Sickle cell disease in pregnancy

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Abstract

Sickle cell disease (SCD) is a chronic, multisystem disease. Despite decades of medical advances in SCD management, studies have revealed an increased risk of stillbirth, preterm delivery, small for gestational age, maternal mortality and preeclampsia, compared to the general population. Pregnant women with SCD should be cared for within the multidisciplinary team, comprised of specialist obstetricians, high risk midwives and haematologists. A national confidential enquiry into patient outcomes and death (NCEPOD), expressed concerns with a lack of consistent care for SCD patients in pregnancy. Within the UK, there is great geographical variation in the prevalence of SCD, with the highest incidence in large urban, multicultural centres. Trainee obstetricians practising outside of these areas may not gain substantial experience in managing these patients: therefore this review aims to highlight the key antenatal, intrapartum and postnatal elements involved in managing pregnant women with SCD.

Keywords antenatal care; contraception; post-partum; pregnancy; sickle cell disease

Introduction

Haemoglobinopathies are a group of genetic disorders affecting haemoglobin structure or synthesis. Sickle cell disease (SCD) has evolved to be the most common monogenetic disorder, affecting 30 million people worldwide, across all continents because of migration and inter-racial relationships. The areas with greatest prevalence include sub-Saharan Africa, South America, the Caribbean, Saudi Arabia, India and Mediterranean countries. Sickle cell trait (SCT) and SCD have a protective effect against malaria, therefore positive selection for the causative genetic mutation occurs in these regions where malaria is endemic. The United Kingdom currently has the highest prevalence of SCD in Europe. In 1995 there were approximately 5000 SCD cases, increasing to 15,000 by 2011, with a national birth prevalence of 1 in 2000. Approximately 8% of black people carry the sickle cell gene.

Improvements in the diagnosis and management of SCD are facilitating pregnancy in women with SCD. Fertility is generally unaffected by the disorder and, in the UK, approximately 150–250 deliveries per year occur in women with SCD.

Pathophysiology

Sickle cell disease is a multi-organ disorder, with an autosomal recessive inheritance. Sickle haemoglobin (HbS) results from a point mutation on the short arm of chromosome 11 in the β-globin gene, causing valine to be replaced by glutamic acid (GAG to GTG) as the 6th amino acid. SCD occurs when HbS is combined with another abnormal haemoglobin (e.g. HbSC, HbSE). The most common types of SCD in the UK are:

1. HbSS (sickle cell anaemia)
2. HbSC (haemoglobin SC disease)
3. HbSβ^0 (sickle beta thalassemia zero or HbSβ$^+$sickle beta thalassemia plus)

Other types of sickle cell disease include HbSD-Punjab, HbSO-Arab, HbSHPFH and HbSE.

Sickle cell trait is the result of inheriting HbS from one parent and a normal HbA from the other parent.

Deoxygenation of sickle cell haemoglobin causes a reduction in HbS solubility, resulting in polymerization of the molecules leading to the red blood cell adopting a sickle (crescent) shape. Dehydration, hypoxia, cold, stress, over-exertion and acidosis increase erythrocyte sickling rates. The deformed cells are friable and prone to haemolysis, leading to anaemia. The damaged cell membrane exposes adhesion molecules on the cell surface, making the red cells adhere to vascular endothelium. This results in stagnant blood flow, microvascular occlusions, tissue hypoxia and end-organ ischaemia or infarction. In pregnancy, higher levels of von Willebrand factor, fibrinogen, and factor VIII also enhance erythrocyte adhesion.

Clinical features

Sickle cell disease most often presents in childhood with dactylitis (inflammation of the digits), infection or severe anaemia from splenic sequestration. The key clinical complications of SCD include; vaso-occlusive/bony crises, acute chest syndrome, stroke, renal insufficiency, hepatic necrosis, osteonecrosis, leg ulcers, venous thromboembolism and pulmonary hypertension (Table 1). The extent of these complications is similar amongst the different sickle genotypes, however variable in severity.

Anaemia is very common due to haemolysis of the abnormal red blood cells. HbS releases oxygen to tissues more readily, and therefore SCD patients are able to tolerate a lower baseline haemoglobin level. Folate deficiency occurs due to the haemolytic anaemia, therefore folic acid supplements are advised prenatally, with a higher dose in pregnancy. The main treatment option for symptomatic anaemia is a blood transfusion, to improve oxygen carrying capacity and reduce the proportion of sickled cells. Previous blood transfusions carry a 18–36% risk of alloimmunization (formation of antibodies to red cell antigens)

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Clinical complications of sickle cell disease

Acute complications	• Vaso-occlusive bony crisis • Acute chest syndrome (ACS) • Overt stroke • Priapism • Sequestration (spleen, liver) • Aplastic crisis
Infection	• Osteomyelitis • UTI • Sepsis • Meningitis • Acute cholecystitis
End-organ damage	• Hyposplenism • Avascular necrosis • Nephropathy • Pulmonary hypertension • Leg ulceration • Cerebrovascular disease • Retinopathy • Endocrine failure

Table 1

and also iron overload. Routine use of iron supplements is not recommended, unless a low ferritin is demonstrated. Baseline haemoglobin levels tend to be lower in HbSS patients compared to HbSC patients.

