ISSN: 2378-3516

Lazo et al. Int J Respir Pulm Med 2017, 4:073
DOI: 10.23937/2378-3516/1410073
Volume 4 | Issue 3
Open Access

International Journal of
Respiratory and Pulmonary Medicine

REVIEW ARTICLE

Pulmonary Complications of Sickle Cell Disease in the Pregnant Patient

Kevin G Lazo[1]*, Joanna B Eldredge[2], Anne Press[3] and Bushra A Mina[4]

[1]*Department of Medicine, Long Island Jewish Medical Center, USA*

[2]*Department of Medicine, Lenox Hill Hospital, USA*

[3]*Department of Medicine, NYU Langone Medical Center, USA*

[4]*Division of Pulmonary Medicine, Lenox Hill Hospital, USA*

***Corresponding author:** *Kevin G Lazo, Department of Medicine, Long Island Jewish Medical Center, New Hyde Park, NY, USA, E-mail: klazo@northwell.edu*

Abstract

Respiratory complaints are common symptoms in pregnancy, and it is important to delineate whether the causative factor is cardiac, pulmonary, or physiologic in origin. The pathophysiology of Sickle Cell Disease (SCD) can further complicate the differential diagnosis. To our knowledge, there is little to no literature devoted to the management of pulmonary complications in the pregnant sickle cell patient. Therefore we present a review of the current literature and feature reports on the incidence and prevalence of the pulmonary complications in a sickle cell pregnancy. These include Acute Chest Syndrome (ACS), Pulmonary Hypertension (PH), Pulmonary Embolism (PE), and sickle cell chronic lung disease. We also aim to recommend management strategies that address the SCD-related pulmonary complications in the pregnant state.

Introduction

Sickle cell anemia refers to a group of autosomal recessive disorders characterized by a single point mutation in the gene encoding for the beta chain of the hemoglobin molecule. This mutation causes a shift in the synthesis from Hemoglobin A (Hb A), which is characterized by two alpha and two beta chains to Hemoglobin S (Hb S) [1]. Hb S contains a single beta chain substitution of the amino acid valine for glutamic acid. The result of this abnormal biochemistry is a defect in the oxygen carrying capacity of hemoglobin. This defect has more severe clinical consequences in those patients who are homozygous for the mutation Hemoglobin SS (Hb SS) - and these patients are known to suffer from SCD [2]. The most severe clinical consequences occur in the homozygous mutation because there is a nearly complete elimination of Hb A, and the majority of the hemoglobin phenotype is represented as Hb SS. Those patients who are heterozygous for the mutation generally do not experience the same degree of symptoms as their homozygous counterparts, because they only have one abnormal copy of the gene. These patients are known to have a sickle-cell trait, and are thus referred to as carriers [3]. The carrier condition is generally benign, and is characterized by one allele of beta globin chain of Hb A carrying the point mutation, while the other allele is normal. This produces the Hemoglobin AS (Hb AS) phenotype.

There are other sickle cell syndromes which are characterized by the inclusion of any hemoglobinopathy in which the sickle mutation is inherited in combination with another globin gene mutation. These syndromes may have different clinical severity compared with Homozygous Sickle Mutation (Hb SS). For instance, if the other beta globin allele carries another mutation resulting in either a mild or severe reduction of beta chain expression (β+-thalassemia), complete gene deletion (β0-thalassemia), or an alternative abnormality (hemoglobin C), then that individual will have a sickle cell variant disease in the form of hemoglobin Sβ0, hemoglobin Sβ+, or hemoglobin SC [4].

In the setting of low oxygen states, Hb S changes configuration, causing the red blood cell to take on a

Citation: Lazo KG, Eldredge JB, Press A, Mina BA (2017) Pulmonary Complications of Sickle Cell Disease in the Pregnant Patient. Int J Respir Pulm Med 4:073. doi.org/10.23937/2378-3516/1410073

Received: April 03, 2017; **Accepted:** July 11, 2017; **Published:** July 14, 2017

sickle shape. This "sickled" erythrocyte alters the rheologic properties of the cell, resulting in the impairment of flow through the body microvasculature. As a consequence, hemolytic anemia and vaso-occlusive episodes may ensue. This cellular phenomena leads to acute and chronic changes such as osteonecrosis of the femoral and humeral heads, chronic kidney disease, autosplenectomy, organomegaly, PH, pulmonary infarctions, stroke, leg ulcers, and infections [5-7].

