



Royal College of
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Management of Sickle Cell Disease in Pregnancy

Green-top Guideline No. 61

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Management of Sickle Cell Disease in Pregnancy

This is the first edition of this guideline.

1. Purpose and scope

The purpose of this guideline is to describe the management of pregnant women with sickle cell disease (SCD). It will include preconceptual screening and antenatal, intrapartum and postnatal management. It will not cover the management of women with sickle cell trait.

2. Background and introduction

SCD is a group of inherited single-gene autosomal recessive disorders caused by the ‘sickle’ gene, which affects haemoglobin structure.¹ SCD has its origins in sub-Saharan Africa and the Middle East,^{2,3} hence it is most prevalent in individuals of African descent as well as in the Caribbean, Middle East, parts of India and the Mediterranean, and South and Central America. Owing to population migration, SCD is now of increasing importance worldwide and there are increasing numbers of affected individuals in Europe and the USA.⁴⁻⁷

The term SCD includes sickle cell anaemia (HbSS) and the heterozygous conditions of haemoglobin S and other clinically abnormal haemoglobins. These include combination with haemoglobin C (giving HbSC), combination with beta thalassaemia (giving HbSB thalassaemia) and combination with haemoglobin D, E or O-Arab. All of these genotypes will give a similar clinical phenotype of varying severity.³ Haemoglobin S combined with normal haemoglobin (A), known as sickle trait (AS), is asymptomatic, except for a possible increased risk of urinary tract infections and microscopic haematuria, and is not considered further in this guideline.

SCD is the most common inherited condition worldwide. About 300 000 children with SCD are born each year;^{8,9} two-thirds of these births are in Africa.¹⁰ In the UK, it is estimated that there are 12 000–15 000 affected individuals and over 300 infants born with SCD in the UK each year who are diagnosed as part of the neonatal screening programme.⁷ There are approximately 100–200 pregnancies in women with SCD per year in the UK; pregnancy outcome in this group is currently being assessed by the UK Obstetric Surveillance System [<https://www.npeu.ox.ac.uk/ukoss/completed-surveillance>].

The pathophysiology of SCD is a consequence of polymerisation of the abnormal haemoglobin in low-oxygen conditions, which leads to the formation of rigid and fragile sickle-shaped red cells. These cells are prone to increased breakdown, which causes the haemolytic anaemia, and to vaso-occlusion in the small blood vessels, which causes most of the other clinical features, including acute painful crises. Other complications of SCD include stroke, pulmonary hypertension, renal dysfunction, retinal disease, leg ulcers, cholelithiasis and avascular necrosis (which commonly affects the femoral head and may necessitate hip replacement). SCD was previously associated with a high early mortality rate, but now the majority of children born with SCD in the UK live to reproductive age and average life expectancy is at least the mid-50s.^{11,12}

3. Identification and assessment of evidence

This RCOG guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines.¹³⁻¹⁵ Medline, Embase, the Cochrane Database of Systematic Reviews, the Cochrane Control Register of Controlled Trials (CONTROL), the Database of Abstracts of Reviews and Effects (DARE), the ACP Journal Club and the Ovid database were searched for relevant randomised controlled trials, systematic reviews and meta-analyses between 1980 and August 2009. Search terms included: ‘sickle cell’, ‘hydroxycarbamide’, ‘antenatal’, ‘pregnancy’, ‘intrapartum’, ‘penicillin prophylaxis’, ‘ACE inhibitor’, ‘transfusion’, ‘ultrasound’, ‘Doppler’, ‘echocardiogram’, ‘anticoagulation’, ‘prophylaxis’, ‘sickle cell and risk factors’, ‘preconceptual’ and ‘sickle cell crisis’ and included all relevant MeSH terms and subheadings. The search was limited to humans and

the English language. The National Library for Health and the National Guidelines Clearing House were also searched for relevant guidelines. Where possible, recommendations are based on available evidence; areas where evidence is lacking are annotated as good practice points (designated by a tick).

4. Preconception care

4.1 What are the additional risks to the woman and baby?

SCD is associated with both maternal and fetal complications and is associated with an increased incidence of perinatal mortality,¹⁶⁻²¹ premature labour,¹⁶⁻²² fetal growth restriction¹⁶⁻²³ and acute painful crises during pregnancy.^{17-19,24,25} Some studies also describe an increase in spontaneous miscarriage,²² antenatal hospitalisation,²³ maternal mortality,²⁶ delivery by caesarean section,^{23,26} infection, thromboembolic events²⁷ and antepartum haemorrhage.²⁶ An increased risk of pre-eclampsia and pregnancy-induced hypertension has been described in some studies^{1,6,18,19,23,26} but not in others.^{17,20,22} In HbSC there are fewer reported adverse outcomes, but there is evidence of an increased incidence of painful crises during pregnancy,²⁸ fetal growth restriction, antepartum hospital admission and postpartum infection.²¹

4.2 What is the importance of planning pregnancy and how can outcomes for the woman and baby be improved?

From adolescence, the intentions of women with SCD regarding pregnancy and contraception should be documented at each contact with their sickle care team.

D

Women with SCD should be seen preconceptually by a sickle specialist to receive information about how SCD affects pregnancy and how pregnancy affects sickle cell disease, and how to improve outcomes for mother and baby. This consultation should include optimisation of management and screening for end organ damage.

D

Primary care physicians have a key role in preconceptual screening, including the provision of contraceptive advice. Women with SCD should receive not only the general preconceptual care which is given to all women but also additional advice about vaccinations, medications and crisis avoidance.

✓

Advise women to have a low threshold for seeking medical help.

✓

Reproductive planning and contraceptive choice should be part of the regular outpatient consultation in the sickle cell clinic.