Acute painful crises, or acute painful episodes, are a common complication of SCD, with a third being triggered by infections. Patients can have generalized or localized pain during a crisis. Acute chest syndrome (ACS) is a serious complication resulting in pleuritic chest pain, tachypnoea, cough and fever, with leucocytosis and new infiltrates on chest X-ray. ACS is thought to be caused by intrapulmonary vascular sickling, fat emboli and/or infection. Patients initially presenting with a bony crisis may go on to develop ACS, therefore vigilance for this complication is required. Chronic haemolytic anaemia and frequent crises can lead to organ damage, impairing the quality of life and the eventual survival of patients with SCD.

Hyposplenism results in an increased risk of infection, particularly from encapsulated organisms such as *Streptococcus pneumoniae*, *Neisseria meningitidis*, *Haemophilus influenzae* and *Salmonella* species. Vaccination is recommended against *Haemophilus influenza* type B, conjugated meningococcal C, hepatitis B and annual influenza. Penicillin prophylaxis is also recommended. There is good evidence of its value from randomized trials in children, but not in pregnant women.

Renal impairment is relatively common. Microalbuminuria and proteinuria are frequent findings. Protein: creatinine ratios have not been extensively validated in pregnancy and normal ranges have not been established in pregnant women with SCD. Despite this, a baseline level of proteinuria and microalbuminuria is important to establish early in pregnancy. In the non-pregnant population ACE inhibitors or angiotensinogen receptor blockers are used in severe proteinuria/microalbuminuria, to limit further renal deterioration, however these are generally contraindicated in pregnancy and should be stopped as early as possible. Women with SCD are also prone to urinary tract infections (UTI). Recurrent UTI occurs in 6% of pregnant women with SCD, with a greater incidence in women with HbSC. 16% of pregnant women will demonstrate microscopic haematuria, representing localized microscopic renal vasculature infarcts.

The retina, iris, conjunctivae and choroidae can be damaged by vaso-occlusion, hypoxia and subsequent neovascularisation, leading to proliferative retinopathy. Proliferative retinopathy is often more severe in HbSC than HbSS disease. The RCOG guideline recommends preconceptual eye screening however there is no randomized evidence supporting routine over symptomatic screening.

Gallstones are common in SCD, secondary to red cell breakdown, and may lead to acute cholecystitis or pancreatitis.

Pulmonary hypertension carries a high mortality amongst patients with SCD. It occurs as a result of chronic haemolysis leading to endothelial damage, and localized areas of pulmonary infarction. An echocardiogram demonstrating an elevated tricuspid regurgitant jet velocity (TRV) $\geq$ 2.5 m/s can be an indicator of pulmonary hypertension. Maternal mortality may be as high as 30–50%. Effective contraceptive advice is vital in women with SCD and pulmonary hypertension, and the option of termination of pregnancy to protect maternal life should be considered if conception occurs.

Endocrine failure may result from iron overload or glandular vaso-occlusive damage. General treatment principles include replacing the particular hormone and optimising SCD management.

Infection is the most common cause of death in sickle cell disease sufferers, followed by stroke.

Complications in pregnancy

Maternal complications

Pregnancy and labour are associated with an increased risk of SCD related complications. Optimal management of the prenatal patient and multidisciplinary care within pregnancy, can help to manage these risks. Vaso-occlusive crises are more common in pregnancy, especially from the second trimester onwards and in the postpartum period. Exacerbating factors include dehydration from nausea and vomiting in pregnancy, stress of labour, uncontrolled preeclampsia, infections and haemorrhage. Between 2010 and 2011 the UK Obstetric Surveillance System (UKOSS) reported on the outcomes of pregnancies complicated by SCD. The incidence of painful crises was 52% and acute chest syndrome was 6%, whilst 12% were diagnosed with a UTI. All complications were more common in HbSS pregnancies compared to HbSC pregnancies, apart from acute chest syndrome.

SCD is thought to increase the risk of venous thromboembolism (VTE), with an incidence as high as 5.5%, compared with 0.1–0.2% in pregnancies not complicated by SCD. All women should receive thromboprophylaxis (low molecular weight heparin) if admitted to hospital. Antenatal thromboprophylaxis should be provided if further venous thromboembolism risk factors are present, as per RCOG guidance. Postnatal thromboprophylaxis is recommended for all women with SCD: 7 days duration following vaginal delivery and 6 weeks following

caesarean section. The UKOSS study reported no differences between the incidence of VTE between HbSS and HbSC pregnancies.

Patients with SCD generally have a lower baseline haemoglobin. This anaemia is worse in pregnancy due to normal physiological dilution and loss of red cells in vaso-occlusive crises, or transient red cell aplasia. High dose folic acid (5 mg) is important for neural tube defect prevention and should be continued throughout pregnancy due to the folate deficiency from haemolysis. Supplementation with oral iron should only be considered in confirmed cases of iron deficiency.

