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REVIEW



# Pregnancy and sickle cell disease: an overview of complications and suggested perinatal care

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## ABSTRACT

**Introduction:** Pregnancy in women with sickle cell disease (SCD) has been identified as high risk owing to increased incidence of materno-fetal complications across various studies and reports. These complications include consequences related to the underlying hemoglobinopathy; chronic anemia/associated inflammation, and pregnancy related including the risk for thromboembolism, bleeding and maternal mortality. Outcomes of neonates born to women with SCD has been suboptimal over the years with recent improvement due to strict monitoring, preventive and therapeutic measures. Much is yet to be unraveled regarding the optimal management of women with SCD during pregnancy, identifying target hemoglobin, delivery mode or timing among others.

**Areas covered:** This review includes a summary of available data of the maternal and fetal outcomes; in addition to current recommendations for monitoring and management of women with SCD during pregnancy.

**Expert opinion:** To have a successful pregnancy, women should be closely monitored, and interventions provided as needed to guarantee adequate management of anemia, as well as prevention, diagnosis and management of disease. They should also be educated regarding their reproductive health, emphasizing that pregnancy is possible, and achieving optimal results depends on providing adequate care in a health care facility with expertise in high-risk pregnancies and SCD.

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## KEYWORDS

Pregnancy; sickle cell disease; maternal; fetal; fertility; perinatal care

## 1. Introduction

Sickle cell disease (SCD) is the most common inherited hemoglobinopathy, widely prevalent in Sub-Saharan Africa, the Mediterranean region/Middle East and India [1], including a variety of homozygote and double heterozygote genotypes [2]. The underlying pathophysiology of sickle cell anemia is related to an inherited mutation that causes a change in the sixth amino acid in the beta-globin chain, from the hydrophilic glutamic acid to the hydrophobic valine, resulting in crystallization of the hemoglobin molecule with sickling of red blood cells at low oxygen levels [3,4]. This leads to different systemic complications that have been associated with significant morbidity and mortality, including vaso-occlusive pain crisis (VOC), thromboembolic events and cardiovascular manifestations among others [3]. The polymerization of hemoglobin S with the associated sickling results in a chronic hemolytic anemia as well as a self-perpetuating cycle of vaso-occlusion, chronic vascular damage/inflammation and cell activation with over expression of adhesion mediators [3].

Pregnancy in patients with SCD has been associated with significant maternal and fetal complication; however with the recent advances in the care for these individuals, their life expectancy has improved tremendously, allowing more women to reach reproductive age and thus either express their desire or actually attempting pregnancy. In addition,

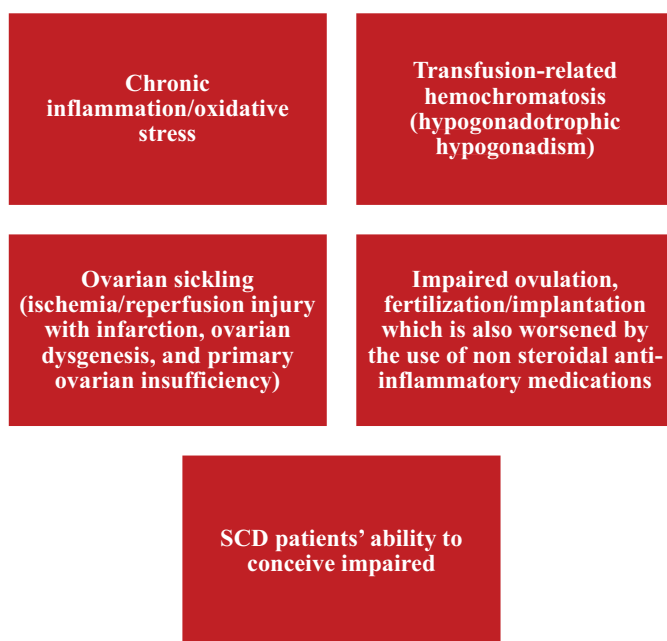
the introduction of preconception care has led to significant improvements in maternal and fetal outcomes. We herein present an overview of the pregnancy associated complications in SCD, as well as the suggested perinatal care that might lead to a successful pregnancy and delivery of a healthy baby.