SCD is a chronic, lifelong condition and there are recommendations for clinical care which apply to all patients, including women planning to become pregnant.²⁶ Women should be reviewed at least annually by a specialist sickle service for the monitoring of chronic disease complications and the imparting of information.²⁹

Information that is particularly relevant for women planning to conceive includes:

- the role of dehydration, cold, hypoxia, overexertion and stress in the frequency of sickle cell crises
- how nausea and vomiting in pregnancy can result in dehydration and the precipitation of crises
- the risk of worsening anaemia, the increased risk of crises and acute chest syndrome (ACS) and the risk of increased infection (especially urinary tract infection) during pregnancy
- the increased risk of having a growth-restricted baby, which increases the likelihood of fetal distress, induction of labour and caesarean section^{16,17,18,22,23}
- the chance of their baby being affected by SCD
- an up-to-date assessment for chronic disease complications.

Evidence level 4

The assessment for chronic disease complications should include:

- Screening for pulmonary hypertension with echocardiography. The incidence of pulmonary hypertension is increased in patients with SCD and is associated with increased mortality.³⁰ A tricuspid regurgitant jet velocity of more than 2.5 m/second is associated with a high risk of pulmonary hypertension.³¹ Screening should be performed if this has not been carried out in the last year.²⁹
- Blood pressure and urinalysis should be performed to identify women with hypertension and/or proteinuria. Renal and liver function tests should be performed annually to identify sickle nephropathy and/or deranged hepatic function.²⁹
- Retinal screening. Proliferative retinopathy is common in patients with SCD, especially patients with HbSC, and can lead to loss of vision.³² There is no randomised evidence on whether routine screening should be performed or if patients should be screened only if they experience visual symptoms, but we recommend that women are screened preconceptually.
- Screening for iron overload. In women who have been multiply transfused in the past or who have a high ferritin level, T2* cardiac magnetic resonance imaging may be helpful to assess body iron loading. Aggressive iron chelation before conception is advisable in women who are significantly iron loaded.
- Screening for red cell antibodies. Red cell antibodies may indicate an increased risk of haemolytic disease of the newborn.

Evidence level 4

4.3 What is the importance of genetic screening and what procedure(s) are involved?

Women and men with SCD should be encouraged to have the haemoglobinopathy status of their partner determined before they embark on pregnancy. If identified as an ‘at risk couple’, as per National Screening Committee guidance, they should receive counselling and advice about reproductive options.

D

General practitioners have a key role to play in partner screening and genetic counselling. Women should be encouraged to have the haemoglobinopathy status of their partner tested. If a partner is a carrier of, or affected by, a major haemoglobinopathy, the couple should receive appropriate counselling regarding the risk of having affected offspring (Table 1).³³ The methods and risks of prenatal diagnosis and termination of pregnancy should be discussed with the couple.³⁴ In addition, they should receive counselling about the availability of preimplantation genetic diagnosis and referred for this if appropriate. Partners will not always be available or willing to undergo preconceptual testing. Women with SCD should be aware that if their partner’s status is unknown, the fetus should be treated as high risk for a haemoglobinopathy.³³ Sperm donors should also be screened for haemoglobinopathies for couples considering in vitro fertilisation.

Further information can be obtained from the NHS Sickle Cell & Thalassaemia Screening Programme website³³ or the Programme’s *Handbook for Laboratories*.³⁵

Table 1. Conditions requiring counselling when the mother is affected by SCD³⁵

Condition	
HbS	Carrier state in partner which requires referral for counselling and offer of prenatal diagnosis
β thalassaemia	
O-Arab	
HbC	
D-Punjab	
DB thalassaemia	Carrier state in partner which requires counselling and may need further investigation
Lepore	
HbE	
Hereditary persistence of fetal hemoglobin (HPFH)	

4.4 What is the importance of antibiotic prophylaxis and immunisation?

Penicillin prophylaxis or the equivalent should be prescribed.

D

Vaccination status should be determined and updated before pregnancy.

D

Patients with SCD are hyposplenic and are at risk of infection, in particular from encapsulated bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae*. There is clear evidence that penicillin prophylaxis is of benefit in young children with SCD,³⁶ but there is no randomised trial evidence in older patients or pregnant women. UK guidance is that daily penicillin prophylaxis is given to all patients with SCD, in line with the guidelines for all hyposplenic patients.^{29,37} People who are allergic to penicillin should be recommended erythromycin.

Evidence level 4

In addition, women should be given *H. influenza* type b and the conjugated meningococcal C vaccine as a single dose if they have not received it as part of primary vaccination. The pneumococcal vaccine (Pneumovax®, Sanofi Pasteur MSD Limited, Maidenhead, UK) should be given every 5 years.³⁸

Evidence level 1

Hepatitis B vaccination is recommended and the woman's immune status should be determined preconceptually. Women with SCD should be advised to receive the influenza and 'swine flu' vaccine annually.²⁹

Evidence level 4

Penicillin prophylaxis and vaccinations are usually monitored and administered in primary care, but should be reviewed by the specialist haematologist/obstetrician during pregnancy.

4.5 What vitamin supplements should be given?

Folic acid (5 mg) should be given once daily both preconceptually and throughout pregnancy.

D

Folic acid is recommended in all pregnant women to prevent neural tube defects.³⁹

Evidence level 1

Folic acid at a dosage of at least 1 mg daily is recommended for women with SCD outside pregnancy in view of their haemolytic anaemia, which puts them at increased risk of folate deficiency.⁴⁰

Evidence level 3

Folic acid 5 mg daily should be prescribed during pregnancy to reduce the risk of neural tube defect and to compensate for the increased demand for folate during pregnancy.⁴¹

Evidence level 4

4.6 What medications should be reviewed preconceptually?

Hydroxycarbamide (hydroxyurea) should be stopped at least 3 months before conception.