There is an increased incidence of hypertension and pre-eclampsia. The incidence of pre-eclampsia is highest in HbSS women (OR 2.43 95% CI 1.75–3.39) and they are more likely to have an eclamptic fit (OR 4.89 95% CI 1.97–12.16). Aspirin, at a dose of 75–150 mg daily, should be considered from 12 weeks' gestation in women with additional risk factors for pre-eclampsia.

Any underlying asymptomatic cardiopulmonary disease can be exposed due to the physiological stress of pregnancy. Respiratory changes include increased tidal volume and oxygen uptake, with a reduced functional residual capacity. Respiratory alkalosis can develop, which favours placental gas exchange, but can also trigger red cell sickling.

There may be an acceleration of end organ damage such as nephropathy or eye disease.

Cardiotocograph (CTG) monitoring in labour is advised due to an increased risk of still birth, placental abruption and compromised placental reserve, leading to fetal hypoxia. The incidence of caesarean sections is increased in women with SCD, secondary mainly to presumed maternal or fetal compromise. Routine caesarean sections are not recommended and should only be performed for the usual obstetric reasons. Several studies have demonstrated improved clinical outcomes after vaginal delivery, related to a reduction in operative risks and complications.

A systematic review and meta-analysis in 2015 reported a maternal mortality rate for women with HbSS almost six-fold higher than women without haemoglobinopathy (RR 5.98 95% CI 1.94–18.44). Better outcomes occur when women with SCD deliver in a hospital setting where access to expertise in managing medical complications is readily available. Pregnancy in women with pulmonary hypertension carries a mortality rate of approximately 30–40%, and all women with SCD should be screened by echocardiogram, at least once during pregnancy.

Different SCD types can be associated with different pregnancy risks. Studies have found that HbSC is associated with more favourable obstetric outcomes including fewer miscarriages, less preeclampsia, greater birth weights and an higher rate of live births when compared with HbSS disease. However there are no definitive prediction tools to determine which patients will develop severe SCD complications in pregnancy, therefore close monitoring is still important for all sickle genotypes.

Fetal complications

Miscarriage rates are thought to be elevated in women with SCD and have been reported to be as high as 36%. Intrauterine growth restriction (IUGR), preterm delivery and perinatal mortality are also more common.

There is a reported four-fold increase in the risk of stillbirth and small-for-gestational-age babies in women with HbSS and a two-fold increase in women with HbSC. This is likely to be the impact of vaso-occlusive events within the uteroplacental circulation; the umbilical arterial circulation is usually unaffected by this acutely. Red cell alloimmunization is more common in women with SCD, and can put the fetus at a higher risk of haemolytic disease of the newborn.

Women who require chronic opioid therapy during pregnancy, should be counselled on the risks of neonatal withdrawal syndrome shortly after birth.

Management of sickle cell disease

SCD should be managed within specialist multidisciplinary teams which include an obstetrician, haematologist, specialist midwife and specialist nurse with experience in managing high risk pregnancies. Each patient should have an individualised assessment and care plan recorded. The assessment should start with preconception counselling; to discuss potential SCD complications and risks to the pregnancy, review medications and include contraceptive advice for both sexes. Partner screening for sickle and other haemoglobin variants is encouraged at this stage.

Preconception counselling and contraception

Preconception counselling provides an opportunity to risk assess patients with SCD (women and men) of child bearing age; optimising disease management, including psychosocial aspects, and giving information on maternal and fetal risks associated with pregnancy. Early, comprehensive assessment of the medical condition is recommended, to optimise the maternal health for the pregnancy. Hydroxycarbamide is a chemotherapeutic agent that increases the production of fetal haemoglobin to mitigate against the effects of HbS. It has been used for selected patients with SCD since the 1990s and has been shown to reduce the frequency of sickling crises, admissions to hospital and blood transfusions. Due to concerns about teratogenicity, both men and women are advised to discontinue hydroxycarbamide for at least three months prior to attempting conception. Pregnancies have, however, been conceived on hydroxycarbamide without any associated fetal abnormalities. ACE inhibitor and iron chelating agents should be stopped prior to conception. If chelation is necessary secondary to iron overload the pregnancy should ideally be postponed. Vaccinations should be updated as necessary, although live vaccines should be postponed until the postnatal period.

For prenatal work up should suffice women with relatively mild disease. Women with more significant disease, i.e. evidence of end-organ damage, will require a more detailed multi-organ assessment, including a review of renal function, retinal disease, cardiac function (with an echocardiogram) and iron status.

Women should be informed of the impact that pregnancy might have on their SCD, with a possible increase in the frequency of crises and urinary tract infections. Risks to the pregnancy include preeclampsia, pulmonary embolism and anaemia. The associated fetal risks include the risk of the baby being affected by SCD, an increased rate of preterm delivery, fetal growth restriction and stillbirth. There will need to be a greater level of fetal surveillance with regular ultrasound scans and a higher rate of induction of labour and caesarean section.