## 2. Fertility in SCD

Multiple factors are known to affect fertility and the reproductive health of individuals with SCD. These include but are not limited to poor nutrition, prior blood transfusion with subsequent iron overload, recurrent vaso-occlusive crisis and infections/hospitalizations [5]. Delayed menarche and sexual development have long been reported in women with SCD [6]. Figure 1 illustrates the possible effect of SCD on fertility with the underlying pathophysiology of impaired ovulation and implantation, including the oxidative stress that characterizes SCD, associated ovarian sickling leading possibly to primary failure; as well as the possibility of hypogonadotropic hypogonadism related to secondary iron overload, and prostaglandin production inhibition related to chronic use of non-steroidal anti-inflammatory drugs (NSAIDs) for the management of pain crisis [7–9].

**Article highlights**

- Multiple factors are known to affect fertility and the reproductive health of individuals with SCD. These include but are not limited to poor nutrition, prior blood transfusion with subsequent iron overload, recurrent vaso-occlusive crisis and infections/hospitalizations.
- Complications of women with SCD during pregnancy and in the post-natal period can be disease related, pregnancy related, maternal or fetal
- Women with SCD should be educated regarding their reproductive health, emphasizing that pregnancy is possible, and achieving optimal results depends mainly on providing adequate care in an experienced health care facility with expertise in high risk pregnancies and SCD.
- The optimal care for these women depends on the establishment of a multidisciplinary approach creating a complete care plan that starts from preconception planning to the post-natal management



**Figure 1.** The effect of SCD on fertility.

### 3. Maternal complications

The rate of reported complications during pregnancy in women with SCD has varied significantly among previously published reports, related to geographic as well as study variations. Several physiologic adaptations are expected during pregnancy, however these might overburden organs which have already been exposed to recurrent injuries related to their underlying SCD [3]. Complications during pregnancy and in the post-natal period can be disease related, pregnancy related, maternal or fetal. These have led to significant maternal morbidity and increased mortality among women with SCD in the peri-natal period. Disease-related complications that are worsened by the multiple physiological changes expected during pregnancy include aggravation of vaso-occlusive crisis, increased incidence of acute chest syndrome, skin ulcers, thromboembolic events and osteonecrosis among others [10]. Data from 2004 to 2010 Multistate Medicaid databases showed that women with SCD had higher risk of venous

thromboembolic events (VTEs), infections and transfusions, among multiple other complications [11]. In addition, anemia is expected to worsen during pregnancy with higher transfusion requirements. Pregnancy in individuals with SCD has been associated with a higher risk for cesarean section delivery, eclampsia, and pre-eclampsia [12]. A systematic review and meta-analysis of studies in pregnancy in SCD previously confirmed significant increases in maternal mortality, pre-eclampsia, stillbirth, preterm delivery and infants with low birth weight [13], with meta-regression demonstrating that increased relative risks were associated with genotype (HbSS versus HbSC) and low gross national income, and these findings were again confirmed in a more recent systematic review and meta-analysis [14]. A recent data including a 10-year retrospective study at the University of Illinois Health System (UIH), reported outcomes of 177 women over the age of 18 with SCD and pregnancy (208 pregnancies) [15]. The majority had HbSS genotype (around 63%), and were 18 to 25 years of age, with single pregnancies reported in around 77% of females. Around 45% required a cesarean delivery, while the cohort had a statistically significant increased risk of VOC during pregnancy when compared to the 12 months before or after, with a slight trend of increase in thromboembolic events. In addition, this data identified VOC and HbSS genotype as significant predictors of adverse maternal outcomes including C-section and transfusion requirement at delivery [15]. Data from 99 participants followed in a prospective cohort reported increased incidence of acute pain during pregnancy 49.5% (n = 74) as compared to that in the post-partum period-18.2% (n = 18), with a significantly increased pain rate (6 fold) as well as acute chest syndrome (4 fold-0.4 versus 0 events/patient-years (P = 0.001; Wilcoxon rank test) during pregnancy, mostly during the third trimester [16]. Lewis et al also reported higher incidence of acute chest syndrome (adjusted relative risk (aRR) 13.7; 95% CI 4.1–45.5), urinary tract infection (aRR 12.8, 95% CI 1.3–125.9), as well as maternal mortality, among 71 women with SCD (SS genotype) who had 177 pregnancies when compared to controls [17].

