southern Turkey, the Eastern and Western Provinces of the Kingdom of Saudi Arabia, India, and equatorial Africa carry the genome.[8-13] In Africa alone, approximately 200,000 infants are born each year with homozygous sickle hemoglobin (Hb SS). Approximately 8% of Americans of African descents have a sickle hemoglobinopathy.[14,15] In the USA, approximately 2,000 infants with sickle hemoglobinopathies are born annually.[5] In the Arabian Peninsula, the population is characterized by a high incidence of hemoglobinopathies, including β-thalassemia, Hbs and Hbc.[15] The β-S gene is quite frequent. In KSA the gene frequency varies from 0 (in the non malaria northern provinces) to 0.145 in the Eastern provinces (Hb AS=21.3%).[16] Of interest are the western provinces in which the sickling gene is linked to the Benin haplotype of African origin, while in the eastern provinces it is linked to the Arab-India haplotype which is of Indo-European origin.[17,18] The clinical picture of sickle cell anemia linked to Benin and Bantu haplotype is more severe than the disease linked to the Arab-India haplotype.[19,20] In Bahrain[21] and Kuwait[22,23] the Arab-India type predominates among carriers of the sickle gene. Sickle cell disease was the first genetic disorder precisely delineated at the chemical level. Pauling et al[24] demonstrated the electrophoretic differences of sickle hemoglobin and deduced that the electrochemical difference was the source of the sickling phenomenon. Sickle cell disease is a group of inherited disorders distinguished by the presence of sickle hemoglobin (Hb S). Sickle cell disease consists of a family of hemoglobinopathies inherited as an autosomal recessive disorder that affects the β-globin subunit. Ingram demonstrated the presence of a substitution at the sixth position of valine for glutamine that results in Hb S. Sickle hemoglobin has a propensity for increased cell membrane rigidity, irreversible red cell deformation, and tactoid formation in the face of deoxygenation.[25] Homozygous sickle cell disease (Hb SS) is the prototype; the β-globin gene on each chromosome contains the classic sickle mutation. However, one of the β-globin genes may contain another mutation or alteration.[25] Hemoglobin C results from the substitution of lysine for glutamine at the sixth position of the b-globin gene. Thalassemia results from the unmatched production of β-chains and α-chains and is denoted as β^{o}-thal or β+-thal.[26] In the African-American population 3 common forms of SCD are observed: 1. sickle cell anemia (Hb SS) 2. sickle-hemoglobin C disease (Hb SC), and (3) sickle-β-thalassemia syndromes. The 3 common diseases and the more than 700 known hemoglobin variants are all inherited by the autosomal recessive mode. Hemoglobin AS is known as sickle cell trait (SCT). In Hb AS a single S gene is present and the Hb S levels within the red cells are less than 50%.[23] An individual with Hb AS is typically asymptomatic, whereas patients with Hb SS experience the most severe disease symptoms (**Table 1**).

It is important to know what type of sickle hemoglobinopathy the patient has as the severity of disease varies among the types. Regardless of whether the patient is homozygous or heterozygous and asymptomatic, these individuals should be made aware of their genotype for family planning and other related potential medical issues. Certain clinical and anemia signs should lead the clinician to search for the presence of abnormal hemoglobin. Some of the abnormal hemoglobin manifestations include sickle cell formation seen on peripheral blood smears, microcytosis, target cells, Heinz body formation, an increased red blood cell mass, and formation of methemoglobin in an individual.[23] All of these signs indicate the presence of an abnormal hemoglobin (**Figure 1**). Currently in the USA the issue of early diagnosis has been addressed by the implementation of newborn screening programs in 42 states, the District of Columbia, Puerto Rico, and the U.S. Virgin Islands. Universally, the overall mission in newborn screening programs is to identify newborns for the institution of prophylactic penicillin administration.[27] In the Gulf Cooperation Council (GCC) states several health measures have been undertaken over the last few years to alleviate the sickle cell morbidity among the populous. In Bahrain, universal screening of all pregnant women for the sickle gene was introduced some 30 years ago, and screening of all newborns of sickler parents is also a routine; now there is the setting up of compulsory premarital services which include screening for the sickle gene. The incidence of various hemoglobinopathies in Bahrain is the highest in the Gulf region which could be explained by the fact that the Bahraini islands have been on the sea trade lines between east Africa, India and Mesopotamia since the ancient times. Other factors,

Table 1 - Bahrain prevalence status.