Antenatal screening for haemoglobinopathies

All women in the UK are screened for SCD and other haemoglobin variants at their booking appointment. Those with positive results are contacted by a haemoglobinopathy counsellor and, offered an appointment for counselling, as part of UK national antenatal haemoglobinopathy screening programme introduced in 2001. Women with SCD, or carriers (sickle cell trait), are encouraged to have partner testing to determine the risk of sickle cell disease in the fetus. The aim of counselling is to provide information on the chances of having a child affected with SCD and the implications of this. Women whose partners are found to be HbAA (normal adult haemoglobin), can then be reassured that no further antenatal testing of the fetus is required. Women who are at risk of having a child with SCD (partner is a carrier or affected), should be referred promptly (preferably before 11 weeks), to discuss the option of prenatal diagnosis by chorionic villus sampling (CVS), or amniocentesis. Recently non-invasive prenatal diagnostic tests (NIPT) using cell-free DNA in maternal circulation has shown promise in detecting β-thalassemia from paternal mutations in maternal circulation and further work is required to assess this in SCD. Screening should occur as early as possible to allow options to be discussed, including termination of pregnancy where appropriate. The decision making for continuing the pregnancy can be affected by psychosocial factors, economic status, religious beliefs, experience from the presence of an affected child and the future reproductive chances of having a healthy child.

Obstetric management of women with sickle cell disease

Multidisciplinary antenatal care

Women with SCT can be managed as for low risk women (unless other risk factors are present), with an awareness of an increased risk of UTI.

Booking appointment: the schedule of antenatal care in women with SCD can be found in Table 2.

Booking history and assessment: the medical antenatal booking appointment should be undertaken as early as possible, to allow for an individualised assessment of the pregnant woman with SCD. A detailed medical and surgical history should be obtained. A medical history should include;

- SCD complications including details of established end organ damage
- sickling crisis type and frequency, and details of analgesia taken during self-managed crises
- a red cell transfusion history, including history of alloimmunization
- current medications and vaccination history (confirming that hydroxycarbamide, ACE inhibitors and iron chelating agents have been stopped prior to pregnancy)
- other co-morbidities (and referrals considered if necessary)
- a surgical history, highlighting joint surgery, splenectomy, or cholecystectomy (it is important to assess hip mobility in

Schedule of antenatal care for women with Sickle cell disease

Schedule of care		Tests
7–9 weeks	Early pregnancy unit	USS to confirm viability
Booking appointment 8–10 weeks	Midwife	Partner testing Routine booking bloods Extended red cell phenotyping (if no previous results are available)
Prenatal counselling appointment <10 weeks	Haemoglobinopathy counsellor and/or consultant haematologist	Referral to fetal medicine if appropriate
Medical booking appointment <10 weeks	Multidisciplinary team (obstetrician, haematologist, specialist midwife and nurse)	Retinal screening Echocardiogram (for second trimester) Urinalysis Renal and liver profile, reticulocyte counts and LDH Vitamin D levels 24 h urine if proteinuria or established renal disease Assess VTE risk Consider anaesthetic referral
Dating and screening scan 11–14 weeks	Fetal medicine or US department	CVS or amniocentesis if desired and indicated by partner testing
Medical ANC at 16 weeks, then 2-4 weekly until 32 weeks, and 1–2 weekly thereafter until delivery	Multidisciplinary team (obstetrician, haematologist, specialist midwife and nurse)	Renal and liver profile, FBC, reticulocyte count and LDH at least monthly or more frequently if crises Urinalysis ± MSU
Anomaly scan and uterine artery doppler at 20–22 weeks Growth scans at 28, 32,36 and 38 weeks	Fetal medicine or US department	Uterine artery dopplers at 20–22 weeks Growth, liquor volume, and umbilical artery doppler
Medical ANC 38–39 weeks	Arrange date for delivery by 40 weeks	Arrange cross-match for delivery if atypical red cell antibodies

Table 2

women with avascular necrosis, or previous hip replacements, in order to plan and discuss positions in labour)

If partner testing has not been performed it should be discussed alongside prenatal diagnosis. A detailed history of previous pregnancies will help to establish the likelihood of problems during the index pregnancy, and may help to plan mode of delivery.

A baseline haemoglobin level should be documented and evidence of iron overload explored. Repeated full blood count assessments should be performed throughout the pregnancy, the frequency depending on the woman's prenatal disease pattern, or clinical symptoms. Extended red cell phenotyping (including full rhesus typing C, D, E and Kell typing) should occur at booking and re-evaluated at 24–28 weeks, during delivery and before blood transfusions. Other baseline investigations include renal function and liver function tests, ferritin, HIV, hepatitis and urine protein/creatinine ratio. Blood pressure should be monitored at every visit and a baseline oxygen saturation recorded and, if low, investigated with echocardiogram and lung function testing. Monthly screening for asymptomatic bacteriuria should be performed with urinalysis and urine culture.