D

Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers should be stopped before conception.

D

Hydroxycarbamide has been demonstrated to decrease the incidence of acute painful crises and ACS in individuals with severe clinical manifestations of SCD.⁴² Hydroxycarbamide is teratogenic in animals and, consequently, current UK advice is that women with SCD on hydroxycarbamide should use effective contraception and stop taking hydroxycarbamide 3 months before they conceive. There are published reports of women receiving hydroxycarbamide both for SCD and for other indications becoming pregnant, some of whom have continued the medication throughout pregnancy without adverse effects on the baby. While pregnancy should be avoided in women on hydroxycarbamide, these case reports provide help when counselling women: if they become

Evidence level 3

pregnant while taking hydroxycarbamide, it should be stopped and a level 3 ultrasound performed to look for structural abnormality, but termination is not indicated based on exposure to hydroxycarbamide alone.^{43,44}

Evidence level 3

Renal dysfunction, proteinuria and microalbuminuria are common in SCD. Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are used routinely in patients with SCD with significant proteinuria (protein-creatinine ratio of more than 50 mg/mmol), since there is evidence that these agents reduce proteinuria and microalbuminuria.^{45,46} These drugs are not safe in pregnancy and should be stopped in women who are trying to conceive.

5. Antenatal care

5.1 General aspects

This section should be read in conjunction with National Institute for Health and Clinical Excellence (NICE) clinical guideline no. 62: *Antenatal care. Routine care for the healthy pregnant woman*.⁴⁷

Antenatal care should be provided by a multidisciplinary team including an obstetrician and midwife with experience of high-risk antenatal care and a haematologist with an interest in SCD.

D

Women with SCD should undergo medical review by the haematologist and be screened for end organ damage (if this has not been undertaken preconceptually).

D

Women with SCD should aim to avoid precipitating factors of sickle cell crises such as exposure to extreme temperatures, dehydration and overexertion.

D

Persistent vomiting can lead to dehydration and sickle cell crisis and women should be advised to seek medical advice early.

D

The influenza vaccine should be recommended if it has not been administered in the previous year.

D

Many women become pregnant without preconceptual care. Therefore, all of the actions outlined in section 4, including vaccinations, review of iron overload and red cell autoantibodies, should take place as early as possible during antenatal care. Live attenuated vaccines should be deferred until after delivery.

The development of multidisciplinary care seems to be associated with an improvement in maternal and fetal outcomes. The establishment of comprehensive sickle cell centres in the USA was associated with decreases in the spontaneous miscarriage and perinatal death rates and incidence of preterm labour.²⁴ Active prenatal management in an African setting, which included providing information and education about SCD, improving nutritional status, malaria prevention and early detection of bacterial infection, has also been shown to have a positive impact on SCD-related morbidity and mortality.⁴⁸ A retrospective nationwide data analysis of all pregnancy-related discharges with the diagnosis of SCD for 2000–2003 in the USA also demonstrated improved outcomes, principally as a result of committed multidisciplinary care.²⁶

Evidence level 2

In UK practice, provision of multidisciplinary care is complicated by the wide variation in prevalence of SCD in different parts of the country. If there is a relevant multidisciplinary team available within reasonable travelling distance, women should go there. If this is not available, women should be cared for by ‘high-risk’ teams who have shared care arrangements and shared protocols with the specialist teams.

Women with HbSC experience fewer adverse outcomes, but there is still evidence of an increased incidence of painful crises during pregnancy,²⁸ fetal growth restriction, antepartum hospital admission and postpartum

infection.²¹ Although outcomes among women with HbSC are better than in women with HbSS, some do have serious, unpredictable complications, and women with HbSC should therefore be monitored in the same way as those with HbSS. There is a paucity of data on pregnancy outcomes in women with HbSB thalassaemia, HbSD, HbSE or HbSO-Arab, but anecdotal evidence indicates that such women should also be monitored and treated with the same level of vigilance and care.

5.2 *Antenatal haemoglobinopathy screening*

If the woman has not been seen preconceptually, she should be offered partner testing. If the partner is a carrier, appropriate counselling should be offered as early as possible in pregnancy – ideally by 10 weeks of gestation – to allow the option of first-trimester diagnosis and termination if that is the woman's choice.

D

It is essential that any woman who has a potentially affected infant (i.e. their partner is a carrier or is affected by a significant haemoglobinopathy) is aware of this and receives appropriate counselling. Prenatal diagnosis should be offered as early in pregnancy as possible. Partner status and subsequent counselling should be clearly documented in the notes. Further information can be obtained on the NHS Sickle Cell & Thalassaemia Screening Programme website,²³ which includes information about the laboratories that can perform prenatal diagnostic testing. The objective of the screening programme is to ensure that screening tests are offered by 8–10 weeks of pregnancy by primary care or maternity services.

5.3 *What medication should be given during pregnancy?*

If women have not undergone a preconceptual review, they should be advised to take daily folic acid and prophylactic antibiotics (if not contraindicated). Drugs that are unsafe in pregnancy should be stopped immediately.

D

Iron supplementation should be given only if there is laboratory evidence of iron deficiency.

D

Women with SCD should be considered for low-dose aspirin 75 mg once daily from 12 weeks of gestation in an effort to reduce the risk of developing pre-eclampsia.

D

Women with SCD should be advised to receive prophylactic low-molecular-weight heparin during antenatal hospital admissions.

D

While older studies demonstrated iron deficiency to be common in SCD, a more recent study examining a small number of pregnant women with SCD showed no evidence of iron deficiency, and some of these women were iron overloaded.^{49,50} Iron status should be assessed and iron supplementation should be recommended only if there is evidence of iron deficiency.

