bjh guideline

Management of sickle cell disease in pregnancy. A British Society for Haematology Guideline

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Keywords: sickle cell anaemia, sickle cell disease, pregnancy, antenatal, intrapartum, preconceptual.

This guideline was compiled according to the British Society of Haematology (BSH) process at https://b-s-h.org.uk/guidelines/proposing-and-writing-a-new-bsh-guideline/. The Grading of Recommendations Assessment, Development and Evaluation (GRADE) nomenclature was used to evaluate levels of evidence and to assess the strength of recommendations. The GRADE criteria can be found at http://www.gradeworkinggroup.org

Literature review details

This BSH guideline was developed and updated from a previous Royal College of Obstetricians and Gynaecologists (RCOG) Green-top guideline[1] in accordance with the standard method of producing BSH guidelines. 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 2000 and August 2018. In all, 218 papers were identified. Search terms included: 'sickle cell', 'hydroxycarbamide', 'antenatal', 'pregnancy', 'intrapartum', 'penicillin prophylaxis', 'ACE inhibitor', 'transfusion', 'ultrasound', 'Doppler', 'echocardiogram', 'anti-coagulation', 'prophylaxis', 'sickle cell and risk factors', 'preconceptual' and 'sickle cell crisis' and included all relevant Medical Subject Headings (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.

Review of the manuscript

Review of the manuscript was performed by the BSH Guidelines Committee, General Haematology Task Force, the BSH Guidelines Committee and the members of the sounding board of BSH. It was also placed on the members' section of the BSH website for comment. It has also been reviewed by the Royal College of Obstetricians and Gynaecologists, Sickle Cell Society and BSH Obstetric Haematology Special Interest Group; these organisations do not necessarily approve or endorse the contents.

Introduction

The purpose of this guideline is to describe the management of sickle cell disease (SCD) in pregnancy in the UK. It will cover preconception screening and antenatal, intrapartum and postnatal management of women with the condition. It will not cover the management of women with sickle cell trait. Updates from the previous guideline[1] include new information on pre-implantation genetic diagnosis (PGD), more comprehensive information on pre-conceptual screening and medication review, updated information on thromboprophylaxis, aspirin and vitamin D, changes to advice on antenatal care including frequency of ultrasonography (USS) scanning. It also includes reference to the most recent National Institute for Health and Clinical Excellence (NICE) and RCOG guidelines. SCD comprises a group of conditions

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First published online 19 August 2021
doi: 10.1111/bjh.17671
 British Journal of Haematology, 2021, **194,** 980–995

caused by the inheritance of the abnormal haemoglobin sickle gene (HbS). The most severe form of SCD is homozygous SCD (HbSS) but SCD can also be due to compound heterozygous genotypes of HbS and another haemoglobin variant (e.g., HbC, HbD^{Punjab}, HbE or β thalassaemia, see Table I).

Sickle cell disease is one of the most common inherited condition worldwide, with over 300 000 children born with the condition each year globally, three-quarters of whom are born in Africa.[3] The prevalence of SCD varies considerably across different ethnic communities, predominantly affecting people of African or African–Caribbean origin. Owing to population migration, SCD is now of increasing importance worldwide and there are increasing numbers of affected individuals in Europe and the United States. Within Europe, the UK has the largest population with the condition. In the UK it is estimated that there are 15 000 affected individuals, and approximately 300 infants born with the condition each year.

The pathophysiology of SCD is the consequence of polymerisation of the abnormal sickle haemoglobin in low oxygen conditions leading to the formation of rigid and fragile sickle-shaped red cells. These cells are prone to increased breakdown, which causes haemolytic anaemia and the sickle-shaped red cells do not flow through blood vessels easily, causing blockage (vaso-occlusion) in small vessels, leading to most of the clinical features, including acute painful crises. Other complications of SCD include acute chest syndrome, pulmonary hypertension (PH), stroke, renal dysfunction, retinal disease, leg ulcers, cholelithiasis and avascular necrosis. SCD was previously associated with high childhood mortality, but now, in high-resource countries with neonatal screening and lifelong treatment, life expectancy is at least the mid-50s. With the majority of individuals born with SCD in the UK living to reproductive age and beyond, management of this condition in pregnancy is now more pertinent.

There are approximately 110–200 pregnancies in women with SCD per year in the UK.[4] Pregnancy in women with SCD is associated with higher risk of mortality and morbidity.[4,5] Data from a national study in the UK showed an increased risk of both sickle-related complications (acute pain, acute chest syndrome) and pregnancy-related complications [hypertension, venous thromboembolism (VTE) and urinary tract infections].[4] A retrospective study has shown that pregnancy-related VTE in women with SCD appears to be 1·5–5 times greater than in the general population.[6] Women with SCD were more likely to require blood transfusion or admission to the critical care unit. Women with SCD were more likely to deliver before 37 weeks of gestation and the babies were more likely to have a reduced birth weight. Whilst most of these complications were more common in women with HbSS than HbSC, both groups of women experienced an increased risk of complications. A systematic review and meta-analysis of studies in pregnancy in SCD confirmed these findings showing significant increases in maternal mortality, pre-eclampsia, stillbirth, preterm delivery and infants that are small for gestational age.[5] Meta-regression demonstrated that increased relative risks were associated with genotype (HbSS *versus* HbSC) and low gross national income.

Although women with HbSC experience fewer adverse outcomes than women with HbSS, they are still susceptible to increased painful crises during pregnancy, fetal growth restriction, antenatal hospital admission and postpartum infection[4,7,8] and these women should have the same level of vigilance and care as for those with HbSS. There are fewer data on pregnancy outcomes in women with HbS/βthalassaemia, HbSD, HbSE or $HbSO^{Arab}$, but anecdotal evidence indicates that these too should be similarly monitored and treated.

Table I. Significant maternal haemoglobinopathies.[2]

Significant maternal haemoglobinopathies
HbSS
HbSC
$HbSD^{Punjab}$
HbSE
$HbSO^{Arab}$
HbS/Lepore
HbS/β^0 thalassaemia
HbS/β^+ thalassaemia

Preconception care

Discussion of pregnancy and conception should be embedded into routine care for women with SCD and be part of the comprehensive annual review (at least) from young adulthood onwards[9] and this should begin in paediatric clinics where appropriate. This should include discussion of reproductive options, partner screening, optimisation of health prior to conception, preconception folic acid supplementation and review of teratogenic medications. Preconception clinics should be available and accessible.

Genetic screening

Women with SCD who have a partner who is a carrier of a β globin variant (e.g., HbS, HbC, β thalassaemia) will have a risk of up to 50% in each pregnancy of having a child with a sickling disorder. Women with SCD should be counselled about their reproductive options (non-intervention, prenatal diagnosis or PGD) by an appropriately trained professional and this should be clearly documented.