Insufficient evidence exists regarding the routine use of antiplatelet therapy to treat the thrombotic effects of SCD on the placenta. The use of antiplatelet agents has been shown to moderately reduce the risk of pre-eclampsia and preterm births <34 weeks, but there is no clear evidence of its benefit with regard to these pregnancy complications in the subgroup of women with SCD. However, 75 mg aspirin should be offered to women with SCD who have any other, additional, risk factors for pre-eclampsia, from 12 weeks' gestation. If partner testing has not been performed it should be encouraged, and the option of prenatal diagnosis should be re-discussed if required.

All women should have a VTE assessment performed at booking. SCD is considered an intermediate risk factor in the RCOG guideline (37a: *Reducing the Risk of Venous Thromboembolism during Pregnancy and the Puerperium),* hence thromboprophylaxis should be considered antenatally if additional risk factors are present. All women with SCD should be commenced on LMWH if admitted to hospital, unless contraindicated.

General advice and recommendations: all women should be advised to avoid precipitating factors for SCD crises including overexertion, stress, dehydration, and extremes of temperature. Women should be advised to have a low threshold for attending hospital for a crisis that cannot be managed with simple analgesia at home. Penicillin V 250 mg twice daily is recommended regardless of whether it is taken by the patient outside of pregnancy. Vitamin D (10 mcg) supplementation daily is advised, and higher doses used if there is proven deficiency. Patients with SCD can use non-steroidal anti-inflammatory drugs (NSAIDs) between 12 and 28 weeks and postnatally, if necessary. All women should be advised to attend for routine whooping cough and flu vaccinations at 28 weeks' gestation.

Timing of delivery: there is no specific data on the optimal timing of delivery for women with SCD. The general recommendation is that induction of labour should be offered between 38 and 40 weeks, as for other high risk pregnancies. Induction of labour is offered due to increased perinatal mortality in later pregnancy and an increased risk of abruption, preeclampsia, cardiomyopathy, and sickling crises. Earlier delivery than this would be for obstetric or significant medical indications.

Predicting adverse factors in pregnant women with sickle cell disease

Variations in the clinical phenotypes of SCD can make predicting the course of the pregnancy difficult. However factors that have been associated with future pregnancy complications include:

- multiple pregnancy
- frequent vaso-occlusive crises
- age >25 years
- red cell alloimmunization
- prior thromboembolism
- pulmonary hypertension
- low baseline oxygen saturations <94%
- multiparity
- genotypes SS, Sβ and SC

Management of acute sickle cell complications

Painful crises (bony crises)

There is consistent evidence that painful crises occur more commonly in pregnancy, the UKOSS study reporting painful crises in 76.5% of HbSS pregnant women and 27.3% of HbSC patients. The incidence of crises in pregnancy increases as the pregnancy advances and continues through to the postnatal period. Crises can also occur in women with historically mild disease, therefore vigilance is important and crises should be managed quickly and aggressively (Table 3). Women should be admitted to the medical wards in early pregnancy and then labour ward (ideally obstetric HDU for initial assessment), from the second trimester. Regardless of location, women with SCD require timely multidisciplinary care, with early recourse to the intensive care unit for the very unwell patient, or for those failing to respond to initial therapeutic measures. A history should illicit the patient's baseline disease, acknowledge the symptom as typical sickle pain and identify triggers e.g. infection. Note that the white cell count (WBC) is commonly raised in SCD, and cannot be relied on alone to support a suspicion of infection. Any atypical pain, chest symptoms or abnormal neurology should alert care-givers to the possibility of acute chest syndrome, sepsis or stroke: as these require immediate intervention. Examination should focus on the site of pain, as well as ensuring a thorough systemic review is conducted.

Despite improvements in patient care, certain management issues are yet to be resolved, including the optimal analgesic regime for SCD and the best policy for prophylactic blood transfusions. There is no specific RCT evidence for the management of painful crises in pregnancy, so local or national SCD protocols should be employed. The key features of management in acute crises include adequate analgesia, rehydration, oxygenation and early treatment of suspected infections.

Analgesia should be administered promptly within 30 min of hospital admission and be therapeutic within 60 min. The WHO pain ladder should help guide management, alongside the patient's own experience of analgesia in sickle crises and the pain team. Analgesia should not be withheld, if evidence of a crisis is presented, due to potential 'drug seeking' concerns.

Outline of management of acute pain in sickle cell crisis during pregnancy

Rapid clinical assessment
If pain is severe and oral analgesia is not effective, give strong opioids (e.g. morphine).
  Give adjuvant non-opioid analgesia: paracetamol, NSAID (if 12–28 weeks of gestation).
  Prescribe laxatives, antipruritic and antiemetic if required.
Monitor pain, sedation, vital signs, respiratory rate and oxygen saturation every 20–30 min, until pain is controlled and signs are stable, then monitor every 2 h (hourly if receiving parenteral opiates).
Give a rescue dose of analgesia if required. If respiratory rate is less than 10/min, omit maintenance analgesia; consider naloxone.
  Consider reducing analgesia after 2–3 days and replacing injections with equivalent dose of oral analgesia.
Discharge the woman when pain is controlled and improving without analgesia, or on acceptable doses of oral analgesia.
Arrange any necessary home care and outpatient follow-up appointment.