Trait	Prevalence (%)
Hb SS (Sickle cell disease)	1.2
Hb AS (Sickle trait)	14
Hb AC (C trait)	(Rare (non Bahrani)
Hb AD (D trait)	0.2
Hb AG (G trait)	0.3
HPFH trait	0.1
α-Thalassemia	
α-Thalassemia silent carrier (3 functional genes)	30
α-Thalassemia trait (2 functional genes)	3
β-Thalassemia	0.1
Glucose 6 phosphate dehydrogenase deficiency (G6PD)	23

Hb - hemoglobin
HPFH - hereditary persistence of fetal hemoglobin

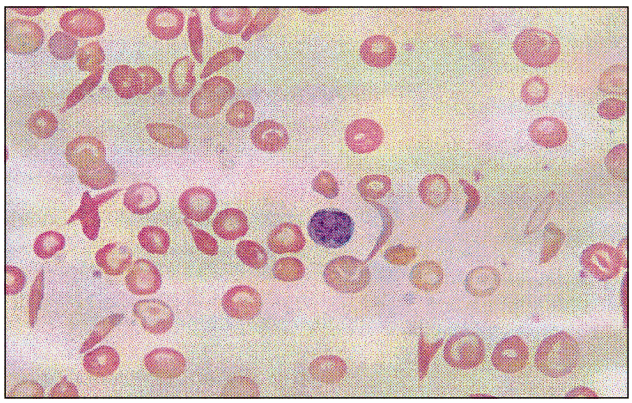

Figure 1 - Peripheral smear showing normochromic, normocytic cells. Irreversibly sickled cells are present and confirm the diagnosis of a sickle hemoglobinopathy.

such as small endogamic villages, consanguinity and malaria, which used to be endemic in Bahrain, have all contributed to the current prevalence.[22,23] Haplotyping delineates the specific form of homozygous disease. Some authors suggest that knowing the haplotype will aid in predicting the severity of disease and could thus be key to the management of patients with SCD. Current data on homozygous SS patients show that heterozygous haplotype combinations have no effect on hemoglobin levels. However, data on hemoglobin types affirm that patients with haplotype no. 3 (3/3) have the highest Hb F levels and are least affected whereas children with homozygosity for haplotype no. 20 (20/20) are the most severely affected of patients with sickle cell anemia.[28]

Pathophysiology. The hemoglobin molecule of the red blood cell is formed by 2 α- and 2 β- chains. Fetal hemoglobin is composed of 2 α- and 2 g-globin chains. Four oxygen molecules can attach to the available binding sites on each of the hemoglobin molecules. A reversible deformation occurs with removal of the oxygen molecules from the binding sites: however, in SCD the deformation may be permanent. In sickle hemoglobin, the glutamyl residue is replaced by valine and is uncharged, the result of which is a hydrophobic bond and an electrically neutral side chain. In normal red blood cells, the sum attractive and repulsive force between molecules is negative. The valine substitution at P6 results in a net attractive force and rodlets form when in the deoxygenated conformation.[29] Sickling of red cells results in increased viscosity and sludging. The end result of this stagnation in blood flow is microvascular occlusion, hemolysis, and endothelial infarction of vulnerable organ systems.

The clinical manifestations of sickle cell pathophysiology can be divided into 3 domains. Constitutional signs include susceptibility to infection secondary to a compromised immune system. Vaso-occlusive signs are manifested as painful crises and end organ damage from microinfarction and macroinfarction. Finally, anemia signs include anemia from hemolysis, aplastic crisis, and splenic sequestration.

Modifiers of disease severity. A sickle cell crisis is better described as a vaso-occlusive crisis and is the most frequent complication seen in SCD. Hemolysis and infarction secondary to microvascular occlusion occur. It has been suggested that the term sickle cell crisis does not convey the evolutionary course of the painful event. The term painful episode may better connote the process and may temper some patients' perspectives from a life of catastrophising.[30,31] Of the patients with homozygous disease, 30% rarely have vaso-occlusive crisis pain and the remaining 50% have only one severe crisis per year, multiple mild crises, or other variations. Approximately 20% of patients with SCD have frequent and severe episodes.[32]

Gender. Gender has been shown to make a slight difference in the patient profile. Female patients generally have a higher Hb F level than do male patients. In the 1980s, the median age at death among patients homozygous for SCD was 42-years for males and 48 years for females. Among patients with Hb SC disease, the median age at death was 60-years for males and 68-years for females.[33] The longer survival of females with both types of hemoglobinopathy was a typical finding in other populations.

Hemoglobin F levels. A lifetime elevation of Hb F to greater than 20% or 1.2 g/dL modifies the severity of clinical manifestations and provides protection to patients with sickle cell anemia. A Hb F levels of greater than 13% decreases the risk of stroke in children. However, nearly 90% of the patients born in the USA do not have such increased levels of Hb F.[34] Affected patients of Saudi descent and Bahrainis may have a milder disease course as of high levels of Hb F. Studies by El-Hazmi et al[35] showed that Hb F levels are significantly higher in patients with the combination of sickle cell anemia and β-thalassemia than in Hb S heterozygotes. Hemoglobin F levels were higher in the female population than in an age matched male group.[26] The presence of a higher concentration of Hb F has been associated with less morbidity but is not a predictor of patient prognosis.

