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. SCD has its origins in sub-Saharan Africa and the Middle East, where it is most

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Importance of antibiotic prophylaxis and vaccination

Penicillin prophylaxis or the equivalent should be prescribed.

Vaccination status should be determined and updated before pregnancy.

Patients with SCD are hyposplenic and are at risk of infection, in particular from encapsulated bacteria, such as *Neisseria meningitides, Streptococcus pneumonia and Haemophilus influenzae*. There is clear evidence that penicillin prophylaxis is of benefit in young children with SCD, but there is no randomised trial evidence in older patients or pregnant women. The guidance is that daily penicillin prophylaxis is given to all patients with SCD, in line with the guidelines for all hyposplenic patients. People who are allergic to penicillin should be referred early to hospital.

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.

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.

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

Vitamin supplements should be given

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

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

Folic acid at a dosage of at least 5 mg daily is recommended for women with SCD outside pregnancy in view of their haematinic anaemia, which puts them at increased risk of folate deficiency.[1]

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

Medications should be reviewed preconceptually

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

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

Hydroxycarbamide has been demonstrated to decrease the incidence of acute painful crises,

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

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 g/mol), since there is evidence that these agents reduce proteinuria and microalbuminuria. These drugs are not safe in pregnancy and should be stopped in women who are trying to conceive.

5. Antenatal care

General aspects

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

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.

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

infection. 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 HbSβ 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.

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.

It is essential that any woman who has a potentially affected infant (i.e. their partner is a carrier or is affected

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

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

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]

Blood pressure and urinalysis the antenatal for and each consultation and midstream urine

patient ·o ort, in·luding alloi unisation, · delay, e· transfusion rea·tions, trans ission o· if e·tion and iron overloa·. A ran·o ise· ·ontrolle· trial and a, retrospe·tive stu· ave de onstrate· t at prop y la·ti· transfusion de·rease· t e in·ide·e o· ·aternal pa·if ul ·rises but did not if luen·e ·etal or ·aternal out·o e A sy ste ati· review ! indi·ate· t at t ere is insuf i·ient evide·e to draw ·on·lusions about t e role o· transfusion in pregnan·.

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Table 2. Specific antenatal care for wo en with SCD

Appointment	Care for women with SCD during pregnancy
What should happen at at the first appointment?	Offer information, advice and support in relation to optimising general health (D)
Primary care or hospital appointment	Offer partner testing if not already done, review partner results if available and discuss PND if appropriate (D) Take a clinical history to establish extent of SCD and its complications Review medications and its complications, if taking hydroxycarbamide, ACE inhibitors or ARBs, these should be stopped (D) Women should already be taking 5 mg folic acid and antibiotic prophylaxis if no contraindication (D) Discuss vaccinations (D) Offer retinal and/or renal and/or cardiac assessments if these have not been performed in the previous year (D) Document baseline oxygen saturations and blood pressure Send MSU for culture
7– weeks	Confirm viability in view of the increased risk of miscarriage (D)
What should happen at the booking appointment?	Discuss information, education and advice about how SCD will affect pregnancy (D)
See midwife with experience in high-risk obstetrics if possible	Review partner results and discuss PND if appropriate (D) Baseline renal function test, urine protein/creatinine ratio, liver function test and ferritin should be performed (D) Extended red cell phenotype if not previously performed (D) Confirm that all actions from first visit are complete (D) Consider low-dose aspirin from 12 weeks of gestation (D)
16 weeks see midwife plus multidisciplinary review	Routine as per NICE, repeat MSU Multidisciplinary review (consultant obstetrician and haematologist)
20 weeks see midwife plus multidisciplinary team	Detailed ultrasound as per NICE antenatal guideline Repeat MSU Repeat FBC
24 weeks see multidisciplinary team	Ultrasound monitoring of fetal growth and amniotic fluid volume. Repeat MSU
26 weeks see midwife	Routine check including blood pressure and urinalysis
2 weeks see multidisciplinary team	Ultrasound monitoring of fetal growth and amniotic fluid volume Repeat MSU Repeat FBC and group and antibody screen
30 weeks see midwife and offer antenatal classes	Routine check including blood pressure and urinalysis
32 weeks see multidisciplinary team	Routine check Ultrasound monitoring of fetal growth and amniotic fluid volume Repeat MSU and FBC
34 weeks see midwife	Routine check including blood pressure and urinalyis
36 weeks see multidisciplinary team	Routine check Ultrasound monitoring of fetal growth and amniotic fluid volume Offer information and advice about • timing, mode and management of the birth • analgesia and anaesthesia, arrange anaesthetic assessment • care of baby after birth
3 weeks see midwife and obstetrician	Routine check Recommend induction of labour or caesarean section between 3 and 40 weeks of gestation
3 weeks see midwife	Routine check and recommend delivery by 40 weeks of gestation
40 weeks see obstetrician	Routine check and offer fetal monitoring if the woman declines delivery by 40 weeks of gestation

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 indi ated for wo en wit acute ana e ia. A ute ana e ia a be attributable to transient red ell aplasia, acute splenic sequestration or t e increased ae oly sis and volu e e pansion encountered in SCD. T ere is no absolute level at w i transfusion s ould be undertak en and t e de ision ust be ade in onjun tion wit lini al f indings, but ae oglobin under g/dl or a f all of over g/dl f ro baseline is of ten used as a guide to transf usion require ent

E ange transfusion f or ACS was de onstrated to be eff e tive in one prospe tive rando ised trial and is accepted as best pra tice

E ange transfusion is also indicated f or acute stro e

T e de ision to re o end transfusion s ould be ade by an e perien ed ae atologist and obstetri ian. Indi ations f or transfusion are su arised in Table .