Women are often not aware of the possibility of PGD and hence do not have the opportunity to consider or participate in this. A review conducted in a London tertiary referral centre showed that 60 at-risk couples referred over a five-year period, over all having 74 cycles of PGD, had a live birth rate

of 63% per couple.[10] This was much higher than the previously reported 17% live birth rate.[11] This paper noted that there were significant barriers to referral, and a separate survey of parents of children with SCD found that only 41% had been aware of PGD prior to pregnancy.[12] Care givers should ensure that discussion of PGD and relevant referrals take place in a timely fashion.

Recommendations

- **As part of the annual review, all women with SCD should be encouraged to engage with partner testing prior to embarking on pregnancy (1C).**
- **High-risk couples should be counselled prior to pregnancy about their reproductive options: non-intervention, prenatal diagnosis or pre-implantation genetic diagnosis (1C).**

Preconception comprehensive review of complications

A comprehensive annual review is part of recommended routine care; discussion of reproduction, pregnancy and contraceptive options and review of chronic complications should be part of this annual review. The outcomes of the most recent annual review should be assessed in any woman who is actively planning pregnancy; investigations of particular importance preconceptually include assessment of renal dysfunction and cardiopulmonary disease. Renal complications occur in up to 60% of those with SCD during their lifetimes and are characterised by glomerular hyper-filtration and microalbuminuria from young adulthood with the development of proteinuria and chronic kidney disease in later years.[13]

Prior to pregnancy, women should have blood pressure monitoring and screening with creatinine and urinary protein (albumin:creatinine or protein:creatinine ratio). Women with abnormalities in renal function or proteinuria (protein: creatinine ratio >50 mg protein/mmol creatinine) should be investigated to exclude non-sickle causes. Anti-hypertensive treatment should be considered in women with a persistently raised blood pressure of >130/80 mm Hg.[14] Choice of anti-hypertensive medication should follow the NICE guidance.[15]

Pulmonary hypertension, ventricular diastolic dysfunction and early cardiac death are all increased in SCD and Doppler echocardiography has been used as a non-invasive tool for initial evaluation and screening for PH. A raised tricuspid regurgitant jet velocity (TRV) is associated with increased mortality and increased risk of PH.[16] A small single-centre study has shown that 33% of pregnant women had a raised TRV, but this was not associated with poor outcomes.[17] Women planning pregnancy should have screening with echocardiography if this has not been performed in the previous year and at any time if they have symptoms suggestive of PH.

Other significant previous medical history should also be reviewed, for example, history of auto-immune disease as this may need additional specialist clinical review.

Other complications of SCD that merit screening and optimisation prior to embarking on pregnancy are summarised in Table II.

Recommendations

- **Pregnancy and conception should be discussed with women of child-bearing age with SCD as part of their annual review (1C).**
- **Women should be reviewed by a specialist prior to conception to ensure optimisation of health and screening for disease complications (1C).**
- **Preconception clinics should be available and accessible (1C).**

Preconception medication review

A thorough review of medications should be performed prior to conception. Folic acid is recommended for patients with SCD in view of their haemolytic anaemia that puts them at increased risk of folate deficiency.[18] Folic acid is also recommended in all pregnant women to prevent neural tube defects and should be commenced preconceptually.[19] Therefore, folic acid 5 mg daily should be prescribed when planning pregnancy and during pregnancy both to reduce the risk of neural tube defect and to also compensate for the increased demand during pregnancy.

Vitamin D deficiency is common in patients with SCD and regular monitoring and supplementation for deficient patients are recommended outside pregnancy. Vitamin D supplementation is recommended for all pregnant and breastfeeding women in the UK.[20] Pregnant women with SCD should be prescribed vitamin D as per national recommendations for pregnancy[20] and it may be helpful to monitor vitamin D levels to ensure adequate supplementation.

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*. Penicillin prophylaxis is of benefit in young children with SCD, but there is no randomised trial evidence in pregnant women. In view of their hyposplenism and increased risk of pneumonia, pregnant women with SCD should continue penicillin prophylaxis, or start this if they are not already taking it. Vaccination status should also be reviewed and updated as per national recommendations and this should include annual influenza vaccination and pneumococcal vaccination if this has not been given within the previous five years.[9]

The optimal analgesics to use during pregnancy should be discussed with women as part of their pain management plan. Paracetamol and codeine-containing analgesics can be

Table II. Preconception review of chronic sickle complications.

Chronic complication	Action to be taken
Renal disease and hypertension	Blood pressure, creatinine and urinary protein monitoring
Pulmonary hypertension	Echocardiography if not performed within 1 year or if symptomatic. Abnormalities should be discussed with a cardiologist
Chronic lung disease	Oxygen saturations on all women. Sleep studies and pulmonary function tests if indicated
Avascular necrosis	Review hip complications which may worsen during pregnancy
Stroke	If history of previous stroke consider role of transfusion during pregnancy if not already receiving this
Chronic pain	Women on long-term opioids should be referred to a chronic pain clinic for assessment and managed by pain specialist during pregnancy

offered during pregnancy as first-line agents.[21,22] If these are not effective, non-steroidal anti-inflammatory drugs (NSAIDs) should only be used with caution before 12 weeks and avoided after 31 weeks of gestation owing to concerns regarding the risk of premature closure of the patent ductus.[21] Opioid intake should be assessed, with referral to a chronic pain team if needed.

As part of standard care potentially teratogenic medications should be reviewed and particular attention should be paid to those that are commonly used in SCD including angiotensin-converting enzyme inhibitors (ACEi) or angiotensin II receptors blockers (ARBs) for renal dysfunction, hydroxycarbamide and iron chelators.

The recent Renal Association Guidelines (2019) recommend that women with chronic kidney disease who are taking ACEi have a plan for discontinuation/conversion guided by the strength of indication for renin–angiotensin blockade and the likelihood of early pregnancy confirmation and that ARBs are discontinued in advance of pregnancy.[21,23] In these women renal function and proteinuria should be carefully monitored at least monthly throughout pregnancy.

Many women will be taking hydroxycarbamide prior to pregnancy as this has been shown to decrease the incidence of acute painful crisis and acute chest syndrome in individuals with severe clinical manifestations of SCD and is the only currently licensed treatment for SCD in the UK.[24] Hydroxycarbamide is teratogenic in animals and its use in pregnancy has been discussed in a previous BSH guideline.[25] This advises stopping hydroxycarbamide preconceptually in female patients. If women are taking hydroxycarbamide due to frequent and severe sickle pain episodes, treatment with regular red cell erythrocytapheresis should be discussed as an alternative.