Hypertensive disorders of pregnancy have been commonly reported in women with SCD, related to the underlying chronic inflammation and endothelial damage, with pre-eclampsia rates as high as 12% [18] and risk increased by around 2.42 folds [19]. Splenectomy and defective splenic functions are known to add to the already increased risk of infections associated with pregnancy; and the hypercoagulable state that characterizes pregnancy is further exacerbated by the coagulopathy of SCD thus leading to significantly increased risk of thromboembolic events during pregnancy and in the post-natal period.

### 4. Fetal complications

Placental vaso-occlusion can lead to necrosis and infarction causing uteroplacental insufficiency and thus fetal hypoxia resulting in several fetal complications [20]. These include spontaneous abortions/stillbirths, impaired intrauterine growth with low birth weight, and preterm delivery among others. The general health of the mother, severity of anemia,

multiple pregnancies, and possible history of drug abuse can further adversely impact fetal outcomes [21]. Intrauterine growth retardation has been reported to be as high as fivefold in women with SCD compared to the general population [3].

A meta-analysis including more than 26,000 pregnancies with various SCD genotypes documented a higher risk of small for gestational age neonates compared to the control group (reaching more than 3.7 in those with HbSS) [12]. A statistically significant difference was also reported in the mean birth weight/percentile among neonates born to mothers with SCD (2918 g) compared to the control group (3176 g) [22]. The risk for preterm delivery has also been reported to be increased in SCD, despite the failure to identify clear underlying mechanisms; nonetheless multiple contributing factors have been suggested including increased production of prostaglandins, anemia with the associated hypoxia, placental disorders, among multiple others more commonly affecting pregnancy associated with SCD. Multiple other fetal/neonatal complications are increased including respiratory distress syndrome and neonatal jaundice [23]. The rate of neonatal death has varied across studies depending on the geographic location and thus socioeconomic status (the risk of stillbirth can be increased by around 5 folds in developing countries [24]. Recent data reported by Lewis et al documented increased risk of low-birth weight (aRR 3.0, 95% CI 1.6–5.3) and preterm deliveries in women with SCD (71 women-177 pregnancies) [17]. Table 1 includes recently reported maternal and fetal complications among SCD women.

Importantly, risk factors for adverse outcomes have been suggested utilizing data from a retrospective cohort of pregnant women with SCD. Genotype has been identified as a predictor of both maternal and fetal outcomes, on the other hand low hemoglobin during the first trimester, prior VOC requiring hospitalization, need for multiple transfusion preconception, and a history of cardiac complications were significant factors affecting maternal outcomes; while younger age, and LDH affected fetal outcomes [29]. Maternal weight gain (especially during weeks 25–30 gestation) has been shown to have a significant impact on birthweight, while this relationship is delayed among women with sickle cell disease

[30]. Pain crisis during pregnancy has been associated with a significant reduction in crown-heel length at birth [31].

## 5. Perinatal care

The achievement of optimal outcomes for any pregnancy in women with SCD depends on the utilization of a multidisciplinary management approach that ideally should be initiated at the preconception stage and continued until the post-partum period. This should include continuous integrative communication between hematologists, obstetricians with experience in high-risk pregnancies, and pain specialists.

### 5.1. Prenatal period

Women with SCD should be regularly counseled regarding fertility and pregnancy planning during each follow up visit, where information regarding previous medical history as well as vaccination status should be regularly updated.

For women on hydroxyurea, counseling should be provided regarding the need to discontinue therapy prior to conception [32]. The Sickle Cell Disease Implementation Consortium reported data on the use of hydroxyurea and pregnancy outcomes among 1285 women (1788 pregnancies), where use during conception and pregnancy led to an increase in the risk of miscarriage or stillbirths (OR 2.21; 1.40–3.47), a risk which was not confirmed when use of hydroxyurea was limited to time of conception [33]. These results provide evidence that the use of hydroxyurea might be safe until conception, while caution should be advised regarding its continued use during pregnancy. In addition, prenatal diagnosis and genetic counseling should be offered to all couples. Diagnostic procedures include chorionic villos sampling during the first trimester, amniocentesis or cordocentesis during the second trimester [34]. Multiple additional prenatal diagnostic procedures in addition to preimplantation genetic diagnosis can also be utilized for optimal decision making.