Table 3

NSAIDs are generally avoided, but can be used in individual cases between 12 and 28 weeks if required. Use after 30 weeks' gestation, raises concerns with regards to premature closure of the ductus arteriosus in the fetus. Pethidine should be avoided in women with SCD because it has a longer lasting depressive effect and is metabolised to norpethidine, a renally excreted cerebral irritant causing seizures. Cases are reported of prolonged Entonox use (>1 h)causing neuropathies in patients with low vitamin B12, although it can be considered for short-term use whilst arranging alternative analgesia.

Rehydration should be oral, and intravenous (IV) if necessary, bearing in mind the risk of fluid overload in women with co-existing pre-eclampsia. In SCD crises, a suggested rehydration guideline could be 60 ml/kg/24 h (oral or IV). If sepsis is suspected, antibiotics should be commenced empirically, whilst awaiting culture results. All women admitted with a crisis should be commenced on low molecular weight heparin (LMWH). Incentive spirometry every 2 h helps to reduce respiratory complications during hospital admissions. Oxygen should be given if pulse oximetry shows the oxygen saturation is below the patient's known steady-state level, or <95%. Two small randomized control trials concluded that there were no clinical benefits from routine oxygen administration.

Investigations should include full blood count (FBC), renal and liver function test, LDH levels and a reticulocyte count. A chest X-ray should be considered if there are chest symptoms or signs. A septic screen may be required depending on the circumstances of admission. During the admission, regular assessments of pain, sedation, fluid balance and general observations, particularly respiratory rate and oxygen saturations should be documented. The frequency of observations will depend on the severity of symptoms and dose of opioids.

Saturations of 94% or below in room air, constitute a medical emergency and should prompt a review regarding the diagnosis of acute chest syndrome. Further investigations, such as arterial blood gases (ABG) and chest X-ray, would be necessary to investigate hypoxaemia. During a sickle crisis fetal morbidity and mortality increases, and CTG monitoring of the fetus is indicated beyond 24–26 weeks' gestation. Antenatal corticosteroids should also be considered, as sickle crises can trigger preterm birth and premature rupture of membranes.

Acute chest syndrome

Acute chest syndrome (ACS) is a medical emergency and requires prompt identification. It has been reported to occur in 7–20% of pregnancies complicated by SCD. It is a potentially life threatening complication, defined as an acute illness characterized by fever, audible lung crackles and respiratory symptoms, accompanied by a new infiltrate on chest X-ray. ACS may mimic pneumonia or pulmonary embolism. Hypoxia is considered a marker of severity. If ACS is suspected, close monitoring should be undertaken and the haematology team contacted urgently. Treatment includes antibiotics, oxygen, hydration and transfusion. Urgent exchange transfusion may be required, however in milder cases top-up transfusion may suffice. Women with ACS in pregnancy can be managed in an obstetric HDU or a medical HDU, as respiratory support is sometimes required.

Other complications in pregnancy

Pulmonary embolism

Pulmonary embolism (PE) is more common than DVT in women with SCD. Recent evidence suggests that women with sickle cell trait also share an increased incidence of venous thromboembolism with a pro-thrombotic tendency similar to that found in carriers of the factor V Leiden mutation. PE can be difficult to differentiate from ACS, and a therapeutic dose of LMWH should be commenced before diagnosis is later confirmed or excluded by appropriate investigations (ECG, chest X-ray and VQ scan).

Stroke

There is an increased risk of infarctive and haemorrhagic stroke in women with SCD. Any woman presenting with neurological impairment should be investigated urgently with brain imaging, and the haematology consultant contacted, as emergency exchange blood transfusion is required for overt stroke to help reduce long term neurological sequelae.

The role of blood transfusion in pregnancy

Blood transfusions are used to decrease the percentage of sickled cells in the microvasculature and improve the patient's oxygen carrying capacity. Oxygen delivery approaches that of non-affected women at a HbS level of less than 20%. However, this target would require regular, multiple blood transfusions antenatally, or at least one large volume exchange transfusion. Regardless of this, it would be difficult to maintain normal haemoglobin parameters, as donor erythrocytes have a limited lifespan (90 days for donor erythrocytes versus normal erythrocytes 120 days and HbS erythrocytes 17 days), alongside an ongoing chronic production of HbS containing erythrocytes.

Evidence reports 30%–40% of pregnant women with SCD required a blood transfusion during their pregnancy. UKOSS data confirms that transfusions are more likely in HbSS pregnancies

(43.1%) when compared to pregnancies of women with HbSC (6.8%).