If women do become pregnant whilst taking hydroxycarbamide, it should be stopped as soon as possible. There are reports in the literature of women receiving hydroxycarbamide in pregnancy both for SCD and for other indications and some of these have continued it throughout pregnancy without adverse effects on the baby.[26–29] Concerns have been raised that for women with severe phenotype disease and no other treatment options, the risks of stopping hydroxycarbamide (which include increased risk of pain crises, acute chest syndrome and worsening anaemia) may outweigh the risks of continuing hydroxycarbamide. This is particularly true for women who are not able to receive blood transfusion because of multiple red cell alloantibodies or previous severe delayed haemolytic transfusion reactions. For these women, we recommend a discussion between the haematologist, the obstetrician and the woman prior to pregnancy to provide her with information about the risks and benefits of continuing hydroxycarbamide therapy throughout pregnancy to aid patient-led decision-making. Referral to the fetal medical unit for additional detailed ultrasound scanning for fetal abnormalities may be considered, although the reliability in detecting hydroxycarbamide-induced abnormalities is uncertain.[30] A clinical trial is currently collecting retrospective data on hydroxycarbamide exposure during pregnancy [Hydroxyurea Exposure Limiting Pregnancy and Follow-up Lactation (HELPFUL): NCT04093986].

Iron chelators are not recommended during pregnancy due to a lack of safety data so they should be regarded as potentially teratogenic in the first trimester and should be stopped when a woman is trying to conceive. Women with iron overload should be carefully assessed with liver and cardiac magnetic resonance imaging prior to conception to highlight those at high risks of iron-related complications. If there is evidence of iron overload, this should be treated prior to conception. Cardiac iron overload is unusual in SCD, but if it occurs women should be encouraged to rigorously chelate prior to conception and third-trimester desferrioxamine can be considered.

New medications including voxelotor, crizanlizumab and glutamine are not approved for use during pregnancy and should be stopped prior to conception or when pregnancy is confirmed if unplanned. Although these drugs are not approved for use in the UK at the time of publication they may be approved at some point and women may have been prescribed these drugs from overseas.

Recommendations

- **Folic acid (5 mg daily) should be given from before conception and throughout pregnancy (1A).**
- **Women should be given vitamin D as per national recommendations for all pregnant women (1C).**
- **Daily antibiotic prophylaxis is recommended (2B).**
- **Vaccinations should be kept updated as per national recommendations for SCD and should include flu vaccination (1B).**

- **When attempting to conceive ARBs should be stopped and there should be a plan for stopping/converting ACEi (1C).**
- **Hydroxycarbamide should be discontinued when attempting to conceive unless the woman is considered to be at high risk of serious complications relating to SCD and blood transfusion is not feasible (2C).**
- **Iron chelators should be stopped when attempting to conceive (1B).**

Antenatal care

Antenatal haemoglobinopathy screening

It is essential that any woman who has a potentially affected infant (i.e. whose partner is a carrier or is affected by a significant haemoglobinopathy) is aware of this and receives appropriate counselling. Partner status and subsequent counselling should be clearly documented. Further information can be obtained on the NHS Sickle Cell & Thalassaemia Screening Programme website which includes information about the laboratories that can perform prenatal diagnostic testing.[31] 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, so that early prenatal diagnosis can be offered.

Prenatal diagnosis (by chorionic villus sampling or amniocentesis) should be offered as early as possible in pregnancy to ensure early access to termination of an affected pregnancy if requested. Prenatal diagnosis can be performed from 11 weeks of gestation and is associated with a low risk of miscarriage (~1%). Studies are ongoing using non-invasive prenatal diagnosis via detection of cell-free fetal DNA in the maternal circulation, but this approach is not yet available outside research studies.[32] Non-invasive testing would increase the uptake of prenatal testing, though this needs to be balanced against concerns that non-invasive testing puts couples under increased pressure to have prenatal intervention.[33]

Recommendations

- **If the woman has not been seen preconceptually, she should be offered partner testing (1B).**
- **If the partner is a carrier, counselling regarding the potential for an affected fetus should take place in the first trimester to enable prenatal diagnosis and if an affected fetus is identified the option of termination should be offered (1B).**

Maternal health

Many women become pregnant without preconception care. Therefore, all of the actions outlined in the section on preconception care including vaccinations, review of medications, assessment for organ damage, red cell alloantibodies and iron status, should take place as early as possible during pregnancy. Flu vaccine should be given but live attenuated vaccines should be deferred until after delivery.

Thereafter, the mainstay of antenatal care is monitoring for and prevention of general and SCD-specific complications. Guidance on routine antenatal care for the healthy pregnant woman is provided by NICE CG 62.[34] Prevention of SCD-specific complications necessitates multidisciplinary care involving obstetricians, midwives and Specialised Haemoglobinopathy Teams. Good communication between health professionals is key to patient safety and hospital (or network) protocols for transfusion indications and early detection and management of SCD complications including infection, acute pain and management of labour should be available.

The frequency of routine appointments will depend on medical progress and the presence of complications but a reasonable guide is once per month, for clinical assessment, counselling, blood pressure measurement, blood tests and urinalysis to identify asymptomatic bacteriuria.[5,35] These are summarised in Table III.

At each appointment, opportunities should be offered for giving information and education regarding crisis prevention measures such as rest, warmth and avoidance of dehydration and infections. The woman's housing and work circumstances should be reviewed, and interventions that may reduce the potential provocation of acute crises (e.g., improved heating, allowance for increased hospital visits) should be encouraged. Compliance with prescribed medications such as folic acid and prophylactic antibiotics should be ensured. NSAIDs should be used with caution before 12 weeks and avoided after 31 weeks of gestation owing to concerns regarding premature closure of the patent ductus. Iron supplementation should be given to women with proven iron deficiency (serum ferritin <30 μg/l); it should not be given empirically as for anaemic women without haemoglobinopathy.[36]

Hyperemesis gravidarum can lead to dehydration and sickle cell crisis and women with persistent vomiting should be advised to seek medical advice early. They should be kept hydrated and consideration given to hospital admission and thromboprophylaxis. Multiple gestation in women with SCD substantially increases the risk of pre-eclampia, hypertension, acute pain episodes and acute anaemic events; therefore these pregnancies require close attention and increased monitoring.

Pregnancy-induced hypertension

Women with SCD have an increased risk of pregnancy-induced hypertension and pre-eclampsia.[4,5,37] Aspirin prophylaxis is recommended at 75–150 mg daily from 12 weeks of gestation for women at high risk of pre-eclampsia,[15,38] unless

Table III. Specific antenatal care for women with SCD32.