**Table 1.** Recently reported maternal and fetal complications in SCD.

Maternal Complications					
Author (year)	Maternal Mortality	VOC	ACS	Pre-eclampsia	CS
<b>Lewis et al (2021) [17]</b>	<b>3.6% (n = 5)</b>	<b>16.4% (n = 23)</b>	<b>22.1% (n = 31)</b>	<b>15.7% (n = 22)</b>	<b>NA</b>
Proske et al (2021) [25]	0	83.9% (n = 26)	12.9% (n = 4)	NA	67% (n = 16)
Asare et al (2019) [16]	0	49.5% (n = 74)	15.2% (n = 15)	NA	NA
Gaddikeri et al (2017) [26]	8.3% (n = 4)	58.3% (n = 31)	NA	33.3% (n = 4)	25% (n = 14)
Elena et al (2016) [27]	0%	19% (n = 5)	4% (n = 1)	11% (n = 3)	37% (n = 10)
Boafor et al (2015) [12]	3% (n = 46)	NA	NA	10.3% (n = 229)	35.5% (n = 1354)
Desai et al (2014) [28]	NA	47.3% (n = 62)	NA	6.1% (n = 8)	17.6% (n = 23)
Fetal Complications					
Authors (year)	Prematurity	LBW	IUGR	Stillbirth	Neonatal death
<b>Kroner et al (2022) [33]</b>	<b>35.6% (n = 384)</b>	<b>6.4% (n = 69)</b>	<b>NA</b>	<b>2.6% (n = 40)</b>	<b>NA</b>
<b>Lewis et al (2021) [17]</b>	<b>NA</b>	<b>46% (n = 49)</b>	<b>NA</b>	<b>8.6% (n = 14)</b>	<b>1.1 (n = 2)</b>
Proske et al (2021) [25]	35% (n = 11)	NA	NA	NA	NA
Gaddikeri et al (2017) [26]	25% (n = 14)	84.6% (n = 21)	50% (n = 27)	8.3% (n = 4)	8.3% (n = 4)
Elena et al (2016) [27]	41% (n = 11)	NA	19% (n = 5)	3.7% (n = 1)	0
Boafor et al (2015) [12]	21% (n = 437)	16.5% (n = 322)	12.2% (n = 290)	8.1% (n = 131)	2.5% (n = 24)
Desai et al (2014) [28]	45% (n = 59)	NA	2.8% (n = 3)	9.9% (n = 13)	NA

## 5.2. Ante-natal period & intra-partum care

Women with SCD should be maintained on folic acid throughout pregnancy, with iron supplements, and antibacterial prophylaxis as needed.

In the perinatal period, worsening anemia can be multifactorial and needs to be evaluated adequately and managed as needed, noting that the RCOG guidelines (Royal College of Obstetrician and Gynecologists) [35] and American Society of Hematology (ASH) do not recommend routine prophylactic packed red blood transfusion. Previous studies had suggested prophylactic transfusions prevent materno-fetal complications, however this remains controversial and is not currently recommended by various international guidelines given the increased risks for alloimmunization, iron overload, and transfusion reactions among others, especially with more recent data questioning any significant impact on materno-fetal outcomes, including results from a Cochrane review indicating weak evidence of benefit with scheduled transfusions [35]. A previous randomized trial including 72 women comparing scheduled to on-demand transfusion, showed decreased odds of pain episodes with no effect on fetal complications with the scheduled group [36].

The ASH guidelines recommend consideration of prophylactic transfusion in women with a prior history of SCD associated complications, specifically during pregnancy, or those with additional comorbidities that would require a higher target hemoglobin [37]. Based on available data, an individualized transfusion plan is essential for optimal care, addressing indication, goals and monitoring [38]. Exchange transfusion is generally recommended in stroke and acute chest syndrome. Recently, results from a preliminary retrospective study including 191 pregnancies who were followed at 2 centers between 2005 and 2014, suggested a possible role for targeted transfusion in combination with home-based prophylactic nocturnal oxygen therapy [39,40].

Importantly, the possibility of nutrient deficiency should be considered and adequately evaluated in women with exacerbation of anemia. A recent systematic review showed wide variation in the prevalence of iron deficiency in pregnant women with SCD [36]. The only published randomized controlled trial of prophylactic iron supplementation in this population was too small to draw conclusions. It remains prudent to treat iron deficiency anemia when it arises.