The role of routine prophylactic blood transfusion in pregnant women with SCD remains a controversial issue. A Cochrane review of prophylactic versus selective blood transfusions for SCD in pregnancy concluded that only one study was adequately designed to assess this. A prospective RCT, with 37 women in each arm, found that prophylactic transfusions may reduce the incidence of painful crises, but had little effect on the overall outcome for mother and baby. In more recent times authors are supporting prophylactic red blood cell transfusion in select high risk cases; e.g. a history of perinatal mortality/morbidity, severe anaemia, chronic organ dysfunction. The goal in this situation would be to provide transfusions every 3–4 weeks, with the aim of maintaining a haemoglobin level at 10–11 g/dl and HbS $\leq$30%. A meta-analysis of five population studies raised concerns that the previous information about prophylactic blood transfusions in pregnancy was inaccurate due to a variation in blood transfusion strategies. This meta-analysis, and other recent reviews, have suggested that prophylactic transfusions could reduce vaso-occlusive pain, chest complications, pyelonephritis, preterm birth, perinatal and maternal mortality. Women already established on a regular blood transfusion regime, for example those with severe SCD, or as part of stroke prevention, should continue their regime throughout pregnancy. Common medical and obstetric reasons for transfusion include;

- severe antenatal anaemia, or low haemoglobin at term, particularly if a caesarean section is planned (ideally > Hb 10 g/dl).
- frequent crises, refractory painful crises (relapse in <1 week, no improvement in >10 days)
- recurrent ACS
- multiple pregnancy
- intrapartum complications e. g haemorrhage
- women with reticulocytopenia (e.g. from Parvovirus B19 infection).
- women with ongoing pre-eclampsia despite initial treatment

There is no specific haemoglobin level at which blood transfusions must be given; in general a haemoglobin level below 6 g/dl or a fall in >2 g/dl are criteria for transfusion. The decision for transfusion is usually shared between the haematology and obstetric team. Based on the clinical urgency of the situation, a decision has to be made between simple transfusion and exchange transfusion. Many women with SCD in pregnancy have never been transfused and it is important to establish a woman's views on transfusion at the booking visit. Multiple transfusions carry a risk of alloimmunisation, transfusion reaction, transmission of viruses, lung injury, iron overload and might even provoke acute sickling due to hyperhaemolysis syndrome or venous thromboembolism. Standard precautions during transfusions include keeping the patient warm with blood warmers, and ensuring that blood is CMV negative and has undergone extended phenotype matching, to reduce the risk of alloimmunisation.

Intrapartum care of a woman with SCD

Women with SCD should be delivered on an obstetric unit that is equipped to manage high risk pregnancies. The risk of crises (bony and ACS) increases in labour, especially if protracted. Dehydration, pain, extremes of temperature and sepsis can contribute to this risk. If crisis occurs in labour, the progress of labour should be assessed and delivery expedited if not imminent. Anecdotal reports suggests that at the onset of fetal distress (decelerations) on the CTG, transfusion may help to resolve the suspected fetal hypoxaemia.

On admission, all women with SCD should be reviewed by a member of the on-call obstetric team and the plan for delivery reviewed. The on-call anaesthetist and haematologist should also be informed of the admission. Intravenous access should be established and bloods sent for group and save (+/- cross match depending on presence of antibodies), FBC, renal and liver profile, reticulocyte count and LDH to establish a baseline. Early intravenous cannulation is important as venous access can be difficult due to previous admissions, cannulations and transfusions. Women known to have 'difficult' access should be assessed in the antenatal period in order to plan IV access and to consider central access if necessary. Avoiding dehydration is important and fluids should be monitored with a fluid balance chart. Women should be encouraged to drink fluids in labour to avoid dehydration; if this is not possible then intravenous fluids should be commenced. Routine bladder catheterisation should however be avoided and should only be considered for the usual obstetric reasons.

Adequate analgesia should be provided (avoiding pethidine) and the woman's vital signs, including oxygen saturations, should be monitored regularly. Increased oxygen demands are expected in labour, but if oxygen saturations are <94% then supplemental oxygen should be provided and further investigated with ABG, followed by and liaison with the haematology team.

Continuous electronic fetal monitoring in labour is recommended, because of the increased incidence of fetal hypoxia, and increased prevalence of fetal growth restriction and stillbirth in SCD. Fetal blood sampling can be performed to assess fetal condition if felt necessary, provided labour is progressing satisfactorily.

Labour should otherwise be managed according to local protocols and NICE guidelines.

Analgesia and anaesthesia

All types of analgesia for labour can be offered to women with SCD, apart from pethidine. Other opiates can be used in the normal way. In complex cases, and in women with other comorbidities e.g. history of stroke or requiring antenatal LMWH prophylaxis, an anaesthetic referral should be considered in the antenatal period. The use of intermittent opioids in labour, may prove inadequate, therefore regional anaesthesia is recommended for the best pain relief. Caesarean section should be performed under regional block wherever possible, as the risks of general anaesthetic in pregnant women with SCD are increased over the general population. General anaesthesia carries a higher risk of iatrogenic hypoxia and increases the risk of postnatal crises. Attention to fluid balance, pain relief and patient temperature in theatre and recovery, will reduce the risk of sickling associated with a caesarean section.