Heterozygous inheritance. Patients with SCT are usually asymptomatic and are considered the least affected of patients with sickle hemoglobinopathies. However, when exposed to severe physical duress, these patients can have complications classically found with homozygous (SS) disease. Sudden death from vaso-occlusive crisis has occurred in patients with sickle trait after extreme physical exertion.[36-38]

Studies suggest that this condition occurs in susceptible individuals when poor physical conditioning, dehydration, heat stress, and hypoxic states precipitate sickling.[36] Patients are seen with rhabdomyolysis, cardiac arrhythmia, acute renal failure, and death. Exertional collapse with sudden death has occurred in young athletes with SCT and is usually seen during preseason training.[38,39] These facts suggest that the perioperative management of patients with SCT should hold to the tenets of care applied to homozygous patients, especially if patients are deconditioned or older.[40] Surprisingly, SCT is often unrecognized in African-Americans and sickle cell testing is not routine at most hospitals that care for individuals of African descent.

Haplotyping. β-S gene cluster haplotypes have been proposed as genetic markers of illness frequency and risk. Four haplotypes have been identified as of their association with distinct geographic regions, the haplotypes have been named as follows: Benin and Nigeria (Ben); Central African Republics or Bantu-speaking region (CAR); Senegal (Sen); and Saudi Arabian, (both Benin and Arab Indian), or Cameroon (Cam). Patients with the CAR haplotype have been found to have the highest frequency of soft tissue organ failure, whereas patients with the Benin haplotype display minimal severity. Haplotyping by region may be helpful and provides additional valuable information disease manifestation.[34] Presently; haplotyping is not a predictor of disease severity and outcome.

Anemia and pregnancy. Severe anemia has been used as a predictor of glomerulopathy in patients with SCD.[41] Patients with hematocrits below 20% were found to have significant microalbuminuria, which is indicative of glomerular injury.[42] Pregnancy and infection are major determinants of the SCD severity.[28] Crises are more common particularly the vaso-occlusive type, in the second half of pregnancy. Although aplastic crises have been reported to be the most frequent in pregnancy, we do not find this situation in Bahrain.

Severity index. A severity index that takes into account the frequency of crises, past history of stroke, acute chest syndrome, aplastic crisis, and hematocrit has been suggested by El-Hazmi et al[43] Score totals of 6 or greater are believed to be associated with a higher rate of complications. The maximum score obtainable is 37. The use of a severity index is promising, and it may have a perioperative application, but a severity index has not been used in this setting. As of yet, there is no reliable predictor of perioperative outcome.

Preoperative management of patients with hemoglobinopathies. Patients with sickle cell anemia are presumed to be at higher risk for perioperative complications than the general populations As of the clinical consequences of vaso-occlusive crises (VOC).[29] Well informed patients may therefore be quite anxious. The preoperative visit should be aimed at allaying the patient's fears and concerns in the hope of avoiding medications that may cause cardiorespiratory depression in the perioperative period. Patients are carefully evaluated in regard to past medical and surgical histories, with specific attention given to previous patterns of crises. An all encompassing physical examination should evaluate the extent of end organ damage.[44]

Organ damage is further evaluated through routine laboratory studies, as well as coagulation tests, baseline arterial blood gas determination, liver function tests, chest radiography, and possibly an electrocardiogram if the preoperative cardiac examination findings are abnormal. A complete blood count and differential should be performed. Results of the peripheral smear should be analyzed. Preoperative hemoglobin electrophoresis is suggested to determine the percentage of Hb S.[45,46] Patients may require a simple transfusion to decrease Hb S to 20-30% of the total hemoglobin. Whether a transfusion is given, however, is determined after preoperative consultation with the patient's hematologist as data suggest that not all patients undergoing surgery should routinely receive blood transfusions.[46] Preoperative transfusion of blood may be based on the patient's current laboratory studies, past medical history, and proposed surgical procedure with anticipated blood loss.