With the potential for serious complications, SCD is a serious burden for the pregnant patient. One large retrospective study analyzing the Medicaid-enrolled population with SCD showed increased rates for pregnancy complications that include cerebral vein thrombosis, pneumonia, pyelonephritis, deep-vein thrombosis, PE, and the sepsis syndrome [8]. Such findings corroborate an earlier retrospective study that looked at over 4,000 pregnancies of SCD mothers - who reported increased rates of maternal renal failure, gestational hypertension, and fetal-growth restriction [9].

According to the 2007 ACOG guidelines [10] there are few clear changes in management for patients with SCD. One alternate management guideline is an increased need for folic acid supplementation at 4 mg per day as opposed to the standard dosage of 1 mg of folate per day in this patient population. Other recommendations are not as straightforward. For example, these guidelines provide no clear role for prophylactic transfusions in these patients or set hematocrit level for which a patient should be transfused. Therefore, sickle cell patients should be treated on an individual basis at an institution with experience in managing high risk pregnancies.

Acute Chest Syndrome

Epidemiology & diagnosis

ACS is defined by the Comprehensive Sickle Cell Center as evidence of a new infiltrate on chest radiography in combination with chest pain, respiratory symptoms, or fever [11]. The diagnostic criteria of ACS in a patient with SCD is made clinically, and requires both of the following: 1) A new pulmonary infiltrate involving at least one complete lung segment not consistent with atelectasis and 2) One or more of the following: chest pain, fever > 101.3 fahrenheit, hypoxemia relative to baseline, and/or signs of tachypnea, cough, wheezing, or increased work of breathing [11].

ACS is a dangerous complication of SCD. The incidence of ACS in adults with SCD is estimated to be 8.8, 3.27, 6.98, and 1.95 per 100 pt-years in Hemoglobin SS, SC, $S\beta^0$, and $S\beta^+$ respectively [4]. According to one prospective, multicenter study performed by the National Acute Chest Syndrome Study Group, the most common etiologies of ACS in adults with SCD were infection, followed by fat embolism and pulmonary infarction [12]. However, 52% of cases had no identifiable source. Of the infectious causes with an identified pathogen, chlamydia and mycoplasma were among the most common [12]. A 30-center study analyzing 671 episodes of ACS in 538 patients found that these patients on average were hospitalized for approximately 10.5 days, had a mean partial pressure of arterial oxygen of 70 mmHg at diagnosis and mean oxygen saturation of 92% on room air [13]. Furthermore, 13% required mechanical ventilation and 11% succumbed to hypoxia related neurologic complications [13]. A 2002 review from France and England analyzing patterns of mortality in SCD adults found that approximately one-third of vaso-occlusive related mortalities in SCD are related to ACS [14].

While incidence of this serious complication in pregnancy is estimated to be only 0.06% among all deliveries to women with SCD [15], case reports detail the significant risk that this condition imparts upon both mother and fetus [16,17]. Pregnancy can exacerbate anemia, increased infection risk, and the pro-coagulant state that are preexisting in pregnancy [18]. In a case report of ACS in 2 SCD patients, acute hypoxemia from ACS was implicated in leading to fetal distress and adverse clinical outcome [14].

Management

Management of ACS is similar to nonpregnant women. Based on the literature we recommend that these patients undergo hospitalization, pain control, intravenous fluids, broad spectrum antibiotics (guided by US FDA Pregnancy Category designations), incentive spirometry, supplemental oxygen, and possibly blood transfusions [2]. Furthermore, the 2011 guidelines from the Royal College of Obstetricians & Gynaecologists (RCOG) regarding the management of the SCD pregnant patient recommend that while hydroxyurea has been shown to reduce incidence of ACS episodes in pregnant patients, because of the teratogenic nature of the drug - it should be discontinued 3 months before conception [19].

Prior studies have been conducted to determine the utility of prophylactic blood transfusions for prevention of ACS in this population. A Cochrane Review published in 2013 on the role of prophylactic versus selective blood transfusion in the prevention of maternal complications in pregnant SCD patients evaluated two trials of moderate risk bias consisting of 98 total patients [20]. The reviewers showed that one of the trials indicated no clear differences in the risk of acute chest syndrome (RR 0.67, 95% CI 0.12 to 3.75) between the treatment groups (prophylactic blood transfusion versus selective blood transfusion). They conclude that given the evidence from two small trials of low quality prophylactic blood transfusions in the pregnant SCD population confers no clear clinical benefits when compared with selective transfusion.