Post-partum care and contraception

Recovery

Women with SCD require careful post-partum monitoring, particularly if they have had a prolonged or complicated labour or a general anaesthetic. In the immediate postpartum period, patients should be observed for PPH, hypovolaemia, infection (wound, UTI, endometritis), venous thromboembolism and sickle crises. Sickle crises occur in up to 25% of women in the postpartum period, therefore regular assessments of pain and observations should be undertaken, hourly for at least 4 h post-delivery. Discharge from the labour ward should only occur after medical review. Women who suffer a crisis, or who are unwell in the peri-partum period, should be monitored in an obstetric HDU for at least 24 h post-delivery. Twenty-three per cent of SCD women had an admission to ITU in the peripartum period.

Postnatal care

Postnatal care should be in line with routine care and women should be supported to establish breast feeding. Careful attention should be paid to analgesia. Women with SCD should be encouraged to eat, drink and rest as much as possible. All women should receive thromboprophylaxis in the form of early mobilisation, antithrombotic stockings and LMWH for 7 days after a vaginal delivery and 6 weeks following a caesarean section. A full blood count should be checked before discharge. All women should expect to remain as an inpatient for approximately 2–3 days postnatally, and be reviewed prior to discharge by the obstetric and haematology teams, with a plan for community follow-up within 7 days of discharge. Hydroxycarbamide should be avoided during lactation as it passes into breast milk.

Neonatal screening

Over 300 infants are born in the UK each year with sickle cell disease, detected either through prenatal diagnosis or newborn screening. The baby should be assessed by a neonatologist and haemoglobin electrophoresis performed. Infants with SCD are at an increased risk of infection and penicillin prophylaxis is commenced at 3 months of age to decrease the risks of pneumococcal septicaemia.

Contraception

Contraception should be prescribed for all women who request it, in line with the Faculty of Sexual and Reproductive Healthcare guidelines. In general, progestogen-only preparations (pills, injectables, implants and the levonorgestrel intrauterine system (IUS)), and barrier methods, are considered the methods of choice in women with SCD. The Depo-provera injection and IUS have also been shown to have the added benefit of reducing pain associated with menstrual periods. The combined oestrogen and progesterone preparations are classified as UK Medical Eligibility Category (UKMEC) 2 for women with SCD, due to their increased risk of VTE. The copper IUD is also categorised as UKMEC 2 and should be considered in women who cannot, or choose not to, use a hormonal method, due to concerns with regards to increased rates of pelvic infection and chance of menorrhagia worsening anaemia. Women with SCD can be offered immediate post-partum IUCD or IUS insertion after LSCS or vaginal birth with the usual indications and contraindications. In women who have completed their family, sterilisation either at CS or postnatally should also be offered.

Summary

Sickle cell disease (SCD) is a multisystem disease and pregnancy carries significant risks for mother and baby. Bony crises and chest crises occur more frequently in pregnancy. Pregnant women with SCD also have a higher risk of pre-eclampsia, pulmonary embolism, caesarean section and maternal mortality. Fetal complications include higher rates of miscarriage, prematurity, growth restriction and stillbirth.

Preconceptual care is a vital step in optimising pregnancy outcomes. Antenatal care should be provided through a multidisciplinary team, with the aim of minimising the frequency of sickling crises, monitoring for end organ damage, and performing fetal surveillance.

Despite the presence of several maternal and fetal complications associated with pregnancy in sickle cell patients, careful management has led to significant improvements in patient outcomes. Despite this, certain management issues remain the subject of debate, including best analgesic regimes to manage crises and the role of prophylactic blood transfusions. ◆

FURTHER READING

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Practice points

- HbSS is associated with a 4-fold increase in the risk of stillbirth and a six-fold increased risk of maternal mortality. Multidisciplinary involvement is key to optimise health and limit these risks
- Preconception counselling is an important step in formulating an individualised risk assessment, optimising disease management, reviewing medications and discussing the risks associated with pregnancy and to the infant
- Pregnant women should be made aware of the increased likelihood of crises, need for blood transfusions, risk of fetal growth restriction, induction of labour, fetal distress in labour and caesarean section
- Sickle crises should be assessed and managed promptly and healthcare providers should be vigilant for signs of acute chest syndrome, sepsis and stroke
- Pregnancy in women with pulmonary hypertension carries a mortality rate of approximately 30—40% and all women with SCD should be screened with an echocardiogram at least once during pregnancy.
- Prophylactic transfusions remain controversial, with strengthening opinion that they may reduce the risk of painful crises, chest complications, pyelonephritis, preterm birth, perinatal and maternal mortality. Common practice, however, remains using prophylactic transfusions in select high risk pregnancies (chronic organ dysfunction, previous poor obstetric history)
- Women with SCD should be delivered on an obstetric unit and caesarean section should only be offered for the usual obstetric indications
- There is a higher incidence of pulmonary embolism in people with SCD and even carriers (sickle cell trait) may also share an increased risk of venous thromboembolism
- All women should receive thromboprophylaxis in the form of LMWH during hospital admissions and for 7 days after a vaginal delivery, or 6 weeks after a Caesarean section
- Progestogen-only preparations (pills, injectables, implants and the levonorgestrol IUS), and barrier methods, are considered the first line choice of contraception for women with SCD