Cardiovascular and respiratory considerations. As of the chronic anemia and hyperdynamic circulation associated with SCD,[47,48] compensatory changes may develop and result in cardiomegaly. Systolic murmurs develop secondary to turbulent flow. High-output failure can occur in cases of severe anemia.[32,33] Additionally, cor pulmonale can result from sickle cell anemia-induced pulmonary hypertension and cardiac dysfunction. Congestive heart failure frequently develops in homozygous patients.[33] Pulmonary hypertension is a result of localized areas of infarction associated with sickling of red blood cells in the pulmonary vascular system. The result is chronic fibrotic changes in pulmonary alveolar walls and areas of persistent pulmonary infiltrate.[34] Decreased vital capacity with normal maximum breathing capacity is found in pulmonary function tests.[49-51] Resting PaO2 is usually reduced in part as of intrapulmonary arteriovenous shunting.[33] Chest pain in these patients can be the result of pulmonary infarction, pulmonary embolism, pneumonia, or acute chest syndrome.

Acute chest syndrome (ACS). This is of unknown etiology and is manifested as fever, cough, pleuritic chest pain, pulmonary infiltrates, leukocytosis, and tachypnea.[52] Electrocardiograph changes may also be present. Acute chest syndrome is associated with severe morbidity and a death rate of 60% among patients who are diagnosed to have ACS.[36]

A thorough history and physical examination are essential to the care of patients with sickle hemoglobinopathies. Documentation of sequelae from cerebrovascular accidents is mandatory preoperatively. Residual motor deficits may exist, and a history of seizures is not unknown. Preoperative administration of antiepileptics should be maintained as close to schedule as possible. Past history of aplastic crisis, acute chest syndrome, and vasoocclusive crisis should be noted. Cardiac pathophysiology includes high-output failure and cardiomegaly, even in children with SCD. Increased left ventricular end-diastolic volume and increased cardiac index have been reported in symptomatic children.

General screening of all African Americans for SCD has been suggested. The Sickledex screen does not distinguish between homozygous and heterozygous states. If a positive result is obtained, electrophoretic determination of the hemoglobinopathy should be performed. A history of antibodies developed from past transfusions should be documented.

Preoperative awareness of the frequency of painful episodes, location of the pain, and typical pain patterns are helpful in delineating postoperative pain from acute onset of vaso-occlusive episodes. Patients may have chronic pain or ongoing complications from end organ disease such as cardiomyopathy, leg ulcers, retinopathy, cerebrovascular accidents, or acute chest syndrome. Hemosiderosis can occur as a result of the iron load from transfusions and corpuscular destruction, and iron overload can cause abdominal and joint pain.

Hypoxia and vascular stasis are the principal dangers. Dehydration may occur from diuresis secondary to hyposthenuria. The importance of adequate preoperative hydration cannot be overemphasized. The patient is admitted for at least 8 hours of preoperative hydration. Isotonic crystalloids are preferred. One approach is to limit the time of fasting for clear liquids and to administer 10 mL/kg/hr of crystalloid to patients admitted for same-day surgery. Mild alkalosis can be achieved by the addition of bicarbonate to each liter of crystalloid. Alkalosis appears to make the Hb S resistant to sickling.[53]

Patients with SCD may experience nontraumatic fat emboli manifested as bone pain, joint effusions, pulmonary symptoms suggestive of acute chest syndrome or asthma, or rapid onset of neurologic deterioration.[54] Although most cases of documented fat emboli have been fatal in patients with SCD, nonfatal cases may have been missed or misdiagnosed. Bronchoalveolar lavage is a safe and useful technique for diagnosing pulmonary fat embolism syndrome.[54] Anesthetists will probably be involved in such procedures, especially in pediatric cases, and should conduct an extensive preoperative examination. The patient interview should seek out a history of dyspnea, petechiae, or mental status changes suggestive of such complications of embolic disease.[38] Chest radiographs should be examined for evidence of parenchymal damage, cardiomegaly, and bony integrity.

Transfusion practices range from aggressive volume exchange aimed at achieving an Hb S level less than 30%; simple transfusion that endeavors to raise the hemoglobin content only to 10 g/dL,40 and chronic transfusion which was used for pediatric patients. Vichinsky et al[55-57] performed a national 5-year prospective study and found a conservative regimen to be as effective as an aggressive regimen of transfusion. The risk of transfusion related complications was decreased by 50% when a conservative approach to transfusion was used.

Preparation for elective surgery has in the past often included transfusion to limit the percentage of sickle cells, improve rheology, and provide the patient with functional erythrocytes. Such transfusions are typically performed days to hours before surgery. An alternative preparation for elective procedures may include the manipulation of Hb F levels several weeks in advance. The avoidance of transfusions and their inherent complications may make Hb F manipulation a realistic and beneficial practice. The elevation in Hb F content has been shown to have a positive

effect on the general condition of patients with SCD. Hemoglobin F inhibits the polymerization of sickle cells and partially substitutes bS-globin chains.[58]