A more recent systematic review and meta-analysis by Malinowski, et al. looked at 12 studies (including the same Randomized Controlled Trial (RCT) [21] in the prior Cochrane Review) comparing the risks and benefits of prophylactic versus on-demand PRBC transfusion in pregnant SCD patients [22]. In a meta-analysis of the 12 studies, prophylactic transfusion was associated with a reduction in maternal mortality (7 studies, 955 participants; Odds Ratio [OR], 0.23; 95% Confidence Interval [CI], 0.06-0.91), vaso-occlusive pain episodes (11 studies, 1219 participants; OR, 0.26; 95% CI, 0.09-0.76), pulmonary complications (9 studies, 1019 participants; OR, 0.25; 95% CI, 0.09-0.72), and pulmonary embolism (3 studies, 237 participants; OR, 0.07; 95% CI, 0.01-0.41). The reviewers concluded that prophylactic transfusions do appear to benefit maternal and neonatal outcomes in the pregnant SCD population.

It is likely that the discordance between the 2013 Cochrane Review and the meta-analysis from Malinowski, et al. is attributed to the difference in the number of studies analyzed. The Cochrane Review only had two studies that met their inclusion criteria, whereas the Malinowski, et al. review was a more comprehensive appraisal of 12 studies. It is important to note however that Malinowski, et al. described one of their limitations being that their analysis includes studies of moderate to high risk of bias with heterogeneity of definitions for outcomes of interest. Future studies will be needed in the form of a prospective, multicenter, randomized trial.

ACS is a life-threatening complication of SCD that has the potential for devastating consequences to both mother and fetus if not recognized and treated early and effectively. More focused research is needed to elucidate the etiologies, risk factors, and prognosis of ACS in pregnancy.

Pulmonary Hypertension

Epidemiology & diagnosis

PH is defined as Mean Pulmonary Artery Pressure (mPAP) ≥ 25 mmHg, is an independent predictor of increased mortality in SCD [1]. Two retrospective studies found an increased death rate among even mild PH, and an increasing hazard ratio of 1.6-1.7 for every 10 mmHg increase in mPAP, indicating that the severity of PH directly correlates with the risk of premature death [23,24]. The suspected pathophysiology is multifactorial. Chronic hemolysis causes an increase in cell-free Hb, which leads to increased consumption and resistance to the activity of Nitric Oxide (NO), which subsequently leads to poor vasodilation [25]. In addition, regional hypoxia from pulmonary infection, fat embolism, and undetected vaso occlusion can lead to chronic fibrotic pulmonary changes and vascular remodeling [26]. Approximately 40% of SCD patients with PH will have features of pre capillary PH, while 50-60% will have some degree of post capillary PH, and some will have a mixture of both [27]. It is for this reason that the American Thoracic Society recommends use of Pulmonary Artery Hypertension (PAH) directed therapy only in SCD patients with normal pulmonary artery wedge pressure [28]. For cases in which pre-capillary PH has not been confirmed by RHC, the current recommendation is to avoid all PAH-directed therapies (i.e. phosphodiesterase-5 inhibitor, prostacyclin agonist or an endothelin receptor antagonist) secondary to increased adverse effects from the medications and little data demonstrating any benefit in this population. In all patients with RHC confirmed PH, hydroxyurea is indicated by the American Thoracic Society (ATS). Although this recommendation is extrapolated from indirect evidence that has shown increased survival in patients with recurrent ACS and vaso occlusive crisis, the benefits were determined to strongly outweigh the risks of treatment, which led to a strong recommendation with moderate evidence for hydroxyurea. In patients who are resistant to or unable to take hydroxyurea, the recommendation is to perform chronic transfusion therapy. This recommendation, however, is weaker given the increased risks of alloimmunization, volume overload, fever, and hemolytic reaction that can occur with this therapy.

PH has an established reputation as a high risk condition in pregnancy. PH in pregnant women, regardless of etiology, has established maternal mortality rates between 33% and 56% based on two systematic reviews involving a total of 198 cases between 1978 and 2007 [29,30]. A more recent retrospective multicenter study, between 1999 and 2009, indicated a trend toward improved outcomes, with estimated maternal mortality of 16.7% [31]. This indicates that early detection and referral to a comprehensive treatment center could improve outcomes in PH patients who elect to carry to term. However this study was limited by small sample size, and the improved outcomes could have been secondary to recent recommendations in advising early termination of pregnancy for women with PH. The mortality rate remains significant even in mild to moderate degrees of PH. Deaths from PH were secondary to heart failure, thromboembolism, and sudden death, with the majority of cases of maternal mortality occurring within one month peripartum [30]. A nationwide study of deliveries by women with SCD found a significantly higher risk of PH at the time of delivery than in the general population (OR, 6.3; 95% CI, 2.1-18.8) [14]. Moreover, the current documented prevalence of Right Heart Catheter (RHC) confirmed PH in SCD adults ranges from 6-11% [23,27,32].