Women who are at increased risk of pre-eclampsia are advised to take low-dose aspirin 75 mg from 12 weeks of gestation, unless they have aspirin sensitivity. While there is no specific evidence that aspirin decreases the risk of pre-eclampsia in women with SCD, such women are probably at increased risk of developing pre-eclampsia.^{51,52} SCD should be considered a 'mild' risk factor and aspirin prophylaxis recommended according to NICE guidance.⁵²

There is some evidence that the incidence of venous thromboembolism is increased among pregnant women with SCD. A study from Bahrain examining maternal deaths between 1977 and 1989 reported that 5/12 deaths among women with SCD were attributed to pulmonary embolism.²⁷ Thromboprophylaxis advice should be based on the RCOG Green-top Guideline for women with additional risk factors.⁵³ The use of graduated compression stockings of appropriate strength is recommended in pregnancy for women considered to be at risk of venous thromboembolism, as discussed in the RCOG Green-top Guideline on thromboprophylaxis.⁵³

It is recommended that women receive low-molecular-weight heparin during hospital admission.

Non-steroidal anti-inflammatory drugs (NSAIDs) should be prescribed only between 12 and 28 weeks of gestation owing to concerns regarding adverse effects on fetal development

5.4 What additional care should be provided during the antenatal appointment?

Antenatal appointments for women with SCD should provide routine antenatal care as well as care specifically for women with SCD.⁴⁵

D

Blood pressure and urinalysis should be performed at each consultation, and midstream urine for culture performed monthly.

C

Women with SCD probably have an increased risk of pregnancy-induced hypertension;^{16,18,19,23,26} therefore, blood pressure and the presence of proteinuria should be assessed at each visit. Women with pre-existing proteinuria or known renal impairment will require more frequent monitoring. Women with SCD often have a low blood pressure, so an upward trend in blood pressure, even if modest, should be monitored carefully. Studies have also demonstrated an increase in the incidence of urinary tract infection and asymptomatic bacteriuria,²⁶ so urinalysis should be performed at each antenatal visit and midstream urine should be sent for culture and sensitivity monthly.

Evidence level 2+

At each appointment, opportunities should be offered for information and education. The woman's housing and work circumstances should be reviewed, and interventions which may reduce the potential provocation of acute crises (e.g. improved heating, allowance for increased hospital visits) should be encouraged. Table 2 outlines the recommended frequency and content of antenatal appointments for women with SCD.

5.5 What is the recommended schedule of ultrasound scanning during pregnancy?

Women should be offered a viability scan at 7–9 weeks of gestation.

✓

Women should be offered the routine first-trimester scan (11–14 weeks of gestation) and a detailed anomaly scan at 20 weeks of gestation. In addition, women should be offered serial fetal biometry scans (growth scans) every 4 weeks from 24 weeks of gestation.

✓

A number of studies suggest that women with SCD are at risk of fetal growth restriction^{21,26,28} as well as pre-eclampsia. Serial growth scans allow early detection of fetal growth restriction and hence aid appropriate timing of delivery to reduce perinatal mortality and morbidity.⁵⁴

Evidence level 2+

5.6 What is the role of blood transfusion during pregnancy?

Routine prophylactic transfusion is not recommended during pregnancy for women with SCD.

A

If acute exchange transfusion is required for the treatment of a sickle complication, it may be appropriate to continue the transfusion regimen for the remainder of the pregnancy.

D

Blood should be matched for an extended phenotype including full rhesus typing (C, D and E) as well as Kell typing.

A

Blood used for transfusion in pregnancy should be cytomegalovirus negative.

✓

Early studies recommended prophylactic transfusion during pregnancy as there was a decrease in maternal morbidity and perinatal mortality among transfused women compared with historical controls.^{55–57} There are appreciable risks associated with transfusion in this heavily transfused

Evidence level 1-

patient cohort, including alloimmunisation,^{25,58} delayed transfusion reactions,⁵⁸ transmission of infection and iron overload. A randomised controlled trial⁵⁹ and a retrospective study²⁵ have demonstrated that prophylactic transfusion decreased the incidence of maternal painful crises but did not influence fetal or maternal outcome. A systematic review⁶⁰ indicated that there is insufficient evidence to draw conclusions about the role of transfusion in pregnancy.