Appointment	Care for women with SCD during pregnancy
First appointment (primary care or hospital appointment)	Offer general health information, advice and support Offer partner testing if not already done Review partner results and discuss PND if appropriate Clinical history to assess SCD complications Assess retinal, renal and cardiac complications as necessary Review medications Ensure women are taking 5 mg folic acid and prophylactic antibiotics and discuss vaccinations Document baseline oxygen saturations and blood pressure Send MSU for culture
Booking appointment: see multidisciplinary team plus midwife with experience in high-risk obstetrics if possible	Information, education and advice about SCD and pregnancy Review partner results and discuss PND if appropriate Baseline full blood count, renal function test, urine protein/creatinine ratio, liver function test, ferritin and group and screen Extended red cell phenotype if not previously performed Prescribe 75–150 mg aspirin Start vitamin D prophylaxis if not already on this Risk assessment for VTE and consider thromboprophylaxis Review individual pain management plan
10–14 weeks	First-trimester ultrasound scan
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 review	Detailed ultrasound as per NICE antenatal guideline Repeat FBC and MSU
24 weeks: see multidisciplinary team	Ultrasound monitoring of fetal growth and amniotic fluid volume Repeat FBC and MSU
26 weeks: see midwife	Routine check including blood pressure and urinalysis
28 weeks: see multidisciplinary team	Ultrasound monitoring of fetal growth and amniotic fluid volume Repeat MSU Repeat FBC and group and antibody screen Review VTE risk factors and consider thromboprophylaxis
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 Offer anaesthetic assessment at 32 weeks or earlier if indicated
34 weeks: see midwife	Routine check including blood pressure and urinalysis
36 weeks: see multidisciplinary team	Routine check Repeat MSU and FBC Ultrasound monitoring of fetal growth and amniotic fluid volume Consider whether to stop aspirin prior to delivery Offer information and advice about: • Timing, mode and management of the birth • Care of baby after birth • Analgesia and anaesthesia
38 weeks: see midwife and obstetrician	Routine check Discuss timing and mode of delivery
39 weeks: see midwife	Routine check and review delivery plan
40 weeks: see obstetrician	Routine check and offer fetal monitoring if the woman declines delivery by 40 weeks of gestation

FBC, full blood count; MSU, midstream urine; NICE, National Institute for Health and Clinical Excellence; PND, prenatal diagnosis; SCD, sickle cell disease; VTE, venous thromboembolism.

they have aspirin sensitivity. Although there is no specific evidence that aspirin decreases the risk of pre-eclampsia in women with SCD, in view of their increased risk we recommend that women with SCD and no contraindications should be offered aspirin prophylaxis from 12 weeks.[15] Recent evidence suggests that aspirin may increase the risk of postpartum haemorrhage.[39] so should be stopped at 36 weeks.

Close monitoring for pre-eclampsia is part of antenatal care for all women and 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 and should be discussed with a multidisciplinary high-risk pregnancy team.[23] Women with SCD often have a low blood pressure, so an upward trend in blood pressure, even if modest, should be monitored carefully. A target blood pressure of <130/80 mm Hg should be used, based on recent American Society of Hematology (ASH) recommendations for all patients with SCD.[14] This is lower than recommendations for women without SCD.[15] In women with neurological symptoms it is important to distinguish pre-eclampsia/eclampsia from the neurological complications of SCD.

Recommendations

- **A full assessment, as for preconception care, should be repeated as early as possible in the antenatal period, including review of vaccinations and medications, organ damage and red cell alloantibodies (1B).**
- **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 links to a Specialised Haemoglobinopathy Team (1C).**
- **Regular antenatal appointments for women with SCD should provide routine antenatal care as well as care specifically for women with SCD (1C).**
- **Women with persistent vomiting should be advised to seek medical advice early (1C).**
- **Women should be reminded to take daily folic acid (5 mg) and prophylactic antibiotics (if not contraindicated) and avoid drugs that are unsafe in pregnancy (1A).**
- **Iron supplementation should be given if there is laboratory evidence of iron deficiency (1B).**
- **Women with SCD should be considered for low-dose aspirin 75–150 mg once daily from 12 weeks of gestation in an effort to reduce the risk of developing pre-eclampsia and should be monitored for blood pressure rises and proteinuria (1B).**
- **Aspirin prescription should be reviewed at 36 weeks of gestation to consider stopping prior to delivery (2C).**

Scheduled ultrasound scanning

Standard ultrasound scanning should be performed as per the NICE guidelines.[34] A number of studies suggest an increased risk of fetal anomalies and babies that are small for gestational age in the offspring of women with SCD.[37] Third-trimester growth scans should be undertaken for early detection of fetal growth restriction to aid appropriate timing of delivery and to reduce perinatal mortality and morbidity in view of the four times increased risk of stillbirth.[40] If pregnancy-associated plasma protein A (PAPP-A) levels are performed in the first trimester and the value is <0·5 multiple of the median then consider performing more frequent scans after 20 weeks.[41]

Recommendations

- **Women should be offered serial fetal biometry scans (growth scans) every four weeks from 24 weeks of gestation (1C).**

Blood transfusion during pregnancy

Transfusion has been used in pregnant women with SCD to correct severe anaemia and reduce sickle-related complications. It may also reduce pregnancy complications by reducing the extent of sickling in the maternal and placental circulation and therefore may improve blood flow and oxygen supply to the fetus. These benefits must be weighed up against the side effects of transfusion including the risk of alloimmunisation and risk of delayed haemolytic transfusion reactions. The type of blood selected for transfusion of women with SCD should be cytomegalovirus (CMV)-negative, HbS-negative and extended Rh- and Kell-matched in line with previous BSH recommendations.[42]

A full transfusion history should be taken from the patient at the booking appointment or first obstetric/haematology appointment and should include communication with the transfusion laboratory and national transfusion database to ensure there are no historical alloantibodies. Patients with historic alloantibodies should be referred to the fetal red cell antibody clinic or screening programme for haemolytic disease of the newborn for monitoring of antibody titres.

A key question in the management of pregnant women with SCD regards the best approach to blood transfusion during pregnancy. One approach is to give blood only if required by the clinical situation, for example for acute anaemia or other acute complications. The other approach is to give blood prophylactically throughout pregnancy; if this approach is used then further questions include whether simple or exchange transfusion should be used, at what gestation transfusion therapy should be started and is there a target Hb or HbS% that should be used. This has been discussed in a previous BSH guideline and a recent ASH guideline.[43,44]

There is currently insufficient evidence to recommend prophylactic transfusion over standard care (transfusion as required) and whilst there is some evidence that prophylactic transfusion will reduce vaso-occlusive pain during pregnancy it is not clear if the benefits of transfusion will outweigh the risks of transfusion (e.g., alloimmunisation). The recent ASH guidelines[44] concluded that there was insufficient evidence to recommend a strategy of prophylactic transfusion rather than standard care. A phase 2 clinical trial is currently investigating the role of serial prophylactic exchange blood transfusion in pregnant women with SCD (TAPS-2).[45]