Current European Society of Cardiology guidelines advise against pregnancy, and recommend termination of pregnancy in patients with any severity of PH [33]. Diagnosis during pregnancy, however, can be delayed secondary to the nonspecific symptoms of early PH, which can closely mimic those of a normal pregnancy.

Any female with PH who does not wish to terminate a pregnancy should be referred to a tertiary care center with a multidisciplinary team consisting of a PH specialist, a hematologist specializing in SCD, an obstetrician, an anesthesiologist trained in high risk procedures, and a neonatologist.

With the increased mortality associated with PH, and the implications this has in family planning, should we be screening all SCD patients of child-bearing age for PH, and if so, with what tests? Doppler echocardiography is a non-invasive test which can calculate Tricuspid Regurgitant Velocity (TRV) as a measure of pulmonary artery systolic pressure. Elevated TRV on echocardiography, defined as ≥ 2.5 m/s, has been identified in 40-52% of adult SCD patients and in 24.6% of SCD children [34]. Unfortunately, no specific evidence exists to determine which patients with an elevated TRV will progress to PH on RHC. In a prospective, longitudinal study of 55 SCD patient follow for a median of 4.5 years, 56% showed an increase in TRV, which in turn led to a non significant increase in mortality [35]. In the study by Parent, et al. the Positive Predictive Value (PPV) of TRV ≥ 2.5 m/s in predicting PH was a mere 25%, which improved to 64% when the threshold was increased to 2.9 m/s [32]. This study found a similar increase in PPV of TRV ≥ 2.5 m/s when combined with either an NT-pro-BNP level greater than 164 pg/ml or a 6-minute walk distance less than 333 m. Age at screening may play a factor. In the study by Fonseca, et al. the mean age at diagnosis of PH in SCD was 45.6 ± 10.7 years (p = 0.04), while the mean age for those with TRV ≥ 2.5 m/s was 38 ± 11 years (p = 0.001) [27]. It is likely that elevated TRV in otherwise asymptomatic patients represents a preclinical phase of PH, and could serve as a strong indicator for who should be further evaluated for and followed for the development of PH in a screening population. However, this test is imperfect even when combined with other indicators of PH, and the standard for diagnosis of PH remains mPAP ≥ 25 mmHg measured by RHC. In summary, early detection of PH by screening might be indicated to advise SCD patients in family planning.

Management

Given the previously mentioned severe consequences that undiagnosed PH poses to the pregnant population, and its increased prevalence in adults with SCD, we recommend screening all pregnant SCD patients, or patients who wish to become pregnant, for PH with Dop-

Table 1: Medications for SCD-related Pulmonary Hypertension.

Drug[a]	Side Effects[b]	Pregnancy Category[b]
Hydroxyurea Increases hemoglobin F levels in Red Blood Cells (RBCs)	Nausea, Vomiting, Constipation, Diarrhea, Mucositis, Acute pulmonary reactions (rare), Genetic mutation (long-term use), Myelosuppression, Secondary leukemia (long-term use), Elevated BUN/Creatinine, Hyperuricemia, Renal failure, Rash, Hyperpigmentation, Skin ulcers, Gangrenous disorder	Pregnancy Category: D Lactation: excreted in breast milk, do not nurse
Bosentan Competitive antagonist of endothelin-1; blocks endothelin receptors on vascular endothelium and smooth muscle resulting in inhibition of vasoconstriction	> 10%: Hgb decreased; > 1 g/dL; Inhibition of spermatogenesis; Headache; Nasopharyngitis; Transaminitis; Respiratory tract infection 1-10%: Edema, lower limb, Flushing, Hypotension, Hepatic abnormalities, Palpitations, Anemia, Dyspepsia, Edema, Fatigue, Pruritus < 1%: Hyperbilirubinemia, Vasculitis, Jaundice, Leukopenia, Thrombocytopenia, Leukocytoplastic	Pregnancy Category: X Lactation: Not known if excreted in breast milk; not recommended
Ambrisentan High affinity endothelin (ETa) receptor subtype antagonist, resulting in inhibition of vasoconstriction	> 10%: Peripheral edema, Headache 1-10%: Nasal congestion, Palpitations, Constipation, Dyspnea, Flushing, Abdominal pain, Nasopharyngitis, Sinusitis	Pregnancy Category: X Lactation: Excretion in milk unknown; not recommended
Nitric Oxide (inhaled) Relaxes vascular smooth muscle, resulting in pulmonary vasodilation	> 10%: Hypotension, withdrawal 1-10%: Atelectasis, Hematuria, Hyperglycemia, Sepsis, Infection, Cellulitis, Stridor	Pregnancy Category: C Lactation: not known if excreted in breast milk
Arginine Supplementation Converted by nitric oxide synthase to citrulline plus nitric oxide	1-10%: Headache, Flushing, Nausea, Vomiting, Numbness, Local venous irritation < 1%: Macular rash, Swelling of hands and feet, Hematuria, Hyperkalemia, Skin burn/necrosis, Loss of consciousness, Perioral tingling	Pregnancy Category: B Lactation: Enters breast milk, use caution