Alloi unisation (t e f or ation of antibodies to red ell antigens) is o on in SCD, o urring in – % of patients. Alloi unisation is lini ally i portant as it an lead to dela ed ae oly ti transfusion rea tions or ae oly ti disease of t e newborn and an render patients untransfusable. T e ost o on antibodies are to t e C, E and ell antigens. T e ris of alloi unisation is signif i antly redu ed by giving red ells at ed f or t e C, E and ell antigens, and t is s ould be standard pra ti e f or all patients wit SCD w et er t ey are pregnant or not

at s t e opt a anage ent of acute pa nfu cr s s dur ng pregnancy

painful crisis is the most frequent complication of SCD during pregnancy, with between 30 and 40% of women having a painful crisis during pregnancy, and it is the most frequent cause of hospital admission 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, so treatment of acute pain in pregnant women should follow national recommendations applicable to non-pregnant women

Mild pain may be managed in the community with rest, oral fluids and paracetamol or weak opioids SAIDs should be used only between and 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 any pleural 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 minutes of arriving at hospital and effective analgesia should be achieved within hour

The World Health Organisation analgesic ladder should be used, starting with paracetamol for mild pain, SAIDs can be used for mild to moderate pain between and weeks of gestation Weak opioids such 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 Systemic medicines should be

Fluid intake of at least 4 l/ 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-existing pulmonary, 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 96%. 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 antiemetics 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 deformation 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.

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.

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

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

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

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

7. Postpartum care

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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. ✓

Antit ro boti^ sto^ ings are re^o ended in t e puerperiu , as per RCOG Green-top Guideline o .

outine ^are s ould be provided as per t e ICE guideline on postnatal ^are

T e ris of si^ le ^ell ^risis re ains in^reased in one stud it o^^urred in of wo en and was ore ^o on following general anaest esia. H dration and o y genation s ould be aintained and ear obilisation en^ouraged Crises s ould be anaged as for non-pregnant wo en SAIDs are routinel ad inistered in t e postpartu period and ^an be used during breastfeeding Breastfeeding s ould be en^ouraged, as in wo en wit out SCD

T ro boprop l , is in t e for of low- ole^ular-weig t epar in is re^o ended w ile t e pregnant wo an is in ospital and/or d , s following vaginal deliver or for a period of wee s following ^aesarean se^tion

Evidence level

at postpartu contracept ve adv ce s ou d wo en be g ven

T is se^tion s ould be read in ^onjun^tion wit t e Fa^ult of Se ual & eproduc^tive Heal t ^are guidan^e on postnatal or onal ^ontra^eption Contra^eptive adv i^e will often be t e responsibilit of pri ar ^are

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 levenorgestrel 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 et ods are as saf e and eff e^tive in wo en wit SCD as in t e general populationT ere is onl li ited saf el evidence on or onal ^ontra^eption in SCD a Co^ rane review identified one ran do ised trial w i^ s owed t at wo en ta ing intra^ us^ular depo- edro progesterone a^etate (DMPA) were less li el to ave a pain ful episode Evidence level -

Evidence level -

A s ste ati^ review anal sing ran do ised and non-ran do ised studies de onstrated progestogens to be eff e^tive and saf e in SCD One fur ter stud w i^ ran do l assigned wo en to DMPA or Mi^rog non® (^o bined oral ^ontra^eptive pill, Ba er S^ ering Pha a AG, Berlin, Ger an), s owed a de^rease in pain ful episodes in bot groups, but to a greater degree in t e DMPA group

Evidence level +/

Pauling L, Itano HA, Singer SJ, Wells IC. Sickle cell anemia, a molecular disease. *Science* , – .

Stuart MJ, Nagel RL. Sickle cell disease. *Lancet* , – .

Weatherall DJ, Akinyanju O, Fucharoen S, Olivieri N, Musgrove P. Inherited disorders of hemoglobin. In: Jamison DT, Breman JG, Measham AR, Alleyne G, Claeson M, Evans DB, et al., editors. *Disease Control Priorities in Developing Countries*. Second edition. Washington, DC: The World Bank and New York, NY: Oxford University Press; . p. – .

Chakravarti A, Li CC, Buetow KH. Estimation of the marker gene frequency and linkage disequilibrium from conditional marker data. *Am J Hum Genet* , – .

Davies SC, Brozovic M. The presentation, management and prophylaxis of sickle cell disease. *Blood Rev* , – .

Serjeant GR. The emerging understanding of sickle cell disease. *Br J Haematol* , – .

Streetly A, Latinovic R, Hall K, Henthorn J. Implementation of universal newborn bloodspot screening for sickle cell disease and other clinically significant haemoglobinopathies in England: screening results for – . *J Clin Pathol* , – .

Angastiniotis M, Modell B, Englezos P, Boulyjenkov V. Prevention and control of haemoglobinopathies. *Bull World Health Organ* , – .

Serjeant GR. Sickle-cell disease. *Lancet* , – .

Diallo D, Tchernia G. Sickle cell disease in Africa. *Curr Opin Hematol* , – .

Smith JA, Espeland M, Bellevue R, Bonds D, Brown AK, Koshy M. Pregnancy in sickle cell disease: experience of the Cooperative Study of Sickle Cell Disease. *Obstet Gynecol*

Al Jama FE, Gasem T, Burshaid S, Rahman J, Al Suleiman SA, Rahman MS. Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. *Arch Gynecol Obstet*

Afolabi BB, Iwuala NC, Iwuala IC, Ogedengbe OK. Morbidity and mortality in sickle cell pregnancies in Lagos, Nigeria: a case control study. *J Obstet Gynaecol*

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