Women with SCD should be closely monitored during pregnancy to prevent, properly diagnose and manage any complication to optimize outcomes. Regular surveillance for infections is advised [3]. Monitoring for proteinuria in addition to regular monitoring of blood pressure is essential given the risk of pre-eclampsia, while the initiation of low-dose aspirin is recommended starting from week 12 for those at high risk of pre-eclampsia [18].

In addition, the management of VOC should start with the preparation of a pain control plan to be utilized during pregnancy. For pregnant women with VOC, hospitalization is required for adequate hydration and pain relief, with recommendations to avoid meperidine for associated toxicity [41]. In case of suspected or documented acute chest syndrome, antibiotics in addition to hydration and analgesia is recommended

with consideration of blood transfusion as indicated, in addition to adequate imaging to rule out an associated thromboembolic event. In addition, consideration for the possibility of a cerebrovascular accident is needed with any new neurological complaints.

Decision regarding the optimal timing and mode of delivery should be made with communication between the hematologist and obstetrician. Adequate fluid balance and temperature should be maintained during labor and post-delivery, in addition to appropriate analgesia, with continuous monitoring of fetal heart rate.

The risk of thromboembolic events is increased during pregnancy and in the post-partum period, and thus adequate thromboprophylaxis should be offered to patients during any immobilization and up to at least 6 weeks post-partum, similar to other hypercoagulable conditions. Figure 2 includes suggested monitoring and management across the three trimesters as currently recommended by different guidelines [21,32,38].

## 6. Conclusion

Despite advances in the care for individuals with SCD which has allowed improved survival, thus enabling an increased number of women to reach reproductive age and accordingly attempt pregnancy, there remains an unmet need in the management of these individuals. With the limited available data, and difficulty to plan randomized controlled trials, many unmet needs still constitute a barrier to achieving optimal maternal and fetal outcomes. Pregnancy in women with SCD remains a high-risk entity that requires adequate multidisciplinary approach to prevent, screen for, diagnose and manage complications.

## 7. Expert opinion

With the recent advancement in the care for individuals with SCD, survival has significantly improved, and this has allowed the possibility for improving fertility and attempting pregnancy. Nonetheless, pregnancy among women with SCD remains high risk and can be associated with significant maternal and fetal complications. These include worsening anemia, thromboembolic events (deep vein thrombosis/pulmonary embolus), infections, increased mortality risk, in addition to multiple adverse fetal outcomes such as still-birth, intrauterine growth retardation, prematurity, as well as low birth weight among others. Multiple previous and recent data have documented a significant increase in the risk for these complications in women with SCD. However, the wide variability in the available studies related to geographic location, specific genotype among other characteristics affects the ability to draw clear conclusions regarding outcomes or risk factors.

The optimal care for these women depends on the establishment of a multidisciplinary approach creating a complete care plan that starts from preconception planning to the post-natal management. This usually includes the communication among multiple health care providers namely a hematologist with specific expertise in the management of hemoglobinopathies, an