[a][2]; [b]Adapted from http://reference.medscape.com/drugs.

pler echocardiography, serum NT-pro-BNP, 6-minute walk test, and confirmatory RHC for those that warrant it. In their 2011 recommendations, RCOG also suggests that screening for PH be performed with echocardiography, particularly if it had not been done in the year prior to pregnancy [19].

Once PH is diagnosed, Current recommendations on the control of PH in SCD recommend controlling the primary hematologic disease, while identifying other contributors for focused treatment or disease modulation [2]. Such contributors may include venous thromboembolism or sleep disordered breathing. Typical therapy may include oxygen, diuretics, anticoagulation for VTE, and non-invasive ventilation for sleep-disordered breathing. The pregnant state, however, limits the use of pharmacologic modalities to treat SCD related PAH. For instance, Hydroxyurea - which acts to increase Hemoglobin F levels in red blood cells, is a US FDA Pregnancy Category D medication [36]. A list of medications recommended to manage SCD in PAH are listed in Table 1. Also included is US FDA recommendations for pregnancy, and the side effects of these medications should be considered in the proper clinical setting.

Venous thromboembolism & pulmonary embolism

Epidemiology & diagnosis: The incidence of Venous Thromboembolism (VTE) in patients with SCD has been under-recognized in the past. However, recent literature has emphasized the high prevalence of VTE in this patient population. In fact, one study reported that the rate of VTE in patients with SCD was close to that observed in those with hereditary thrombophilias [37]. In another study, upon evaluation of over 1.5 million SCD admissions between 1979 and 2003, it was found that these patients had a risk of PE approximately 3.5 times higher than their African American controls [38]. Similarly, a study which investigated the rates of PE in Pennsylvania from 2001 to 2006 found a 50 to 100-fold increase in rates of PE in the SCD population compared to the general population [39]. More recently, Naik, et al. reported a history of VTE in 25% of adult SCD patients [40]. Pregnancy or postpartum, oral contraceptive use, surgery and hospitalization were reported to be the most common provoking factors for a first VTE event. In fact, a study which investigated VTE events specifically in pregnant patients with SCD found a relative risk of 32.2 for pregnancy-associated VTE in SCD [41]. Since a history of VTE is associated with a 3-4-fold increase in mortality in patients with SCD [40], these results emphasize the importance of prompt recognition and treatment of VTE in this patient population of patients.

Patients with SCD have numerous pathophysiologic processes that lead to a hypercoagulable state. These abnormalities include thrombocytosis, increased tissue factor levels and plasma concentrations of procoagulant clotting factors [42]. Similarly, pregnancy increases the rate of VTE events through various different mechanisms. These include an increase in coagulation factors, acquired resistance to activated protein C, fall in free protein S, impaired fibrinolysis, diminished venous flow to the lower extremities causing stasis and endothelial damage during vaginal delivery or cesarean section [43]. Therefore, when a patient with SCD presents with hypoxia, especially in the perinatal period, VTE must be properly excluded. Similarly, in SCD patients who are seeking hormonal contraception, the risk of VTE in individualized patients must be adequately assessed.

According the 2011 ATS guidelines all pregnant patients with suspected VTE and no signs of lower extremity DVT should have a chest X-Ray performed for initial risk stratification [44]. D-dimer is not recommended in pregnancy to exclude PE. If the chest X-Ray is abnormal a Computed Tomography Angiography (CTA) is then recommended as the next step in diagnostic testing. However, if the chest X-Ray is normal lung scintigraphy is recommended to save the patient radiation exposure. If the V/Q scan is non-diagnostic a CTA is recommended. However, if there is evidence of DVT, a lower extremity Doppler Ultrasound is recommended as the first step in diagnosis.