Many agents have been investigated in attempts to manipulate the Hb F level. The agents that have proved to be most successful in the manipulation of Hb F levels with the fewest toxic side effects are recombinant human erythropoietin (rHuEpo), hydroxyurea (HU), and g-globulin. Recombinant human erythropoietin, a glycoprotein that acts as a growth factor, is synthesized in response to oxygen deprivation by renal tissues. Erythropoietin receptors on erythroid progenitor cells are stimulated and result in cell differentiation.[59]

Erythropoietin is best used in combination therapy with hydroxyurea (HU). Current citations are case series, or case reports; however, combination therapy appears promising. Patients who have proved to be non-responders to HU alone have had increases in Hb F levels after the addition of erythropoietin. Significant increases in Hb F are found after 4 weeks of combination therapy; however, increases are noticeable within 2 weeks after the initiation of combined therapy.[43,44]

In one report, intravenous rHuEpo was administered weekly at a dose of 400-800 U/kg body weight in combination with oral HU, 20-25 mg/kg daily. Fetal hemoglobin levels increased to 20% and were maintained after the cessation of rHuEpo therapy while HU was continued for 6 months to one year.

Daily rHuEpo at 100 U/kg IV in combination with a single dose of g-globulin, 1 g/kg IV, has been reported as efficacious in the treatment of a patient with SCD who had an aplastic crisis. However, the presence of nucleated red cells may have been the natural course of the disease and not causally related to the administration of erythropoietin and g-globulin.[60] A report by the American Erythropoietin Study Group found a course of 15 daily subcutaneous treatments of erythropoietin to be effective inasmuch as this treatment insignificantly raised hemoglobin levels in normal subjects undergoing orthopedic procedures and reduced the need for perioperative transfusions.[60] Iron and folate supplementation are necessary to maximize the effects of the erythropoietin. Lower doses of rHuEpo alone do not significantly improve hemoglobin levels. Larger studies are needed to better define the possible merits of Hb F manipulation in patients with SCD. Hypertension has occurred as a result of rHuEpo therapy.[61]

Hydroxyurea. Hydroxyurea is a chemotherapeutic agent that arrests cell division via inhibition of the ribonucleoside diphosphatase. It has been shown to reliably increase the production of F cells and Hb F levels in patients with thalassemia and SCD.[62] Currently, HU is used predominantly in adults and is reserved for children with severe disease and frequent crises. The French Study Group on Sickle Cell Disease conducted a 32-month cohort study in children that suggested that HU is well tolerated with minimal morbidity.[63] Transient decreases in leukocytes have been seen. However, the benefits may prove to outweigh the risks. The increase in Hb F has a profound inhibitory effect on the polymerization of sickled erythrocytes. The net effect of Hb F in F cells is simply to dilute the Hb S concentration.[64] Other effects of HU include the ability to increase mean corpuscular volume and hematocrit while reticulocyte counts are decreased. Hydroxyurea has not been effective in decreasing the occurrence of cerebrovascular accidents or mortality.[64]

A proposed additional benefit of HU is reversal of organ damage. Hydroxyurea has been reported to reverse splenic dysfunction with long term use; however, splenomegaly resulted in a need for splenectomy. Yet, the promise of organ reversal lends credence to administration of the drug to young children to avoid severe organ damage.[65] Due to the side effects on the fetus, hydroxyurea is contraindicated during pregnancy.

The immediate preoperative period. Premedication should be conservative yet effective. Avoidance of hypoventilation and hypoxia is mandatory. Baseline oxygen saturation should be determined while the patient is inhaling room air, preferably before the start of sedative administration. Pulse oximetry is desirable at the time of sedation, as well as throughout the perioperative period. Preoperative instruction on the use of incentive spirometry while patients are alert and in control of their mental faculties would be advantageous for postoperative use of the spirometer. Incentive spirometry has been effective in preventing pulmonary complications in patients with SCD in nonoperative settings.[66] As pulmonary complications are the most frequent postoperative problem, it may be advisable for surgeons and anesthetists to routinely include this technique in the preoperative preparation of patients with SCD.

Intraoperative management. Avoidance of hypoxia, acidosis, hypothermia, and dehydration is a classic tenet that anesthetists have long honored. But, just how one should conduct the anesthesia has not been thoroughly investigated. During periods of hypoxia (below 80-85% saturation) or in anoxic conditions,[34] the Hb S molecules stack up in long aggregates.[66] This deformation and stacking of sickle cells lead to vaso-occlusion of blood vessels and further exacerbation of tissue anoxia, which leads to acidosis, heat production, and increased[3,4] diphosphoglycerate levels. Physiologic conditions or precipitating factors that have been implicated include infection, acidosis, dehydration, hypertension, strenuous activity, drug overdose,

hypothermia, blood loss, trauma, severe stress, and high altitude,[67] as well as extreme hyperthermia associated with increased oxygen consumption. Once these adverse events trigger deoxygenation and the sickling process, a cycle is created that contributes to ischemic necrosis and infarction of various organs. This cycle may ultimately result in end organ damage to several organ systems.

