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The obstetric management of sickle cell disease

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Sickle cell disease (SCD) is the most common inherited disease worldwide and is associated with anaemia and intermittent severe pain. Pregnant women who are affected have increased maternal and fetal mortality and morbidity. In view of this obstetricians should have an awareness of this condition and its complications, and pregnancies in women with SCD should be managed by a multidisciplinary team with experience of high risk pregnancies. Ideally women should be seen preconceptually for optimisation of their SCD and partner screening. Antenatal care should include regular outpatient visits with regular monitoring for pre-eclampsia and of fetal growth. Blood transfusion should be used for the treatment of acute anaemia, acute chest syndrome or acute stroke but there is not sufficient evidence currently to recommend its use prophylactically. There is an increased prevalence of sickle crisis during pregnancy and patients should be monitored carefully throughout this time.

Introduction and background

Definitions and classification

Sickle cell disease is an autosomal recessive disorder, caused by the 'sickle' gene which affects haemoglobin (Hb) structure. The term SCD refers to homozygous sickle cell disease (HbSS) and the

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heterozygous conditions which occur when Hb S is co-inherited with another abnormal haemoglobin, most commonly HbC or β-thalassaemia, giving rise to HbSC or HbS-βthalassaemia. Co-inheritance can occur less commonly with HbD, HbE and HbO-Arab. All genotypes give a similar clinical picture, although with varying severity, for example patients with HbSC tend to follow a milder clinical course than patients with HbSS.

Epidemiology

Sickle cell disease (SCD) is the most common inherited condition worldwide with over 300,000 children born with the condition each year,[1,2] two-thirds in Africa.[3] In the UK there are between 12,000 and 15,000 affected individuals with SCD and each year over 300 infants are born with SCD[4] and there are approximately 100–200 pregnancies in women with SCD.

Geographical variation

SCD is most prevalent in individuals of African descent, but is also seen in the Caribbean, Middle East, India, the Mediterranean and South and Central America and with increasing population migration and improving survival it is of increasing importance worldwide.[5]

There is significant geographical variation in prevalence across the UK with two-thirds of patients being based in London, and the majority of others in large cities outside London. This is challenging for provision of obstetric services as whilst large centres may see up to or over twenty pregnancies per annum, smaller non-urban units may only see a sickle pregnancy every few years.

Pathophysiology

The abnormal haemoglobin found in SCD polymerises in low oxygen tension to form long chains of haemoglobin which renders the red cells rigid and fragile. These fragile cells are prone to increased breakdown and this causes the haemolytic anaemia which is associated with a marked decrease in red cell lifespan. The main pathophysiological event is vaso-occlusion, or blockage of the small blood vessels and this leads to the clinical effects of SCD. Vaso-occlusion in the bones leads to the classic symptom of acute severe bony pain but it is a multi-organ process and also leads to the chronic multi-organ complications seen in this condition. Vaso-occlusion is a complex process and is due in part to the abnormal red cells, which are not only less deformable and more fragile than usual because of the polymerisation of the sickle haemoglobin but have an increased tendency to cellular dehydration. In addition there is increased adhesion of red cells to the vascular endothelium. This is due to an increase in the expression of adhesion molecules, up regulation of the thrombotic pathway and endothelial activation which increases vaso-occlusion. Vaso-occlusion is also influenced by the pro-inflammatory state seen in patients with SCD, increased numbers and activation of white blood cells and nitric oxide deficiency.[6,7]

Clinical features

Individuals with SCD have a chronic anaemia and an average haemoglobin level of 6 to 9 g.dl. Patients with the milder genotypes (eg HbSC) may have higher Hb levels, even within the normal range, so having a normal or near-normal haemoglobin does not exclude the diagnosis of SCD. The other major clinical feature is recurrent, unpredictable episodes of severe bony pain, which occur lifelong. Children will typically present with dactylitis (pain and swelling in the fingers and toes) but in older children and young adults pain more typically occurs in the long bones, or in the trunk. These painful episodes (or 'crises') occur with variable frequency and severity. Frequency varies from less than one episode of severe pain per year, to more than one episode per month. These episodes may simply require rest and simple analgesia (e.g. paracetamol, ibuprofen, dihydrocodeine) and can be managed at home, but if severe often require hospital admission for opioid analgesia. These painful episodes can be precipitated by stress, dehydration and infection.