In one randomised trial, including 72 women and published in the 1980s[44] women received standard care or prophylactic transfusion with simple or partial exchange transfusion to achieve Hb 100–110 g/l and HbS% < 35%. In the standard care arm, 44% of women required transfusion. There was a significant reduction in vaso-occlusive crises in the prophylactic transfusion arm [relative risk (RR) 0·28, 95% confidence interval (CI) 0·12–0·67] but no clear differences in other outcomes (maternal mortality, perinatal mortality or severe maternal morbidity) although this may be explained by the small numbers included in the trial. There was no harm identified from the transfusions. A Cochrane review[47] did not find any additional randomised trials and concluded that there were no clear clinical benefits of prophylactic transfusion over standard care. There have been numerous observational trials reporting on outcomes of prophylactic transfusion in pregnancy and a meta-analysis has reported on the previous randomised clinical trial and additional 11 cohort studies involving 1 291 participants.[48] This meta-analysis demonstrated that prophylactic transfusion was associated with a reduction in maternal mortality, vaso-occlusive crises, pulmonary complications, pyelonephritis, perinatal mortality, neonatal death and preterm birth. There was no difference in pulmonary infection, acute chest syndrome, urinary tract infections, pre-eclampsia, intrauterine fetal demise, infants that are small for gestational age or have a low birth weight. The event rates were low for most of the outcomes and they concluded that prophylactic transfusion may positively impact on severe maternal and neonatal outcomes but the evidence comes from a small number of studies.

There has been a further paper looking at outcomes of women with HbSC and comparing 10 women receiving prophylactic exchange transfusion with 14 women receiving transfusion on demand or no transfusion but numbers were small and selection methods were biased so it is not possible to reach conclusions about the role of prophylactic transfusion in women with HbSC.[49]

The risks and benefits of prophylactic transfusion during pregnancy should be discussed with the patient, haematologist and obstetrician in early pregnancy and factors to be considered will include:

1. Genotype (HbSS more likely to benefit than HbSC).
2. Phenotype (severe disease phenotype more likely to benefit).
3. Previous obstetric history (women with a history of previous sickle complications in pregnancy may be more likely to benefit).
4. Twin pregnancy may be more likely to benefit (expert opinion due to adverse outcomes in twin pregnancies).
5. Alloimmunisation (women with a history of multiple red cell alloantibodies or previous delayed haemolytic transfusion reaction are at increased risk of transfusion-related complications).

Women who are already on long-term transfusion therapy should continue on this during pregnancy at the same frequency. Women on hydroxycarbamide will be advised to stop this prior to conception and prophylactic transfusion should be considered if they experience a worsening of their sickle symptoms once they stop hydroxycarbamide or if they have a very severe prehydroxycarbamide phenotype.

If the benefits of prophylactic transfusion are not thought to outweigh the risks, then standard care is to give transfusion on demand, when clinically indicated. There is little evidence to indicate what target Hb or HbS% should be used for optimal care and most evidence comes from the care of non-pregnant patients with SCD. The randomised trial of transfusion described above[46] used an Hb value of <60 g/l as an indication for simple transfusion and this level was used in previous RCOG guidance.[1] Many clinicians would aim for a higher Hb value during pregnancy although this will depend on baseline Hb and symptoms of anaemia. Women with severe sickle complications (e.g., acute chest syndrome, stroke or intractable pain) should be treated with transfusion as recommended in non-pregnant patients with SCD.[43,50]

There is no evidence about the optimal Hb level or HbS% prior to caesarean delivery. A randomised trial looking at elective surgery in non-pregnant patients with HbSS showed that pre-operative transfusion to Hb > 90 g/l was associated with reduced postoperative sickle complications, particularly acute chest syndrome.[51] Caesarean section was not included in this trial and the main complications were probably due to general anaesthesia. Women with marked anaemia (<70 g/l) may benefit from pre-operative transfusion prior to caesarean section.

Recommendations (adapted from Refs.42,43)

- **If transfusion is needed, pregnant women with SCD should be given ABO-compatible, extended Rh- and Kell-matched, CMV-negative units. If there are clinically significant red cell antibodies (current or historical) then the red cells selected should be negative for the corresponding antigens (1C).**
- **The risks and benefits of prophylactic transfusion during pregnancy should be discussed with the patients as part of the haematology/obstetric consultation (2C).**

- **Prophylactic transfusion is not routinely recommended for sickle pregnancy, but should be considered for women with:**
  - a **Previous or current medical, obstetric or fetal problems, related to SCD. (2C).**
  - b **Women previously on hydroxycarbamide due to severe disease (2C).**
  - c **Multiple pregnancy (2C).**
- **Women receiving long-term transfusions for stroke prevention or for the amelioration of severe sickle complications should continue with regular transfusions throughout pregnancy (1B).**
- **Transfusion may be required in women with worsening anaemia (1B).**
- **Transfusion should be considered for those with acute SCD complications (e.g., acute chest syndrome, stroke) (1B).**

Management of acute pain episodes during pregnancy

Pregnancy is associated with an increased incidence of acute painful crises,[52–56] in both HbSS and to a lesser extent HbSC disease.[7] In a prospective UK study, acute pain was the most common complication, affecting 57% of pregnant women with SCD. Severe or extremely severe crises (requiring hospital attendance or admission) occurred in 17·6% of women with HbSS and 9·1% of women with HbSC ($P = 0{\cdot}23$). Postnatal painful crises were also significantly higher in the HbSS women, occurring in 21·6% of HbSS and 2·3% of HbSC women ($P = 0{\cdot}01$).[4]

There are a number of possible reasons for the increased incidence of crisis including increased physical and psychological stress; dehydration, particularly in early pregnancy when nausea and vomiting are common; worsening anaemia, which is common in pregnancy, related to increased iron requirements and red cell turnover; the pro-coagulant state in pregnancy predisposing to vaso-occlusive disease; and the increased risk of infection, for example, urinary infection or influenza, which can precipitate a sickle crisis. Birth, whether by vaginal delivery or caesarean section, is a profound physiological challenge and can increase the risks of dehydration, hypoxia, anaemia, overexertion and significant metabolic derangement, which can all lead to a higher incidence of crisis. Pregnant women with SCD may present with non-sickle causes of acute pain such as placental abruption or appendicitis. A careful history is essential to determine whether the pain is typical for vaso-occlusive pain and if not alternative aetiologies should be explored.

All pregnant women should have a prospective pain management plan for use in the event of a potential crisis that should have been developed and discussed with the multidisciplinary team (MDT) and the woman and shared with all healthcare providers involved with her care including her general practitioner and her community midwife. This should be discussed at her first multidisciplinary clinic appointment and reviewed at subsequent appointments. There should be a low threshold for referring a woman to secondary care and all women with pain that 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.