Management: The RCOG 2011 guidelines recommend that because of the elevated risk of VTE and PE in pregnant patients and SCD patients, the use of graduated compression stockings is recommended. In addition, these women should receive prophylactic doses of low-molecular-weight heparin during their hospital admission [19]. Additionally if an SCD pregnant patient presents with hypoxia there should be a low threshold for considering PE. If a patient is found to have a VTE, Low-Molecular-Weight Heparin (LMWH) is the treatment of choice in this patient population. In order to account for altered pharmacokinetics twice-daily dosing is recommended. There is no need to monitor anti-Xa levels for women on LMWH unless extremes of weight exist or renal insufficiency is present. The duration of therapy should account for the extended timeframe of the inciting event. Hence the patient should be treated for the duration of her pregnancy and six weeks post delivery. Since vitamin K antagonists cross the placenta and are teratogenic, their use is contraindicated during pregnancy but can be used postpartum given the insubstantial secretion in breast milk [45]. Most recommend a planned delivery for women on therapeutic anticoagulation to reduce the dose of anticoagulation prior to delivery, and thereby minimize the risk of bleeding during induction of labor or elective cesarean section [45-48].

Sickle cell chronic lung disease

Epidemiology & diagnosis: Patients who have a history of multiple episodes of ACS are at risk for developing lung fibrosis, particularly at the lung bases [2]. One study identified approximately 90% of 310 homozygous SCD patients having abnormal pulmonary func-

tion tests, with the majority of them exhibiting a mild restrictive disease pattern [49]. Advanced lung disease in patients with SCD has been previously described as sickle cell chronic lung disease [50]. High-resolution CT studies usually reveal a few scattered foci of lung scarring. Similar findings of mild restrictive abnormalities have been observed in more recent cohort studies of adult patients [2].

Management: In a normal pregnancy increases in arterial oxygen, respiratory rate, peak expiratory flow, and forced vital capacity are expected [51]. In the case of a pregnant SCD patient, the possibility of restrictive lung disease and/or propensity for ACS may warrant aggressive incentive spirometry therapy. A prospective randomized trial showed that using an incentive spirometry (10 maximal inspirations every two hours over a period of 14 daytime hours) in hospitalized patients with acute chest or back pain above the diaphragm significantly decreased the incidence of pulmonary complications (atelectasis or infiltrates) in patients with sickle cell diseases [52].

Conclusions

SCD in pregnancy is associated with increased morbidity. Some of the pulmonary complications in SCD patients during pregnancy may include ACS, VTE/PE, and decompensation of pre-existing PH or restrictive lung disease. Our goal was to elucidate the literature regarding the pulmonary complications of SCD, and apply them in the context of the pregnant patient.

In pregnant SCD patients who complain of respiratory symptoms, a full diagnostic workup is necessary to determine causative etiology. We recommend that patients be evaluated for acute chest syndrome (and as an extension - evaluate for pneumonia) and screened for PE or PH. Patients may benefit from incentive spirometry, oxygen supplementation, and blood transfusion when medically indicated. Future studies should include randomized controlled trials to evaluate best practices to treat the pulmonary complications in this population of patients.