Studies show that the anesthetic technique does not appear to have a hit on the parturient outcome. Postoperative morbidity has been highest with isoflurane; however, statistical analysis reveals that the type of anesthetic agent has no impact on postoperative morbidity.[68] The selection of anesthetic agents for induction and maintenance is tailored to the perioperative needs of the patient. Perioperative complication rates have ranged from 25-89%. Severe atelectasis is a major complication that promulgates a deteriorating course. Bone and abdominal pain and sickle cell crises have been reported in the perioperative period.

It appears that SCD may increase the risks associated with anesthesia and surgery but that avoidance of hypoxia, acidosis, hypotension, hypovolemia, and hypothermia are more important.[69] If patients are receiving chronic opioids, the opioids are given as scheduled up to the time of surgery. Additional opioids are given intraoperatively as indicated by the biophysical findings.

Proper patient care in the postoperative period should include frequent respiratory rate observations, ECG monitoring, and pulse oximetry. Pulse oximetry may give variable results in patients with SCD. Values obtained in acute crisis and in steady state situations are lower than the actual arterial oxygen tension and saturation. Despite the lack of correlation, a trend can be followed. Therefore, baseline and subsequent values should be noted.[70-74] Desaturation is common in steady state homozygous disease, and knowledge of the individual's steady state value may be important in interpreting low values during acute complications.[68]

The parturient. The sickle cell hemoglobinopathies most commonly seen in parturients include Hb SS disease, Hb S β-thalassemias, and Hb SC disease. In association with this spectrum of diseases is a suggested increased incidence of fetal morbidity and mortality. Previous studies show that pregnant women with SCD are at increased risk of antenatal and postnatal sickling crises, urinary tract infection, pulmonary complications, anemia, proteinuric hypertension, and maternal death.[73] Fetal complications include an increased incidence of abortion, stillbirth, intrauterine growth retardation, prematurity, preeclampsia, and cesarean section.[69] A recent study suggests that pregnancy in women with SCD is well tolerated by all major genotypes, and infants born to mothers with SCD appear to be healthy, although the infants are at risk of being small for gestational age when born to women with the SS genotype.[74] The clinical course of women with Hb SS was not adversely affected by their pregnancy, as measured by the rate of painful episodes over a 100 day period with good, committed obstetric care.[75] The clinical manifestations encountered in pregnancy are probably the result of increased metabolic demands, the hypercoagulable state, and the increased vascular stasis common to all pregnant patients.[75] The physiologic changes and increased metabolic demands are more likely to trigger vaso-occlusive crises in the latter half of pregnancy when oxygen consumption is significantly increased and physiologic anemia may have worsened a chronic anemic state.

Additionally, a high incidence of infection occurs as a result of the altered immune system associated with pregnancy. This immune system alteration contributes to instances of pyelonephritis, respiratory infection, and septic arthritis. Asymptomatic bacteriuria, urinary tract infection, and pyelonephritis are common during pregnancy. In pregnant patients with SCD, symptomatic manifestations may be exaggerated with consequences of increased prematurity and small-for-gestational-age babies. Therefore, early antenatal screening, urine cultures, and prompt antibiotic therapy are advised. These patients are at a greater risk for surgical delivery as of an increased incidence of placenta previa, placental abruption, preeclampsia, and eclampsia as reported by Koshy and Burd.[76]

Antepartum management. Early prenatal counseling and evaluation of both physical and laboratory status are important for pregnant patients with SCD. The past medical history is evaluated with specific attention to crisis patterns and prior pregnancies.[32] Routine prenatal laboratory tests are performed, as well as hepatitis and HIV screening. Prenatal counseling is given and includes nutritional requirements, factors that precipitate painful episodes, and the need for vitamin supplementation and folic acid and iron therapy. The importance of adequate hydration and frequent prenatal visits is stressed. Patients may be monitored more closely by examination and ultrasound studies than routine obstetric patients are to provide early and aggressive treatment of any complications that may develop. Antenatal testing in the form of nonstress tests, contraction stress tests, and biophysical profiles alone or in combination should begin weekly at 32-34 weeks gestation or earlier if intrauterine growth restriction is suspected.[75]