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 with modifications to account for evidence of safety of specific analgesics for the fetus. Mild pain may be managed in the community with rest, oral fluids and paracetamol or weak opioids (such as co-dydramol, co-codamol or dihydrocodeine). NSAIDs should be used with caution in the first trimester and avoided after 31 weeks of gestation due to the risk of premature closure of the patent ductus.[21,22,57] If a woman needs strong opiate therapy, she will need to be admitted to the hospital. The NICE guidelines for the management of acute crisis advocate that analgesia be given within 30 min of arrival in hospital after a rapid initial assessment and the pain should be controlled within 60 min of starting analgesia.[58] There is no evidence to suggest pregnant women should be treated differently.

For severe pain, morphine, diamorphine or oxycodone can be given by the oral, subcutaneous or intravenous route, depending on the woman's preference and local expertise. Pethidine should be avoided because of the risk of toxicity and pethidine-associated seizures in patients with SCD.

On presentation, a woman with sickle crisis should be assessed rapidly for medical complications and precipitating factors requiring intervention. A full set of observations, using a modified obstetric early warning chart, including systolic and diastolic blood pressure, pulse, respiratory rate, temperature, oxygen saturation and pain score should be recorded and repeated every 1–2 h.[58] With analgesia administration, assessments of pain score, sedation score and respiratory rate should be monitored initially at 20-min intervals. Women should ideally be cared for in an environment with experienced nurses/midwives with training in looking after pregnant women with SCD. Depending on local expertise and the gestation of the woman and the severity of her condition, it may be appropriate to manage her on a medical ward, a haematology ward, an obstetric ward or in a level 2 or 3 critical care setting. Senior obstetricians, haematologists, obstetric anaesthetists, obstetric physicians, specialist nurses and midwives should make up the MDT and care should be coordinated and planned by this group and discussed with the woman and her family.

Fluid status should be assessed and documented carefully. Dehydration should be avoided, and intravenous (IV) fluids may be required to maintain adequate hydration. Fluid status and IV fluid prescription should be reviewed at least 12-hourly, especially in a woman with SCD-related renal disease

or with suspected pre-eclampsia as fluid overload is a potential risk.

Oxygen saturations should be monitored and if oxygen saturation falls below the woman's baseline or below 95% urgent medical review should be requested, due to the risk of acute chest syndrome and pulmonary embolism (PE), and facial oxygen should be prescribed. There should be early recourse to intensive care if satisfactory oxygen saturation cannot be maintained with oxygen via face mask or nasal cannula. Women with back or chest pain should be offered an incentive spirometer.

The woman should be assessed for infection and urine culture and microscopy performed. A chest X-ray should be performed if the woman has abnormalities on chest examination or is hypoxic. Antibiotics as per the local pregnancy-specific guideline 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 pregnant women and in SCD and alone, do not necessarily indicate infection.[59]

Thromboprophylaxis should be prescribed for women with SCD who are admitted to hospital with painful crises, unless there is a contraindication.[60] 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.

In severely unwell woman, an accurate identification of the gestation of the fetus is required. If before the threshold for viability (approximately 24 weeks and 500 g), additional fetal monitoring is not needed. From 24 to 28 weeks, fetal well-being should be monitored by ultrasound scanning. After 28 weeks daily continuous fetal monitoring should be performed in addition to ultrasound scanning (if not performed in the last week).

Recommendations

- **Pregnant women with SCD should have an agreed pain management plan for the treatment of acute painful crisis (1D).**
- **If pregnant women are admitted with acute pain crises they should be looked after by the MDT (1D).**
- **The NICE guidelines[58] on the management of acute painful episodes should be followed (1B).**
- **NSAIDs should be used with caution in the first trimester and avoided after 31 weeks of gestation (2C).**
- **Fluid and oxygen balance should be monitored regularly in women admitted with sickle pain crisis (1D).**
- **Women with SCD should be prescribed prophylactic low-molecular-weight heparin during any antenatal hospital admission (1B).**

Management of acute chest syndrome

Acute chest syndrome is an important complication of SCD affecting up to 10% of pregnant women with SCD.[4] It is characterised by fever and/or respiratory symptoms and a new pulmonary infiltrate on chest X-ray. Patients should be monitored for this complication throughout their hospital stay and all hospitals should have a guideline that includes the treatment pathway.[50] Essential investigations for diagnosis and prognosis include chest X-ray and full blood count. Arterial blood gas analysis should be considered in adults with low oxygen saturations as severe hypoxia is a useful predictor of severity and helps guide treatment. The main differential diagnosis is PE which should be considered in patients with a normal chest examination and chest X-ray. Aetiology is multifactorial and includes infection so careful investigation for infective causes should be undertaken including blood cultures, sputum for microscopy and culture and sputum and nasopharyngeal aspiration for viral testing.

Basic management will include prompt pain relief, incentive spirometry and treatment of bacterial or viral infection. Blood transfusion should be considered early in the hypoxic patient. A simple (top-up) transfusion may suffice in early or less severe disease but exchange transfusion will be necessary if there are features of clinical severity or a lack of response to simple transfusion.

The critical care team should be involved in the care of any patients with severe clinical features or in a deteriorating patient to consider non-invasive or invasive ventilation. Following an episode of acute chest syndrome requiring transfusion, the patient should be offered regular prophylactic blood transfusion throughout the remainder of pregnancy.

Recommendations (adapted from Ref.50)

- **Patients with SCD can present with acute chest syndrome (ACS) or it may develop after the onset of severe pain. Therefore vigilance should be maintained throughout hospital admission (1B).**
- **All hospitals should have a treatment pathway for ACS which should include a referral pathway to the high dependency unit or intensive care unit (1B).**
- **Antibiotics, with cover for atypical organisms, should be used even if blood cultures and sputum cultures are negative (1B).**
- **Simple ('top-up') transfusion should be considered early in the hypoxic patient but exchange transfusion is necessary if there are severe clinical features or evidence of progression despite initial simple transfusion (1B).**

Management of other acute complications

Acute stroke, both infarctive and haemorrhagic, is associated with SCD[61] and this diagnosis should be considered in any

woman with SCD who presents with acute neurological impairment. Acute stroke is a medical emergency and requires urgent brain imaging and referral to the stroke physician and haematologist. Rapid exchange blood transfusion can decrease long-term neurological damage. The role of thrombolysis should be discussed with a stroke physician and senior obstetrician. In women with neurological signs, it is important to distinguish cerebrovascular disease due to SCD from pre-eclampsia/eclampsia.

Acute anaemia in women with SCD may be attributable to erythrovirus infection (parvovirus B19). 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, hence a review by a fetal medicine specialist is indicated to assess fetal anaemia.[62,63] 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.