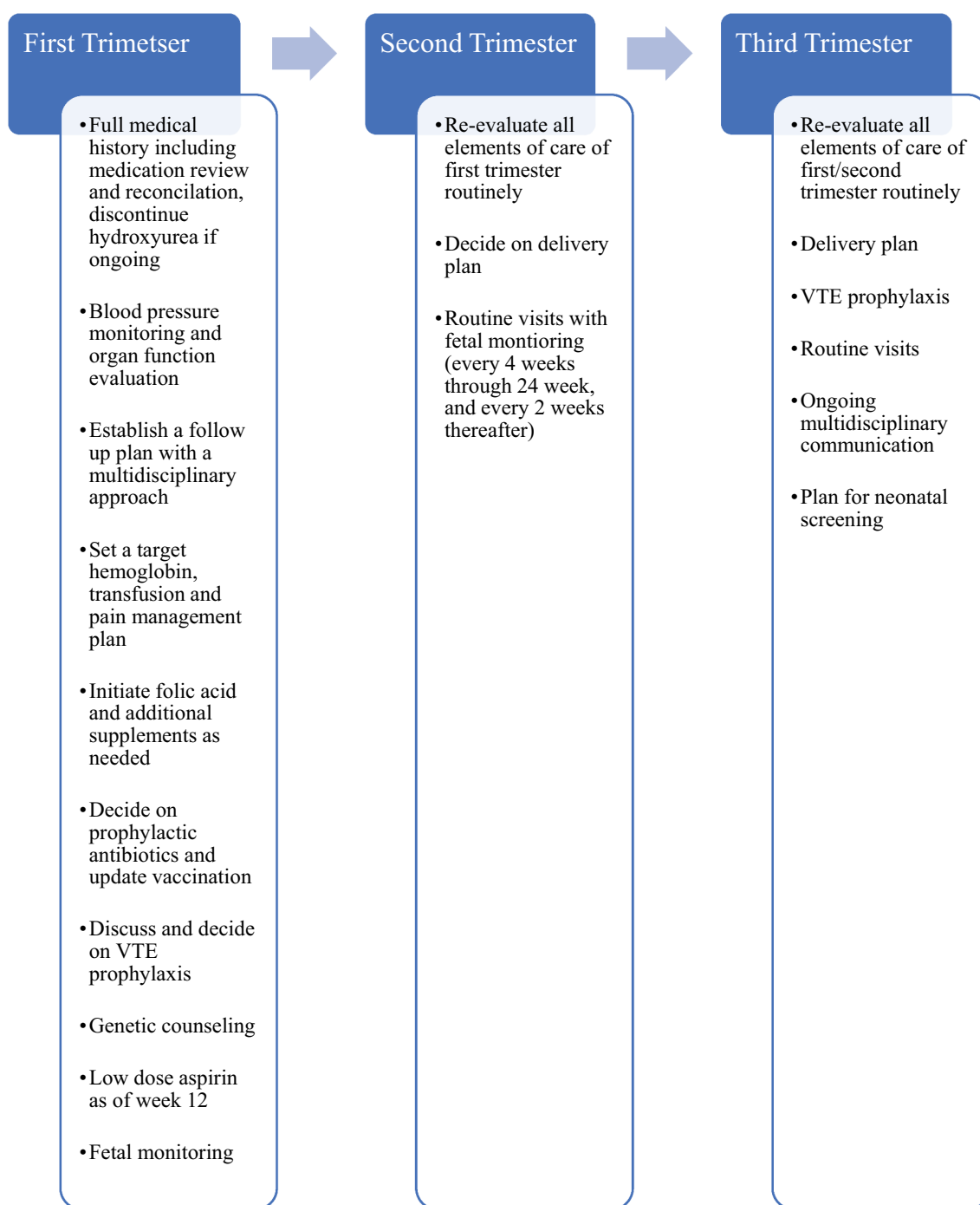


Figure 2. Peri-natal care for women with SCD.

obstetrician with experience in high-risk pregnancies, pain team among multiple others as needed. This integrative approach should be initiated from the preconception period and extended till the post-partum period to include neonatologists that can assess and manage neonates born to women with SCD.

In order to have a successful pregnancy, women should be closely monitored, and interventions provided as needed to guarantee adequate management of anemia, prevention, diagnosis and management of disease, as well as pregnancy associated complications. Periodic visits should be initiated from the first trimester evaluating comorbidities that would further increase the risk of various complications, reviewing

and reconciling medications, discontinuing hydroxyurea if still ongoing in addition to any medication with suggested or documented teratogenic effects. Initiating low dose aspirin around 12 weeks of gestation is recommended. Serial monitoring of the fetus is also recommended to assess for possible intrauterine growth retardation.

Worsening anemia remains among the most commonly encountered adverse events, which can be related to multiple etiologies including acquired infections, nutrient deficiencies, bleeding among others. In the management of anemia, the role of prophylactic transfusion in an attempt to prevent multiple complications and improve outcomes, has remained

controversial, but available data suggest that red blood cell transfusion will be generally required at some point during these pregnancies. With the currently available data, there is limited evidence that the utilization of prophylactic scheduled transfusions would significantly alter the maternal and/or fetal outcomes in SCD. Future trials need to identify risk factors for proper risk stratification of patients to allow the adoption of an individualized transfusion plan. Other preventive measures including low-dose aspirin for women with high risk for pre-eclampsia are generally recommended.

Women with SCD should be educated regarding their reproductive health, emphasizing that pregnancy is possible, and achieving optimal results depends mainly on providing adequate care in an experienced health care facility with expertise in high risk pregnancies and SCD. Nonetheless, much of the data we have available regarding outcomes of pregnancies in women with SCD come from retrospective analysis, single center experience or significantly heterogeneous population. Future data is awaited to adjust monitoring and management recommendations.

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## Declaration of interest

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