Prophylactic blood transfusion in the third trimester has been controversial as of the risks of

transfusion reaction, exposure to hepatitis and other viral infections, or both and alloimmunization. However, given a recent study that showed a trend toward decreased sickling complications in the prophylactically transfused groups in the third trimester,[46] transfusion is considered a viable option in the management of pregnant sickle cell patients. The advantages of transfusion are that it decreases the percentage of circulating Hb S, which increases the patient's overall oxygen carrying capacity and thereby reduces the amount of tissue injury associated with erythrocyte sickling in the microvasculature.[47] Whether a patient receives a simple transfusion or a partial exchange transfusion is dependent on the patient's current hemoglobin level and percentage of Hb S. Transfusions are reserved for women whose hemoglobin concentration falls below 6 g/dL. Other indications may include toxemia, septicemia, acute renal failure, bacteremia, and multiple gestations. The percentage of Hb S should be less than 30, and in urgent situations (such as surgery), a partial exchange transfusion should be considered. The exchange may be carried out manually or by an automated method. The manual process has been noted to be cumbersome and require a period of several hours to lower Hb S levels sufficiently. A recent report of automated red cell exchange with a Baxter CS-3000 Plus cell separator in a pregnant patient at 34 weeks gestation found that the procedure could be performed safely and rapidly and that fetal monitoring showed no untoward effects on the fetus.

Prophylactic antibiotic with Penicillin V throughout the pregnancy has been tried in our department on patients with SCD over a 2-year period and compared to a control group. No significant difference in the incidence of infections or VOC has been found.

Intrapartum and postpartum care. Patients should be managed in a warm environment and given adequate hydration with oxygen therapy as an adjunct. Pain control with adequate analgesia in the form of either IV medications or preferably epidural analgesics can control the pain of labor. Management of sickle cell crisis pain was first cited in the American literature as a case report described by Finer et al[77] in which a 22-year-old primigravida was in active labor and vaso-occlusive crisis. The initiation of epidural analgesia with local anesthetics appeared to abate the vaso-occlusive crisis. Postpartum pain during the first 24 hours was managed by neuraxial fentanyl infusion. The use of dilute local epidural anesthetics as an infusion has been shown to control the pain of labor or associated crises; opioids can be added safely for postsurgical pain. Patients should be given close obstetric monitoring with the goal of shortening labor to minimize stress while avoiding surgery except when routinely indicated. Second stage assisted deliveries may be carried out in some instances to decrease cardiovascular demands. After delivery, supportive therapy is continued with adequate hydration as the postpartum period is characterized by diuresis. Increased catecholamine release occurs whether the delivery is vaginal or surgical and can incite a vaso-occlusive crisis. Oxygen therapy is maintained, and adequate pain control is necessary to prevent a vaso-occlusive crisis associated with increased circulating vasoactive substances.

Pain control with the use of continuous epidural infusions or parenteral therapy (such as patient-controlled analgesia) continues to be important in the postpartum period. Common problems that occur in the postpartum period include infections, thromboembolic phenomena, and vaso-occlusive crises. Close monitoring for acute complications is mandatory.

Postanesthesia care. Postoperative analgesics should be administered as needed. Many health care personnel hold the misconception that these patients are drug seeking and administer analgesics judiciously in the postoperative period. Analgesics should be given as needed, provided that side effects do not prohibit safe administration. Meperidine should be avoided as of its metabolite normeperidine. Morphine may be a better choice. Although caution must be exercised in the administration of opioids, one must consider that subtherapeutic dosing results in patient suffering. The development of an adversarial relationship between the patient and the health care team can result from inadequate response to patient complaints of pain.

Respiratory depression should be vigilantly guarded against inasmuch as pulmonary complications are the most frequent derangement seen postoperatively. Combined pain interventions, including regional techniques, should be encouraged when practical. Epidural analgesia has been used to ameliorate the pain and sequelae of vaso-occlusive crisis.[77-79] Regional techniques and adjunctive medications can minimize opioid requirements and improve the quality of analgesia. Ketorolac, a nonsteroidal antiinflammatory drug, is a potent analgesic with an opiate-sparing effect. A 25-50% reduction in opioid requirements has been witnessed with its use.[80] Thus sedation and hypoventilation from high dose opioids can be minimized.

Hypoventilation may predispose to the development of acute chest syndrome and must be avoided. The use of incentive spirometry and other deep breathing exercises should begin in the postoperative care unit. On the other hand, opioids and other analgesics should not be withheld, especially if patients have been receiving chronic opioid therapy. Approximately 20% of patients with

SCD have frequent and severe episodes. These latter patients may require chronic administration of opioids.

Attitudes the propensity for addiction among adolescents are entrenched in many institutions. Yet, no studies to date have demonstrated a higher risk of addiction than in other patient populations. As of caregivers' fears of drug-seeking behavior, pain relief complaints are often not met. These patients then become victims of pseudo-addiction, an iatrogenic syndrome in which inadequate pain relief results in increased requests for analgesics that are unfortunately perceived as not genuine.[81] Signs and symptoms of withdrawal can greatly complicate issues of postanesthesia care. Such complications must be prevented. If a patient is suspected of addiction, this problem should be handled by a trained addictionologist later in the course of convalescence, not in the immediate postoperative period. The risk of opioid addiction in sickle cell patients is similar to that of the general population.