Recommendations

- **Acute stroke should be considered in women presenting with acute neurological impairment and requires urgent consideration of exchange transfusion (1B).**
- **Acute erythrovirus infection should be considered in women presenting with acute anaemia (1A).**

Management of VTE and thromboprophylaxis

Pregnancy is a well-established risk factor for VTE for women but this risk is magnified in pregnant women with SCD.[64–68] In a recent meta- analysis the risk of VTE [odds ratio (OR) 33·2, 95% CI 9·7–113·4, $P < 0{\cdot}001$] and deep vein thrombosis (OR 30·7, 95% CI 1·6–578·2, $P = 0{\cdot}02$) were increased when compared to a cohort without SCD.[68] The prevalence of VTE was 3·5-fold greater in women with complications such as vaso-occlusive crisis, acute chest syndrome and pneumonia when compared to those without these complications, but was less in those with more severe anaemia.[6] In this study 28·6% and 71·4% of VTE episodes were identified as having occurred in the antenatal and postpartum periods respectively.

SCD is listed as one of the risk factors for thrombosis in the 2015 RCOG Green-top guideline: Reducing the Risk of VTE during Pregnancy and the Puerperium.[60] This guideline provides recommendations for risk assessments for thromboprophylaxis and suggests that:

1. All women with SCD should have risk assessments performed in early pregnancy, if admitted to hospital, in the intrapartum and early postpartum period.
2. Women with SCD should be considered for prophylactic low-weight heparin (LMWH) from 28 weeks of pregnancy until six weeks postpartum and if women have additional risk factors, prophylaxis should start from the beginning of pregnancy.
3. Women admitted to hospital with a vaso-occlusive crisis or for other reasons should be offered LMWH throughout their admission unless there are contraindications.

Due to the higher incidence of PE in women with co-existent chest infections or acute chest syndrome[6] and the overlap in presenting features a high index of suspicion for PE is required when assessing these patients. Women suspected of VTE should be managed according to RCOG Green-top Guideline No. 37b: The Acute Management of Thrombosis and Embolism during Pregnancy and the Puerperium.[69]

Recommendations: (adapted from RCOG Guideline 37a[60])

- **All women with SCD should have risk assessments performed in early pregnancy, if admitted to hospital, in the intrapartum and early postpartum period (1C).**
- **Women with SCD should be considered for prophylactic low-weight heparin (LMWH) from 28 weeks of pregnancy until six weeks postpartum and if women have additional risk factors, prophylaxis should start from the beginning of pregnancy (2B).**
- **Women admitted to hospital with a vaso-occlusive crisis or for other reasons should be offered LMWH throughout their admission unless there are contraindications (1B).**

Intrapartum care

Timing of birth

There are no randomised controlled trials to dictate the appropriate timing of delivery. Recent systematic review and meta-analysis[5,70] confirm increased perinatal mortality, particularly during the later stages of pregnancy, in part due to the complications of SCD. The risks of abruption, unexplained stillbirth, pre-eclampsia, peripartum cardiomyopathy and acute sickle cell crisis are increased and unpredictable. A prospective birth plan should be made, in consultation with the woman to include mode of delivery, place of labour, MDT, positions for labour, analgesia and additional monitoring requirements that may be appropriate. Due to the increased risk of placental insufficiency and pre-eclampsia, delivery between 38 and 40 weeks is often indicated to prevent late-pregnancy complications and associated adverse perinatal outcomes.

Recommendation

- **Pregnant women with SCD who have a normally growing baby should be delivered between 38 and 40 weeks of gestation (2D).**

Mode of birth

Whilst older studies questioned vaginal delivery as the optimal mode of delivery for women with SCD, recent studies reflecting UK practice of supporting vaginal delivery as the recommended mode of delivery, with the need for the caesarean section based on obstetric indications, report satisfactory outcomes.[4,5] Caesarean section increases the woman's risk of infection and VTE so elective caesarean birth should not be advised for women with SCD in the absence of other risk factors or obstetric indications. Women with SCD are more at risk of caesarean section because of the increased obstetric complications such as pre-eclampsia, intra-uterine growth restriction and the need for earlier delivery.[5] Previous avascular necrosis of the hip can lead to poor hip rotation and abduction; and in women with recurrent severe crises, avoiding a long labour may help to minimise the risk of intrapartum SCD crisis.

Recommendations

- **Women with SCD can be offered vaginal delivery and vaginal birth after previous caesarean (VBAC) if there are no other contraindications (2D).**
- **In women who have hip replacements (because of avascular necrosis) suitable positions for delivery should be discussed prior to delivery (1D).**

Optimal intrapartum care

Good analgesia (with a prospective management plan for anaesthetics made prior to labour), with avoidance of dehydration, regular monitoring of oxygen saturations and avoidance of a protracted labour, form the mainstay of the intrapartum management of a woman with SCD. General anaesthesia carries additional risks beyond the normal obstetric case and should be avoided where possible. Women should be offered review by an anaesthetist in the third trimester of pregnancy to discuss these issues. Pethidine should be avoided because of the risk of seizures when administered to a woman with SCD.

There are no randomised controlled trials regarding the place of birth for women with SCD but women should be advised to give birth in hospitals that are able to manage both the complications of SCD and high-risk pregnancies. Obstetricians need to be aware of the increased frequency of sickle cell crisis and ACS in the intrapartum period and of the increased risk of painful crisis with long labour (>12 h). This is often secondary to dehydration and in this situation, the woman should be well hydrated. If 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.

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. If venous access is difficult to obtain the woman should be referred to the anaesthetist. 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 may be considered and oxygen therapy instituted if oxygen saturation is 94% or less.

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 regarding interventions during labour for women with SCD but close observation during labour is essential. Continuous electronic fetal heart rate monitoring is recommended because of the increased rate of stillbirth, placental abruption and compromised placental reserve.[71] Sickle cell crisis in labour should be treated as per the guidance for antepartum crisis above.

Epidural analgesia is safe and effective and should be available for women in labour.

Recommendations

- **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 (1D).**
- **The relevant MDT (senior midwife in charge, senior obstetrician, anaesthetist and haematologist) should be informed as soon as labour is confirmed (1D).**
- **Blood should be cross-matched for delivery if there are atypical antibodies present (since this may delay the availability of blood) (1D).**
- **Women should be kept warm and given adequate fluid during labour, using a fluid balance chart to avoid fluid overload (1D).**
- **Continuous intrapartum electronic fetal heart rate monitoring is recommended owing to the increased risk of fetal distress, which may necessitate operative delivery (1D).**
- **Women with SCD should be offered anaesthetic assessment in the third trimester of pregnancy (2D).**
- **Opiates may be used for analgesia, except for pethidine (1D).**
- **Regional analgesia is recommended for caesarean section (1D).**

Postpartum care

Optimal postdelivery care

It is important for clinicians to remain vigilant postnatally as the risk of sickle cell crisis remains increased with 21–25% of women having a crisis post delivery and crisis being more common following general anaesthesia.[5,72] 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. Neonates and young infants are at risk from the adverse effects of opioids. Codeine should not be given during breastfeeding. Dihydrocodeine and tramadol and other opioids can be used but should be at the lowest effective dose, for the shortest duration and under medical supervision. Infants should be monitored for sedation, breathing difficulties, constipation, difficulty feeding and weight gain.