SCD is a multi-organ disorder and other complications of SCD include an increased risk of stroke, renal dysfunction, pulmonary hypertension, retinal disease, leg ulcers, cholelithiasis and avascular

necrosis. These conditions may pre-exist prior to pregnancy, or may be diagnosed for the first time during pregnancy. SCD was previously associated with an early mortality, but with improved medical care average life expectancy is improving and the majority of women born in the UK will reach child bearing age.[8,9]

Diagnosis

Patients with SCD who are born in England will be diagnosed as part of the neonatal screening programme and will be enrolled into a specialist sickle cell or haematology clinic where they will be reviewed at least annually. They should be reviewed for disease complications at these visits, as well as being counselled about pregnancy. Some women, however, will not be seen in a sickle cell clinic because they have been lost to follow up, or have moved from overseas and have not been referred for specialist care, or because they are not diagnosed until they become pregnant. Whilst a full blood count (fbc) and blood film may suggest a diagnosis of SCD, confirmation of diagnosis is required. The most common diagnostic test used in the UK is High Pressure Liquid Chromatography (HPLC), and this highly accurate, automated test will identify all of the major haemoglobinopathies. Alternative testing strategies include isoelectric focussing, cellulose acetate electrophoresis at alkaline pH or capillary electrophoresis. Abnormal results should be confirmed by an alternative technique to the original one. In the majority of laboratories, the clinician will simply request 'sickle screen' or 'haemoglobin electrophoresis' and the laboratory will perform the appropriate diagnostic and confirmatory investigations.

All pregnant women in England will have antenatal screening for SCD as part of their antenatal booking visit. In high prevalence areas where the fetal prevalence of SCD is 1.5 per 10,000 pregnancies or greater, all women are screened for SCD with a full blood count (fbc) and High Pressure Liquid Chromatography (HPLC). In low prevalence areas (where fetal prevalence is less than 1.5 per 10,000), selective screening of women from a high risk ethnic background as defined by the family origin questionnaire is performed. Whilst antenatal screening is primarily aimed at identifying carrier couples and offering them antenatal choice, it will also identify women who were not previously identified as having SCD. Women with the less severe genotypes are quite commonly diagnosed for the first time in pregnancy and these women may need additional support and information about SCD.[10]

Morbidity and mortality associated with pregnancy in sickle cell disease

Information about pregnancy complications comes from observational studies, many of which are retrospective or old, and as such may not reflect current outcomes with modern obstetric care. Pregnancy outcome in the UK is currently being assessed by the UK Obstetric Surveillance System (UKOSS) and results from this, which will give an updated view of complication rates and current outcomes in the UK are awaited. Data from centres across the world show a large variation in maternal mortality varying from 0.07% in a large retrospective study in the US[11] to over 9.2% in a Nigerian study,[12] with a large variation in other studies.[13–17] In the UK one maternal death or less per annum have been reported by the Confidential Enquiries into Maternal Deaths in England & Wales over the last decade. There is also evidence of an increase in perinatal mortality and still birth rate varying from 48 to 134 per 1000 births.[13,15,18,19]

Pregnancy is certainly associated with an increased incidence of painful episodes, even in women who are mildly affected outside pregnancy.[15,16,20–22] There is an increase in antenatal hospitalisation in pregnant women with SCD[22,23] and whilst this is due in part to increased painful episodes, there is also an increase in infection, pulmonary complications,[19,21,24] thromboembolic events[14] and antepartum bleeding.[11] An increased risk of pre-eclampsia and pregnancy induced hypertension has been shown in large retrospective studies, and smaller observational studies,[11,15,18,20,22,23] and women with SCD should be considered to have a high risk of pre-eclampsia. There is also an increased fetal morbidity with an increase in fetal growth restriction and increased premature labour and delivery.[13,15–18,20,22,24,25] These maternal and fetal complications are associated with an increased rate of caesarean section.[11,22–25] There is limited evidence in patients with genotypes other than HbSS, but although there are fewer adverse events seen in women with HbSC, there is still an increase in painful

crises during pregnancy, increased fetal growth restriction, antenatal hospital admission and postpartum infection.[22,26,27]

Pregnancies in women with SCD are therefore high risk and need careful care and planning, both preconceptually and throughout the antenatal, intrapartum and post natal periods. They are associated with increased morbidity and mortality during pregnancy. It is therefore essential that obstetricians are aware of the complications associated with this condition and methods of optimal prevention and treatment. There is little randomised evidence in this area and many of the recommendations are based on observational studies and expert opinion, and there is an acute need for further research.