The use of supplemental oxygen in the initial postoperative period is recommended. Controversy regarding the inhibition of erythropoietin relates to the prolonged application of oxygen. Inhalation of oxygen at low concentrations for a limited period does not affect erythropoietin production and erythropoiesis.[82,83]

Recommendations for postanesthetic care. Additionally, fluid deficits are replaced in the standard fashion. Isotonic fluids are administered at a rate of 11/2 times the maintenance rate in addition to insensible and blood losses after anesthetic induction during the maintenance phase of anesthesia.

Proper fasting guidelines should be followed for solid foods. Clear liquids should not only be offered but also administered just before the time of absolute fasting. For adult procedures such as placement of central venous access catheters or operations that would normally be classified as minor office procedures, the use of topical local anesthetics is encouraged, along with wound infiltration, and judicious administration of sedation. The patient should be monitored throughout any procedure by designated and qualified personnel. Supplemental oxygen is administered during procedures performed under sedation and for at least the initial postoperative period. Incentive spirometry is initiated as soon as possible, and patients are encouraged to continue the exercises at home.

Postoperative nausea should be managed aggressively. If vomiting should occur, extended stay observation or admission is recommended. Intravenous fluids should be administered until the hydration status is secure as dehydration is to be avoided.

Postoperative complications and theoretical management. The most frequently cited complications are pulmonary complications, acute onset of vaso-occlusive crisis, and bone pain. Pulmonary findings include atelectasis, pneumonia, and acute chest syndrome. Monitoring for the onset of neurologic sequelae should be routinely performed, especially in patients with a history of cerebrovascular accidents with or without residual deficits.[84,85]

The outcome of pregnancy in parturients with SC trait should be unaltered. The death of a SC trait patient during cesarean section due to aorto-caval compression, despite lateral tilting, has recently been reported.[67] Those with SS, SC, or S β-thalassemia disease have been thought to be poor obstetric risks. Anemia becomes more severe during pregnancy and there is an increased risk of abortion, stillbirth, toxemia, chest and urinary tract infections.[68,69] While the incidence of these complications may have decreased due to improvements in general prenatal care and the use of simple or exchange transfusions to control the disease process, there has been a concomitant increased survival and pregnancy rate in high-risk patients in recent years.[86-89]

Geographical variations in reporting the incidence of maternal and fetal complications are also apparent. However, a study of pregnancies in homozygous sickle cell disease patients in Jamaica from 1959-1984 70 showed that 71.5% had a good outcome. Maternal mortality was 1.1% with deaths occurring in late pregnancy or 1-5 days postpartum due to pulmonary emboli, peritoneal hemorrhage or pneumonia. Fetal wastage resulted from spontaneous abortion in 11% and stillbirths in 10.5%. Prematurity and low birth weights are factors in perinatal mortality, possibly as of sickling in the uterine blood vessels and placental infarction. The cesarean section rate of 24% in the Hb SS patients was twice that in other obstetric patients.

The efficacy of prophylactic blood transfusion in altering the fetal or maternal outcome has not been clarified. A retrospective study from the United Kingdom[72] showed no differences between those patients receiving prophylaxis and those who were not transfused. However, the use of transfusion was associated with immediate transfusion reactions in 14% of patients and the formation of red cell antibodies in a further 22%.

The choice of regional or general anesthesia for obstetric patients depends on the patient's general condition and the preference of the anesthetist, rather than specific indications. The relative risks of hypotension and hypoxia using either approach must be assessed in individual cases.

Summary. Patients with SCD are experiencing improved longevity secondary to better recognition

and management of SCD and its complications. Although a marked decrease in the maternal mortality of sicklers has been witnessed, the morbidity rate remains considerable. Current investigational therapies are ameliorating the pathophysiology of SCD. Given these scientific alterations of the course of SCD, it is feasible that obstetricians and anesthetists are likely to see an increasing number of patients for elective procedures unrelated to their hemoglobinopathy. A solid understanding of the pathophysiology, disease course, and sequelae will always be requisite in the armamentarium of the obstetrician, anesthetist and neonatal pediatrician. The issue of transfusion practices will remain the purview of each practitioner. The decision to transfuse should be based on the patient's history, current patient condition, and the complexity of the surgical procedure.

As our knowledge of the management of this group of diseases is rapidly growing, anesthetists and surgeons can safely offer this patient population many techniques that were once deemed inadvisable. Vigilance is extremely important as the key to safe execution of anesthetic management options for this special patient population.

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