Table 2. Specific antenatal care for women with SCD

Appointment	Care for women with SCD during pregnancy
What should happen at the first appointment?	Offer information, advice and support in relation to optimising general health (D)
Primary care or hospital appointment	<p>Offer partner testing if not already done; review partner results if available and discuss PND if appropriate (D)</p> <p>Take a clinical history to establish extent of SCD and its complications</p> <p>Review medications and its complications; if taking hydroxycarbamide, ACE inhibitors or ARBs, these should be stopped (D)</p> <p>Women should already be taking 5 mg folic acid and antibiotic prophylaxis if no contraindication (D)</p> <p>Discuss vaccinations (D)</p> <p>Offer retinal and/or renal and/or cardiac assessments if these have not been performed in the previous year (D)</p> <p>Document baseline oxygen saturations and blood pressure</p> <p>Send MSU for culture</p>
7–9 weeks	<p>Confirm viability in view of the increased risk of miscarriage (D)</p> <p>Discuss information, education and advice about how SCD will affect pregnancy (D)</p>
What should happen at the booking appointment?	<p>See midwife with experience in high-risk obstetrics if possible</p> <p>Review partner results and discuss PND if appropriate (D)</p> <p>Baseline renal function test, urine protein/creatinine ratio, liver function test and ferritin should be performed (D)</p> <p>Extended red cell phenotype if not previously performed (D)</p> <p>Confirm that all actions from first visit are complete (D)</p> <p>Consider low-dose aspirin from 12 weeks of gestation (D)</p>
16 weeks: see midwife plus multidisciplinary review	<p>Routine as per NICE; repeat MSU</p> <p>Multidisciplinary review (consultant obstetrician and haematologist)</p>
20 weeks : see midwife plus multidisciplinary team	<p>Detailed ultrasound as per NICE antenatal guideline</p> <p>Repeat MSU</p> <p>Repeat FBC</p>
24 weeks: see multidisciplinary team	<p>Ultrasound monitoring of fetal growth and amniotic fluid volume.</p> <p>Repeat MSU</p>
26 weeks: see midwife	<p>Routine check including blood pressure and urinalysis</p>
28 weeks: see multidisciplinary team	<p>Ultrasound monitoring of fetal growth and amniotic fluid volume</p> <p>Repeat MSU</p> <p>Repeat FBC and group and antibody screen</p>
30 weeks: see midwife and offer antenatal classes	<p>Routine check including blood pressure and urinalysis</p>
32 weeks: see multidisciplinary team	<p>Routine check</p> <p>Ultrasound monitoring of fetal growth and amniotic fluid volume</p> <p>Repeat MSU and FBC</p>
34 weeks: see midwife	<p>Routine check including blood pressure and urinalysis</p>
36 weeks: see multidisciplinary team	<p>Routine check</p> <p>Ultrasound monitoring of fetal growth and amniotic fluid volume</p> <p>Offer information and advice about:</p> <ul style="list-style-type: none"> • timing, mode and management of the birth • analgesia and anaesthesia; arrange anaesthetic assessment • care of baby after birth
38 weeks: see midwife and obstetrician	<p>Routine check</p> <p>Recommend induction of labour or caesarean section between 38 and 40 weeks of gestation</p>
39 weeks: see midwife	<p>Routine check and recommend delivery by 40 weeks of gestation</p>
40 weeks: see obstetrician	<p>Routine check and offer fetal monitoring if the woman declines delivery by 40 weeks of gestation</p>

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; FBC = full blood count (for the woman); MSU = midstream urine; NICE = National Institute for Health and Clinical Excellence; PND = prenatal diagnosis; SCD = sickle cell disease

'Top-up' transfusion is indicated for women with acute anaemia.²⁹ Acute anaemia may be attributable to transient red cell aplasia, acute splenic sequestration or the increased haemolysis and volume expansion encountered in SCD. There is no absolute level at which transfusion should be undertaken and the decision must be made in conjunction with clinical findings, but haemoglobin under 6 g/dl or a fall of over 2 g/dl from baseline is often used as a guide to transfusion requirement.

Evidence level 4

Exchange transfusion for ACS was demonstrated to be effective in one prospective randomised trial and is accepted as best practice.^{29,61}

Evidence level 1-

Exchange transfusion is also indicated for acute stroke.¹⁶

Evidence level 4

The decision to recommend transfusion should be made by an experienced haematologist and obstetrician. Indications for transfusion are summarised in Table 3.

Alloimmunisation (the formation of antibodies to red cell antigens) is common in SCD, occurring in 18–36% of patients. Alloimmunisation is clinically important as it can lead to delayed haemolytic transfusion reactions or haemolytic disease of the newborn⁶² and can render patients untransfusible. The most common antibodies are to the C, E and Kell antigens. The risk of alloimmunisation is significantly reduced by giving red cells matched for the C, E and Kell antigens,⁶¹ and this should be standard practice for all patients with SCD whether they are pregnant or not.

Evidence level 1

5.7 What is the optimal management of acute painful crisis during pregnancy?

Women with SCD who become unwell should have sickle cell crisis excluded as a matter of urgency.

D

Pregnant women presenting with acute painful crisis should be rapidly assessed by the multidisciplinary team and appropriate analgesia should be administered. Pethidine should not be used because of the associated risk of seizures.

D

Women admitted with sickle cell crisis should be looked after by the multidisciplinary team, involving obstetricians, midwives, haematologists and anaesthetists.

D

The requirement for fluids and oxygen should be assessed, and fluids and oxygen administered if required.

D

Thromboprophylaxis should be given to women admitted to hospital with acute painful crisis.

D

Table 3. Indications for blood transfusion in pregnancy complicated by SCD

Indication	Comments
Women with previous serious medical, obstetric or fetal complications	Exchange or top-up transfusion may be indicated depending on clinical indications and should be decided in the multidisciplinary clinic setting
Women who are on a transfusion regimen before pregnancy for primary or secondary stroke prevention or for the prevention of severe disease complications	Transfusion should be continued during pregnancy
Twin pregnancies	Prophylactic transfusion should be considered owing to the high rate of complications in these women ²⁵
Acute anaemia	Top-up transfusion
Acute chest syndrome or acute stroke	Exchange transfusion

Painful crisis is the most frequent complication of SCD during pregnancy, with between 27% and 50% of women having a painful crisis during pregnancy,^{17,19,24,25} and it is the most frequent cause of hospital admission.²⁴ Avoidance of precipitants such as a cold environment, excessive exercise, dehydration and stress is important. There are no randomised controlled trials examining the management of painful crisis in pregnant women with SCD,⁶³ so treatment of acute pain in pregnant women should follow national recommendations applicable to non-pregnant women.⁶⁴

Mild pain may be managed in the community with rest, oral fluids and paracetamol or weak opioids. NSAIDs should be used only between 12 and 28 weeks of gestation. Primary care physicians should have a low threshold for referring women to secondary care; all women with pain which does not settle with simple analgesia, who are febrile, have atypical pain or chest pain or symptoms of shortness of breath should be referred to hospital.