There is less evidence about the management of the non-HbSS genotypes, but as severe complications can be seen in all genotypes, the recommendations of the authors are that all genotypes are treated as high risk pregnancies.

Preconceptual care

The majority of women with SCD will be seen regularly in a sickle cell or haematology clinic, where they will be monitored for the chronic complications of SCD, many of which will have implications in pregnancy. Some women will present to their general practitioners for pre-conceptual counselling and others may be seen in specialist high risk obstetric clinics.

General advice and care

Patients with SCD should have a review in a specialist clinic at least annually.[28]

This will include blood pressure measurement, urinalysis and assessment of renal function testing to identify women with sickle nephropathy. Both microalbuminuria and proteinuria are common in patients with SCD, and can progress to renal dysfunction and end stage renal failure.[29] Early identification and treatment may prevent this progression, which is thought to worsen during pregnancy.

Pulmonary hypertension is increased in patients with SCD, and is associated with increased mortality.[30] A raised tricuspid regurgitant jet velocity of $>$2.5 ms on echocardiography has been associated with an increased risk of pulmonary hypertension and is a useful screening test, although has a high false positive rate.[31] Women planning pregnancy should have echocardiography performed if this has not been done in the last year.

Proliferative retinopathy is common in SCD, especially in HbSC and can cause permanent visual loss.[32] Whilst there is no evidence that regular screening reduces later visual loss, or that early intervention in patients with proliferative retinopathy can prevent disease progression, in view of anecdotal evidence of progression of retinopathy during pregnancy, we recommend that women are reviewed preconceptually by an ophthalmologist to identify those who are at risk.

Some women with SCD will be on long term blood transfusion regimes, most often for primary or secondary stroke prevention, and these women, and women who have previously had multiple transfusions, should be fully assessed for the complications of iron overload before embarking on pregnancy. This will include a cardiac MRI scan (T2*MRI) to assess cardiac iron overload and, if available a hepatic MRI scan (R2*MRI, Ferriscan) to assess hepatic iron overload. Women with evidence of significant iron overload should be offered aggressive iron chelation before pregnancy.

Patients with SCD have an increased risk of red cell alloimmunization[33] so pre-conceptual screening for red cell antibodies will identify women who are at risk of haemolytic disease of the newborn, and they will need appropriate follow up. Red cell phenotyping should also be performed as there is evidence that the provision of extended phenotyped red cells (full Rh and Kell typed) can minimise the risk of alloimmunization.[33]

Specific issues in women trying to conceive

Conception and contraception should be discussed in sickle cell clinic appointments once the woman reaches child bearing age. They should be aware of the inheritance of SCD and genetic screening of partners should be discussed (see below). The risks of pregnancy and management during pregnancy should be discussed with them. Information given may include the role of dehydration, cold,

hypoxia and stress in precipitating sickle cell crises, the risk of increased pain, worsening anaemia, and increased infections during pregnancy. They should also be counselled about the increased risk of perinatal mortality, fetal growth restriction, premature labour, pre-eclampsia and caesarean section.

Medication and vaccination

Regular medications should be reviewed before patients embark on pregnancy. Many patients will be on regular prophylactic antibiotics, usually penicillin 250 mg bd or erythromycin in penicillin allergic patients. The rationale for this is that 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 of the benefit of prophylactic antibiotics in children below 5 years from a randomised controlled trial,[34] but this benefit has not been shown in adults or in pregnancy. Current UK guidance is that daily penicillin prophylaxis should be given to all patients with SCD in line with the guideline for hyposplenic patients.[28,35] If patients are on penicillin, this should be continued throughout pregnancy and if not the risks and benefits should be discussed with them. A systematic review looking at the pneumococcal C vaccine (pneumovax) has recommended that this should be given to all patients with SCD every 5 years,[36] and the influenza (and swine flu) vaccine should be given yearly to patients with SCD.

Folic acid is recommended for patients with SCD outside pregnancy, because of the haemolysis which puts them at risk of folate deficiency,[37] although there is no clear randomised evidence to support this. However in view of the clear evidence that folic acid is of benefit in pregnant women to prevent neural tube defects,[38] and the increased requirements for folic acid in this group, women planning pregnancy should be commenced on 5 mg folic acid once daily and should continue this throughout pregnancy.