Breastfeeding should be encouraged, as in women without SCD. If the baby is at high risk of SCD (i.e. the partner is a carrier, affected or unknown status) early testing for SCD should be offered. Samples should be sent to laboratories where there is experience in the routine analysis of SCD in newborn samples.

Routine care should be provided as per the NICE guideline on postnatal care.[73] Antithrombotic stockings are recommended in the puerperium.[60] Thromboprophylaxis in the form of LMWH is recommended whilst the pregnant woman is in hospital and for six weeks post delivery.[60]

Women should be given appropriate postpartum contraceptive advice, the timing depending on breastfeeding and the choice of contraception to be used.

Recommendations

- **Women should be advised that they have an increased risk of pain episodes in the postnatal period and precipitants should be avoided (1D).**
- **Women should receive thromboprophylaxis with LMWH for six weeks after delivery (1C).**

Contraception advice for women with SCD

Given the health risks of an unintended pregnancy, counselling about contraception is an important component in the care of women with SCD and appropriate advice should be conveyed to the woman's primary care workers. Used correctly, all hormonal contraceptives have 99% efficacy and the choice of contraception should be individualised, taking into account the woman's preference, lifestyle and ease of compliance.

There is theoretical concern with combined hormonal contraceptives (CHCs) that the risk of thrombosis or sickle crisis may be increased. A retrospective study of 1 257 women with SCD, of which 178 (14·2%) were CHC users, showed a fourfold increased risk of ischaemic stroke associated with CHC. However, when adjusted for confounding cardiovascular risk factors such as smoking, there was no significant difference.[74] A systematic review found no effect of CHCs on the frequency of sickle crises or other adverse events and no effect on haematological parameters associated with sickle crises.[75] However, whilst evidence remains limited, the authors' recommendations are that CHCs should be used selectively, with risk being mitigated by controlling other cardiovascular risk factors. The 2019 updated Faculty of Sexual & Reproductive Healthcare (FSRH) guide classifies CHCs as category 2, where the advantages outweigh the theoretical risks.[76]

Progesterone-only preparations, such as the progesterone-only pill, injectable contraceptives and the levonorgestrel intrauterine system (LNG-IUS) have not been shown to have detrimental effects[77] and indeed there is some evidence of clinical benefit. An early study showed oral progesterone led to an 80% reduction in painful episodes.[78] Intramuscular depo-medroxyprogesterone acetate (DMPA) has been found to reduce painful crises[79] and improve laboratory parameters[80] suggesting an inhibition of *in vivo* sickling. Etonogestrel sub-dermal implant has been associated with improved well-being in women with SCD,[81] with clinical improvement paralleled by elevation of F cells.[82] With the LNG-IUS bleeding may be unpredictable for the first few weeks but most women will see reduced bleeding thereafter.[83] The FSRH classifies progesterone-only preparations as category 1, unrestricted use.[76]

The copper intrauterine device is classified as category 2 due to concern about the potential increased risk of blood loss but it is still considered that the benefits outweigh the risks. Barrier methods are safe in women with SCD but generally less effective than other forms of contraception.

Recommendations

- **Contraceptive advice should be given and conveyed to the woman's primary care team (1D).**
- **The choice of contraception should be individualised but methods that eliminate user failure, such as LNG-IUS and sssntramuscular DMPA are preferred (2B).**
- **There is some evidence for reduction in sickle pain associated with progesterone-only preparations (2C).**
- **CHCs are an option for women with SCD but cardiovascular risk factors should be minimised to mitigate potential risk (2D).**

Conclusion

The majority of women with SCD in the UK will reach reproductive age and discussion of reproduction options and

pregnancy should form part of their annual review. Pregnancy is a time of increased risk for women with SCD with increased rates of maternal and fetal complications. Therefore each hospital should have a protocol for the management of pregnant women with SCD. This should identify an MDT that has responsibility for the care of pregnant women with SCD, including an obstetrician with expertise in managing high-risk pregnancies and a haematologist. Areas with a low prevalence of SCD should be linked to a specialist centre or haemoglobinopathy co-ordinating centre for shared care arrangements and shared protocols and all staff involved in maternity care should receive training in the care of pregnant women with SCD.

The majority of the recommendations in this document are of low certainty, reflecting the limited knowledge base and lack of clinical trials in this area and many are based on expert opinion. As such they are likely to be updated if further clinical evidence becomes available. There is a need for well-designed clinical trials in this area to ascertain optimal treatment options.

Acknowledgements

The authors wish to thank Gareth Hardy (Niche) for help in undertaking the initial literature review. The BSH General Haematology Task Force members at the time of writing this guideline were Mamta Garg, Sara Stuart Smith, Noemi Roy, Barbara De La Salle, Charlotte Bradbury, Emmy Dickens, Savio Fernandes, John Grainger and Ciaran Mooney. The authors would like to thank them, the BSH sounding board, and the BSH Guidelines Committee for their support in preparing this guideline. Thank you to Dr Kate Bramham and Prof Claire Sharpe for their comments. We acknowledge the comments of the BSH Obstetric Special Interest Group (Etienne Ciantar, Jane Graham, Amy Webster, Elizabeth Rhodes Amanda Clark, Charlotte Bradbury).

Conflicts of interest

The BSH paid the expenses incurred during the writing of this guidance. All authors have made a declaration of interests to the BSH and Task Force Chairs which may be viewed on request. The following authors have undertaken advisory board, educational grant and speaker's fees: JH for Novartis, Global Blood Therapeutics, Novo Nordisk, Imara, Forma, Resonance Health, Bluebird Bio. LM is supported by the NIHR Oxford Biomedical Research Centre and is also a part-time employee and shareholder of Sensyne Health plc. The following members of the writing group have no conflicts of interest to declare: EO-N, SP, RH, SR, LO, SP.

Review process

Members of the writing group will inform the writing group Chair if any new evidence becomes available that would alter the strength of the recommendations made in this document or render it obsolete. The document will be reviewed regularly by the relevant Task Force and the literature search will be re-run every three years to search systematically for any new evidence that may have been missed. The document will be archived and removed from the BSH current guidelines website if it becomes obsolete. If new recommendations are made an addendum will be published on the BSH guidelines website (https://b-s-h.org.uk/media/16732/bsh-guidance-development-process-dec-5-18.pdf).

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