On presentation, the woman in sickle crisis should be assessed rapidly for medical complications requiring intervention such as ACS, sepsis or dehydration. History should ascertain if this is typical sickle pain or not, and if there are precipitating factors. Examination should focus on the site of pain, any atypical features of the pain and any precipitating factors, in particular whether there are any signs of infection. Initial investigations should include full blood count, reticulocyte count and renal function. Other investigations will depend on the clinical scenario but may include blood cultures, chest X-ray, urine culture and liver function tests.

Initial analgesia should be given within 30 minutes of arriving at hospital and effective analgesia

Evidence level 4

should be achieved within 1 hour.⁶⁴

The World Health Organization analgesic ladder should be used, starting with paracetamol for mild pain; NSAIDs can be used for mild to moderate pain between 12 and 28 weeks of gestation. Weak opioids such as co-dydramol, co-codamol or dihydrocodeine can be used for moderate pain, and stronger opiates such as morphine can be used for severe pain. Morphine or diamorphine can be given by the oral, subcutaneous, intramuscular or intravenous route depending on the woman's preference and local expertise. Parenteral opiates can be given by intermittent bolus or patient-controlled administration systems. Pethidine should be avoided because of the risk of toxicity and pethidine-associated seizures in patients with SCD.⁶⁴

Women presenting with pain should initially be monitored at 20-minute intervals for pain severity, respiratory rate and sedation. Women whose pain settles following oral analgesia can be discharged home. If the women need strong opiate therapy, they will need to be admitted to hospital: to a medical ward in early pregnancy, or to a level 2 antenatal bed in later pregnancy, under the joint care of obstetricians and haematologists. Ideally, care should be provided by doctors and midwives who are familiar with SCD, but this is not always possible for geographical reasons and in this situation shared care arrangements and protocols should exist with specialist centres. Assessments of pain score, sedation score and oxygen saturation should be performed at least 2-hourly using a modified obstetric early warning chart.⁶⁴⁻⁶⁶ While women are receiving parenteral opiates, they should be nursed in an area where they can undergo hourly observations (Box 1).

Box 1. Outline of management of acute pain⁶⁴

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 minutes until pain is controlled and signs are stable, then monitor every 2 hours (hourly if receiving parenteral opiates)

Give a rescue doses 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.

Fluid intake of at least 60ml/kg/24 hours should be ensured; this can be taken either orally or intravenously if the woman is not able to take adequate oral fluids. There is a risk of fluid overload in women with pre-eclampsia; senior experienced staff should be involved in managing the fluid balance of these women. Oxygen saturations should be monitored and facial oxygen should be prescribed if oxygen saturation falls below the woman's baseline or below 95%.⁶⁴ There should be early recourse to intensive care if satisfactory oxygen saturation cannot be maintained by facial or nasal prong oxygen administration.

The woman should be assessed for infection. Therapeutic antibiotics should be prescribed if the woman is febrile or there is a high clinical suspicion of infection. White blood cell counts are often raised in SCD and do not necessarily indicate infection. Thromboprophylaxis should be provided to women with SCD who are admitted to hospital with painful crises. Other adjuvants may be required to treat the adverse effects of opiates, such as antihistamines to treat itching or laxatives to prevent opiate-induced constipation, and anti-emetics may be required. As the painful crisis resolves, most women are able to reduce their opiate requirement rapidly, but this should be guided by the woman's previous experience.

Opiates are not associated with teratogenicity or congenital malformation but may be associated with transient suppression of fetal movement and a reduced baseline variability of the fetal heart rate. Where a mother has received prolonged administration of opiates in late pregnancy, the neonate should be observed for signs of opioid withdrawal.

5.8 What are the other acute complications of SCD and how are they treated?

All patients, carers, medical and nursing staff should be aware of the other acute complications of SCD, including ACS, acute stroke and acute anaemia.

D

Each hospital should have a protocol in place for the management of ACS in pregnancy, including the use of transfusion therapy.

D

SCD is associated with other acute complications including ACS, stroke and acute anaemia. In the pregnant woman, these complications should be managed in the multidisciplinary setting by an obstetrician and a haematologist, and guidance on the management of these complications can be found in the relevant UK standards.²⁹

After acute pain, ACS is the most common complication, reported in 7–20% of pregnancies.^{18,22,25} ACS is characterised by respiratory symptoms such as tachypnoea, chest pain, cough and shortness of breath in the presence of a new infiltrate on the chest X-ray. The signs and symptoms of ACS are the same as those of pneumonia, so both should be treated simultaneously. Acute severe infection with the H1N1 virus in pregnancy can cause a similar clinical picture, and investigation and treatment for this should be instituted.

Early recognition of ACS is key. Treatment is with intravenous antibiotics, oxygen and blood transfusion, as in non-pregnant women.²⁹ Top-up blood transfusion may be required if the haemoglobin is falling, and certainly if the haemoglobin is less than 6.5 g/dl, but in severe hypoxia, and if the haemoglobin level is maintained, exchange transfusion will be required. If ACS is suspected, the woman should be reviewed urgently by the haematology team to advise on transfusion. If the woman has hypoxia, she should be reviewed by the critical care team and ventilatory support may be required.

Evidence level 4

There is an increased risk of pulmonary embolism among women with SCD. In women presenting with acute hypoxia, there should be a low threshold for considering pulmonary embolism. In this situation, therapeutic low-molecular-weight heparin should be commenced until the woman has been reviewed by senior staff and definitive investigations have been undertaken.