References

1. Gladwin MT, Vichinsky E (2008) Pulmonary complications of sickle cell disease. N Engl J Med 359: 2254-2265.
2. Miller AC, Gladwin MT (2012) Pulmonary complications of sickle cell disease. Am J Respir Crit Care Med 185: 1154-1165.
3. Mehari A, Klings ES (2015) Chronic Pulmonary Complications of Sickle Cell Disease, CHEST.
4. Castro O, Brambilla DJ, Thorington B, Reindorf CA, Scott RB, et al. (1994) The acute chest syndrome in sickle cell disease: incidence and risk factors. The Cooperative Study of Sickle Cell Disease. Blood 84: 643-649.
5. Driscoll MC, Hurlet A, Styles L, McKie V, Files B, et al. (2003) Stroke risk in siblings with sickle cell anemia. Blood 101: 2401-2404.
6. Gladwin MT, Sachdev V, Jison ML, Shizukuda Y, Plehn JF, et al. (2004) Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 350: 886-895.
7. Stuart MJ, Nagel RL (2004) Sickle-cell disease. Lancet 364: 1343-1360.
8. Boulet SL, Okoroh EM, Azonobi I, Grant A, Craig Hooper W (2013) Sickle cell disease in pregnancy: maternal complications in a Medicaid-enrolled population. Matern Child Health J 17: 200-207.
9. Chakravarty EF, Khanna D, Chung L (2008) Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol 111: 927-934.
10. (2007) ACOG Practice Bulletin. Clinical Management Guidelines for Obstetrician-Gynecologists Number 78, July 2007 (Replaces Practice Bulletin Number 64, July 2005): hemoglobinpathies in pregnancy 109.
11. Ballas SK, Lieff S, Benjamin LJ, Dampier CD, Heeney MM, et al. (2010) Definitions of the phenotypic manifestations of sickle cell disease. Am J Hematol 85: 6-13.
12. Elliott PV, Lynne DN, Ann NE, Roger W, Evelyne TL, et al. (2000) Causes and Outcomes of the Acute Chest Syndrome in Sickle Cell Disease. N Engl J Med 342: 1855-1865.
13. Vichinsky EP, Neumayr LD, Earles AN, Williams R, Lennette ET, et al. (2000) Causes and outcomes of the acute chest syndrome in sickle cell disease. National Acute Chest Syndrome Study Group. N Engl J Med 342: 1855-1865.
14. Villers MS, Jamison MG, De Castro LM, James AH (2008) Morbidity associated with sickle cell disease in pregnancy. Am J Obstet Gynecol 199: 125.e1-125.e5.
15. Elsayegh D, Shapiro JM (2007) Sickle cell vasoocclusive crisis and acute chest syndrome at term pregnancy. South Med J 100: 77-79.
16. Nomura RM, Igai AM, Tosta K, Fonseca GH, Gualandro SF, et al. (2009) Acute chest syndrome in pregnant women with hemoglobin SC disease. Clinics (Sao Paulo) 64: 927-928.
17. Leborgne-Samuel Y, Janky E, Venditelli F, Salin J, Daijardin JB, et al. (2000) [Sickle cell anemia and pregnancy: review of 68 cases in Guadeloupe]. J Gynecol Obstet Biol Reprod (Paris) 29: 86-93.
18. de Montalembert M, Deneux-Tharaux C (2015) Pregnancy in sickle cell disease is at very high risk. Blood 125: 3216-3217.
19. Royal College of Obstetricians & Gynaecologists (2011) Management of Sickle Cell Disease in Pregnancy. Green-top.
20. Okusanya BO, Oladapo OT (2013) Prophylactic versus selective blood transfusion for sickle cell disease in pregnancy. Cochrane Database Syst Rev.
21. Koshy M, Burd L, Wallace D, Moawad A, Baron J (1988) Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperative study. N Engl J Med 319: 1447-1452.
22. Malinowski AK, Shehata N, D'Souza R, Kuo KH, Ward R, et al. (2015) Prophylactic transfusion for pregnant women with sickle cell disease: a systematic review and meta-analysis. Blood 126: 2424-2435.
23. Mehari A, Alam S, Tian X, Cuttica MJ, Barnett CF, et al. (2013) Hemodynamic predictors of mortality in adults with sickle cell disease. Am J Respir Crit Care Med 187: 840-847.

24. Castro O, Hoque M, Brown BD (2003) Pulmonary hypertension in sickle cell disease: cardiac catheterization results and survival. Blood 101: 1257-1261.

25. Reiter CD, Wang X, Tanus-Santos JE, Hogg N, Cannon RO, et al. (2002) Cell-free hemoglobin limits nitric oxide bioavailability in sickle-cell disease. Nat Med 8: 1383-1389.

26. Machado RF, Gladwin MT (2005) Chronic sickle cell lung disease: new insights into the diagnosis, pathogenesis and treatment of pulmonary hypertension. Br J Haematol 129: 449-464.

27. Fonseca GH, Souza R, Salemi VM, Jardim CV, Gualandro SF (2012) Pulmonary hypertension diagnosed by right heart catheterisation in sickle cell disease. Eur Respir J 39: 112-118.

28. Klings ES, Machado RF, Barst RJ, Morris CR, Mubarak KK, et al. (2014) An Official American Thoracic Society Clinical Practice Guideline: Diagnosis, Risk Stratification, and Management of Pulmonary Hypertension of Sickle Cell Disease. Am J Respir Crit Care Med 189: 727-740.

29. Weiss BM, Zemp L, Seifert B, Hess OM (1998) Outcome of pulmonary vascular disease in pregnancy: a systematic review from 1978 through 1996. J Am Coll Cardiol 31: 1650-1657.

30. Bédard E, Dimopoulos K, Gatzoulis MA (2009) Has there been any progress made on pregnancy outcomes among women with pulmonary arterial hypertension? Eur Heart J 30: 256-265.

31. Duarte AG, Thomas S, Safdar Z, Torres F, Pacheco LD, et al. (2013) Management of Pulmonary Arterial Hypertension During Pregnancy: A Retrospective, Multicenter Experience. Chest 143: 1330-1336.

32. Parent F, Bachir D, Inamo J, Lionnet F, Driss F, et al. (2011) A hemodynamic study of pulmonary hypertension in sickle cell disease. N Engl J Med 365: 44-53.

33. European Society of Gynecology (ESG); Association for European Paediatric Cardiology (AEPC); German Society for Gender Medicine (DGesGM), Regitz-Zagrosek V, Blomstrom Lundqvist C, Borghi C, Cifkova R, et al. (2011) ESC Guidelines on the management of cardiovascular diseases during pregnancy: the Task Force on the Management of Cardiovascular Diseases during Pregnancy of the European Society of Cardiology (ESC). Eur Heart J 32: 3147-3197.

34. Lee MT, Small T, Khan MA, Rosenzweig EB, Barst RJ, et al. (2009) Doppler-defined pulmonary hypertension and the risk of death in children with sickle cell disease followed for a mean of three years. Br J Haematol 146: 437-441.

35. Desai PC, May RC, Jones SK, Strayhorn D, Caughey M, et al. (2013) Longitudinal study of echocardiography-derived tricuspid regurgitant jet velocity in sickle cell disease. Br J Haematol 162: 836-841.

36. http://reference.medscape.com/drugs

37. Cohen W, Castelli C, Suchon P, Bouvet S, Aillaud MF, et al. (2014) Risk assessment of venous thrombosis in families with known hereditary thrombophilia: the MARseilles-NImes prediction model. J Thromb Haemost 12: 138-146.

38. Stein PD, Beemath A, Meyers FA, Skaf E, Olson RE (2006) Deep venous thrombosis and pulmonary embolism in hospitalized patients with sickle cell disease. Am J Med 119: 897.e7-897.e11.

39. Novelli EM, Huynh C, Gladwin MT, Moore CG, Ragni MV (2012) Pulmonary embolism in sickle cell disease: a case-control study. J Thromb Haemost 10: 760-766.

40. Naik RP, Streiff MB, Haywood C Jr, Segal JB, Lanzkron S (2014) Venous thromboembolism incidence in the Cooperative Study of Sickle Cell Disease. J Thromb Haemost 12: 2010-2016.

41. Porter B, Key NS, Jauk VC, Adam S, Biggio J, et al. (2014) Impact of sickle hemoglobinopathies on pregnancy-related venous thromboembolism. Am J Perinatol 31: 805-809.

42. Ataga K (2009) Hypercoagulability and thrombotic complications in hemolytic anemias. Haematologica 94: 1481-1484.

43. Townsley DM (2013) Hematologic complications of pregnancy. Semin Hematol 50: 222-231.

44. Leung AN, Bull TM, Jaeschke R, Lockwood CJ, Boiselle PM, et al. (2011) An official American Thoracic Society/Society of Thoracic Radiology clinical practice guideline: evaluation of suspected pulmonary embolism in pregnancy. Am J Respir Crit Care Med 184: 1200-1208.

45. Greer IA (2012) Thrombosis in pregnancy: updates in diagnosis and management. Hematology/the Education Program of the American Society of Hematology. American Society of Hematology. Education Program 2012: 203-207.

46. Bates SM, Greer IA, Middeldorp S, Veenstra DL, Prabulos AM, et al. (2012) VTE, thrombophilia, antithrombotic therapy, and pregnancy: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 141: 691-736.

47. Greer IA, Nelson-Piercy C (2005) Low-molecular-weight heparins for thromboprophylaxis and treatment of venous thromboembolism in pregnancy: a systematic review of safety and efficacy. Blood 106: 401-407.

48. Leonhardt G, Gaul C, Nietsch HH, Buerke M, Schleussner E (2006) Thrombolytic therapy in pregnancy. J Thromb Thrombolysis 21: 271-276.

49. Klings ES, Wyszynski DF, Nolan VG, Steinberg MH (2006) Abnormal pulmonary function in adults with sickle cell anemia. Am J Respir Crit Care Med 173: 1264-1269.

50. Powars D, Weidman JA, Odom-Maryon T, Niland JC, Johnson C (1988) Sickle cell chronic lung disease: prior morbidity and the risk of pulmonary failure. Medicine (Baltimore) 67: 66-76.

51. Grindheim G, Toska K, Estensen ME, Rosseland LA (2012) Changes in pulmonary function during pregnancy: a longitudinal cohort study. BJOG 119: 94-101.

52. Bellet PS, Kalinyak KA, Shukla R, Gelfand MJ, Rucknagel DL (1995) Incentive spirometry to prevent acute pulmonary complications in sickle cell diseases. N Engl J Med 333: 699-703.