Acute stroke, both infarctive and haemorrhagic, is associated with SCD⁶⁷ and this diagnosis should be considered in any woman with SCD who presents with acute neurological impairment. Acute stroke is a medical emergency and a rapid-exchange blood transfusion can decrease long-term neurological damage. If a stroke is suspected, the woman should have urgent brain imaging and the haematologist should be called for consideration of urgent exchange transfusion. Thrombolysis is not indicated in acute stroke secondary to SCD.²⁹

Acute anaemia in women with SCD may be attributable to erythrovirus infection. Infection with erythrovirus in SCD causes a red cell maturation arrest and an aplastic crisis characterised by a reticulocytopenia. Therefore, a reticulocyte count should be requested in any woman presenting with an acute anaemia and, if low, may indicate infection with erythrovirus. Treatment is with blood transfusion and the woman must be isolated. With erythrovirus infection there is the added risk of vertical transmission to the fetus, which can result in hydrops fetalis, hence a review by a fetal medicine specialist is indicated.⁶⁸ Women with SCD can develop anaemia owing to bleeding or any other causes of anaemia incidental to the SCD. Rare causes of anaemia in SCD include malaria and, occasionally, splenic sequestration in women with a mild phenotype.

Evidence level 4

6. Intrapartum care

This section should be read in conjunction with NICE clinical guideline no. 55: *Intrapartum care. Care of healthy women and their babies during childbirth*.⁶⁹

6.1 What is the optimal timing and mode of delivery?

Pregnant women with SCD who have a normally growing fetus should be offered elective birth through induction of labour, or by elective caesarean section if indicated, after 38+0 weeks of gestation.

D

SCD should not in itself be considered a contraindication to attempting vaginal delivery or vaginal birth after caesarean section.

D

Blood should be cross-matched for delivery if there are atypical antibodies present (since this may delay the availability of blood), otherwise a 'group and save' will suffice.

D

In women who have hip replacements (because of avascular necrosis) it is important to discuss suitable positions for delivery.



There are no randomised controlled trials to dictate the appropriate timing of delivery. Studies from the USA, UK, Jamaica and Africa have highlighted increased perinatal mortality, particularly during the later stages of pregnancy, in part owing to the complications of SCD.²¹⁻²⁶ The risks of abruption, pre-eclampsia, peripartum cardiomyopathy and acute sickle cell crisis are increased and unpredictable. It is the opinion of the developers that, like most 'high-risk' conditions, delivery of the baby at 38–40 weeks of gestation will prevent late pregnancy complications and associated adverse perinatal events.

Some older studies questioned vaginal delivery as the optimal mode of delivery for women with SCD. However, other studies demonstrating improved clinical outcomes^{21,22,24,26} all support vaginal delivery as the recommended mode of delivery with the need for caesarean section based on obstetric indications.⁷⁰

Evidence level 2+

6.2 What is the optimum care and place of birth for a woman with SCD?

Women with SCD should be advised to give birth in hospitals that are able to manage both the complications of SCD and high-risk pregnancies.

D

The relevant multidisciplinary team (senior midwife in charge, senior obstetrician, anaesthetist and haematologist) should be informed as soon as labour is confirmed.

D

Women should be kept warm and given adequate fluid during labour.

D

Continuous intrapartum electronic fetal heart rate monitoring is recommended owing to the increased risk of fetal distress which may necessitate operative delivery.

D

There are no randomised controlled trials with regard to place of birth for women with SCD. There is an increased frequency of sickle cell crisis and ACS in the intrapartum period. There is an increased risk of painful crisis with protracted labour (more than 12 hours), but this is often secondary to dehydration. In this situation, if the woman is well hydrated and labour is progressing, the labour should be carefully supervised; caesarean section should be considered if labour is not progressing well and delivery is not imminent.²⁶

Evidence level 2+

During labour, if oral hydration is not tolerated or is inadequate, intravenous fluids should be administered using a fluid balance chart to prevent fluid overload. Venous access can be difficult, especially if they have had multiple previous admissions, and as such anaesthetic review/intravenous access should be obtained early. The demand for oxygen is increased during the intrapartum period and the use of pulse oximetry to detect hypoxia in the mother is appropriate during labour. Arterial blood gas analysis should be performed and oxygen therapy instituted if oxygen saturation is 94% or less.

Evidence level 4

Routine antibiotic prophylaxis in labour is currently not supported by evidence, but hourly observations of vital signs should be performed. A raised temperature (over 37.5°C) requires investigation. The clinician should have a low threshold to commence broad-spectrum antibiotics.

There are no randomised controlled trials with regard to interventions during labour for women with SCD. Experience reported in cohort observational studies from sickle cell centres in Jamaica,²² the USA^{18,21,24} and the UK^{16,25} recommend close observation, as described above. Continuous electronic fetal heart rate monitoring is recommended because of the increased rate of stillbirth, placental abruption and compromised placental reserve.^{71,72}

Evidence level 2+

6.3 What is the optimal mode of analgesia and anaesthesia?

Women with SCD should be offered anaesthetic assessment in the third trimester of pregnancy.

D

Avoid the use of pethidine, but other opiates can be used.

D

Regional analgesia is recommended for caesarean section.

D

Pregnant women with SCD are at risk of end organ damage as well as experiencing a higher rate of caesarean section. General anaesthesia carries additional risks beyond the normal obstetric case and should be avoided where possible. Regional anaesthesia during labour may reduce the necessity of general anaesthesia for delivery. It is also likely to reduce the need for high doses of opioids if the woman has sickle-related pain in the lower body. An anaesthetic assessment in the third trimester is warranted. Pethidine should be avoided because of the risk of seizures when administered to a woman with SCD.⁶⁴ Other opiates can be used (see section 5.7). Indications for epidural analgesia in labour are the same as per NICE intrapartum guidelines and are determined by the level of pain experienced, maternal choice and the absence of contraindications.⁶⁹

Sickle cell crisis in labour should be treated as per the guidance for antepartum crisis above (section 5.7).

7. Postpartum care

7.1 What should be the optimum care post-delivery?

In pregnant women where the baby is at high risk of SCD (i.e. the partner is a carrier or affected), early testing for SCD should be offered. Capillary samples should be sent to laboratories where there is experience in the routine analysis of SCD in newborn samples. This will usually be at a regional centre.

D

Maintain maternal oxygen saturation above 94% and adequate hydration based on fluid balance until discharge.

D

Low-molecular-weight heparin should be administered while in hospital and 7 days post-discharge following vaginal delivery or for a period of 6 weeks following caesarean section.

D

The same level of care and vigilance should be maintained as has been described for antenatal care, since acute crisis and other complications of SCD remain a risk in the puerperium.

✓

Antithrombotic stockings are recommended in the puerperium, as per RCOG Green-top Guideline No. 37a.⁵³

Routine care should be provided as per the NICE guideline on postnatal care.⁷³

The risk of sickle cell crisis remains increased: in one study it occurred in 25% of women and was more common following general anaesthesia.⁷⁴ Hydration and oxygenation should be maintained and early mobilisation encouraged. Crises should be managed as for non-pregnant women. NSAIDs are routinely administered in the postpartum period and can be used during breastfeeding. Breastfeeding should be encouraged, as in women without SCD.

Thromboprophylaxis in the form of low-molecular-weight heparin is recommended while the pregnant woman is in hospital and for 7 days following vaginal delivery or for a period of 6 weeks following caesarean section.

Evidence level 4

7.2 What postpartum contraceptive advice should women be given?

This section should be read in conjunction with the Faculty of Sexual & Reproductive Healthcare guidance on postnatal hormonal contraception.⁷⁵ Contraceptive advice will often be the responsibility of primary care.

Progestogen-containing contraceptives such as the progesterone only pill (Cerazette®, Organon Laboratories Ltd, Hoddesdon, UK), injectable contraceptives (Depo-Provera®, Pfizer Ltd, New York, USA) and the levonorgestrel intrauterine system (Mirena®, Bayer Schering Pharma AG, Berlin, Germany) are safe and effective in SCD.

B

Estrogen-containing contraceptives should be used as second-line agents.

D

Barrier methods are as safe and effective in women with SCD as in the general population. There is only limited safety evidence on hormonal contraception in SCD; a Cochrane review⁷⁶ identified one randomised trial which showed that women taking intramuscular depo-medroxyprogesterone acetate (DMPA) were less likely to have a painful episode.⁷⁷ Evidence level 1-

Evidence level 1-

A systematic review analysing randomised and non-randomised studies demonstrated progestogens to be effective and safe in SCD.⁷⁸ One further study which randomly assigned women to DMPA or Microgynon® (combined oral contraceptive pill; Bayer Schering Pharma AG, Berlin, Germany) showed a decrease in painful episodes in both groups, but to a greater degree in the DMPA group.⁷⁹

Evidence level 2+3

Prescribers have been reluctant to recommend the combined oral contraceptive in women with SCD because of the concern about an increased risk of venous thromboembolism, but there is no evidence using definitive outcome points of venous thromboembolism to confirm this. The UK Medical Eligibility Criteria⁸⁰ are based on the World Health Organization criteria classifying contraceptive use and define the combined oral contraceptive and copper intrauterine device as category 2, indicating that the advantages outweigh the disadvantages.⁸⁰ Other methods of contraception, such as the progestogen only pill, Depo-Provera, the levonorgestrel intrauterine system (Mirena) and emergency contraception, are rated level 1, indicating there is no restriction on their use.

Evidence level 4

8. Clinical governance

Each hospital should have a protocol for the management of pregnant women with SCD. This should identify a multidisciplinary team which has responsibility for the care of pregnant women with SCD, including an obstetrician with expertise in managing 'high-risk pregnancies' and a haematologist.



All staff involved in maternity care should receive training in the care of pregnant women with SCD.



Areas with a low prevalence of SCD should be linked to a specialist centre or care network for shared care arrangements and shared protocols.



9. Suggested audit topics

- The proportion of staff who receive appropriate training.
- The proportion of women receiving folic acid.
- The proportion of women receiving penicillin prophylaxis.
- The proportion of women receiving preconception advice.

The latter three standards could be audited within primary care.

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APPENDIX

Clinical guidelines are ‘systematically developed statements which assist clinicians and women in making decisions about appropriate treatment for specific conditions’. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1: *Development of RCOG Green-top Guidelines* (available on the RCOG website at <http://www.rcog.org.uk/guidelines>). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research might be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels		Grades of recommendations
1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias	A At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias	B A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
1-	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias	C A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
2++	High-quality systematic reviews of case-control or cohort studies or high-quality case-control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal	D Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+
2+	Well-conducted case-control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal	
2-	Case-control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal	
3	Non-analytical studies, e.g. case reports, case series	
4	Expert opinion	
Good practice point		
	 Recommended best practice based on the clinical experience of the guideline development group	

This guideline was produced on behalf of the Guidelines Committee of the Royal College of Obstetricians and Gynaecologists by:

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The final version is the responsibility of the Guidelines Committee of the RCOG.

The guidelines review process will commence in 2014 unless evidence requires earlier review.

DISCLAIMER

The Royal College of Obstetricians and Gynaecologists produces guidelines as an educational aid to good clinical practice. They present recognised methods and techniques of clinical practice, based on published evidence, for consideration by obstetricians and gynaecologists and other relevant health professionals. The ultimate judgement regarding a particular clinical procedure or treatment plan must be made by the doctor or other attendant in the light of clinical data presented by the patient and the diagnostic and treatment options available within the appropriate health services.

This means that RCOG Guidelines are unlike protocols or guidelines issued by employers, as they are not intended to be prescriptive directions defining a single course of management. Departure from the local prescriptive protocols or guidelines should be fully documented in the patient's case notes at the time the relevant decision is taken.