Hydroxycarbamide is used in SCD to decrease the incidence of acute painful crisis and acute chest syndrome.[39] There is evidence that it is teratatogenic in animals however and current UK advice is that women with SCD on hydroxycarbamide use effective contraception and stop taking this drug three months before they conceive. This should therefore be discussed regularly in women of child bearing age. ACE Inhibitors and Angiotensin receptor II blockers (ARBS) are used in patients with SCD with proteinuria, but these are not safe in pregnancy and should be stopped in patients who are trying to conceive. Women who are on iron chelation agents (e.g. desferrioxamine, deferiprone, defirasirox) should be reviewed before pregnancy and these should be stopped if possible. Women should also be counselled about the safety of their usual analgesics during pregnancy and in particular warned that non-steroidal anti-inflammatory drugs (e.g. ibuprofen, diclofenac) are not recommended before 12 weeks and after 28 weeks of gestation and should only be taken after medical advice in the second trimester.

Genetic screening

This may be provided in either the specialist sickle cell clinic, or by the general practitioner. Women with SCD should be encouraged to have the haemoglobinopathy status of their partners tested. If the partner is a carrier of, or affected by, a major haemoglobinopathy the couple should receive appropriate counselling regarding the risk of having affected offspring, the methods and risks of prenatal diagnosis and termination of pregnancy and the availability of pre-implantation genetic diagnosis. Further information can be obtained from the National Screening committee and Programme website[40] or in the Handbook for Laboratories.[10]

Antenatal care

General advice

Many women present without preconceptual care, and some women, especially those with mild disease phenotypes may present for the first time in pregnancy. In these women, the advice in the preconceptual care section should be followed with respect to general counselling, investigation and

monitoring of chronic disease complications, medications and vaccines and review of red cell antibody status, and should be completed as early in pregnancy as possible.

Whilst there are no randomised trials examining the most effective methods of providing antenatal care, there is evidence from the US and Africa that the provision of multidisciplinary teams providing antenatal care and active prenatal management providing information about SCD and specific SCD care can improve obstetric outcomes.[11,21,41] Antenatal care should therefore be provided by a multidisciplinary team including an obstetrician and midwife with experience in high risk antenatal care and a haematologist with an interest in sickle cell disease. Where there are sufficient patient numbers it may be possible to have a specific sickle-obstetric clinic, but in the majority of centres, who will only see patients with SCD infrequently, it is important that they are looked after by a team experienced in the care of high risk pregnancies, that there are clear protocols for care and that there is a clear referral pathway to a specialist sickle cell centre for women who develop sickle complications during pregnancy.

Genetic screening

If the woman's partner has not been screened preconceptually this should be done urgently. If the partner is a carrier of, or affected by, a major haemoglobinopathy the couple should receive appropriate counselling regarding the risk of having affected offspring and the methods and risks of prenatal diagnosis and termination of pregnancy, ideally by ten weeks gestation.[10,40]

Medications and vaccinations

If the woman has not been seen pre-conceptually, the same advice should be given as outlined above. This will include taking daily folic acid and stopping any drugs that are unsafe in pregnancy. Iron supplementation should not be given routinely to women with SCD, unless they are proven to be iron deficient, because of the risk of pre-existing iron overload.[42] There is evidence from a systematic review that low dose aspirin (75 mg daily) taken from 12 weeks of gestation can decrease the risk of pre-eclampsia in women who are at high risk of this complication.[43] Whilst there is no specific evidence regarding the role of aspirin in patients with SCD, they are at high risk of pre-eclampsia, and in view of this, and the evidence of improvement in placental function in patients with anti-phospholipid syndrome, the authors recommend 75 mg aspirin daily from early pregnancy.

There is evidence from observational studies that the risk of venous thromboembolism is increased in pregnancy in SCD.[11,14] Thromboprophylaxis advice should be based on the RCOG Green-top guidelines, so women will only receive routine antenatal thromboprophylaxis if they have additional risk factors, but should receive low molecular weight heparin during hospital admission.[44]

Antenatal appointments

Women should be seen regularly throughout pregnancy by members of the specialist sickle obstetric or high risk obstetric team. We recommend an early booking appointment, monthly visits to the multidisciplinary team until 24 weeks, fortnightly visits to 38 weeks and weekly visits thereafter. In view of the increased risk of pregnancy induced hypertension and urinary tract infections,[11] blood pressure and urinalysis should be performed at each visit, with more frequent monitoring in women with pre-existing proteinuria, and midstream urine should be sent for culture and sensitivity monthly.

At the booking visit, in addition to the usual booking procedure, the issues outlined in the pre-conceptual and antenatal care sections above should be covered, including genetic screening, review of assessments for chronic complications and review of medications and vaccinations. The usual schedule for ultrasound examinations should be followed and in addition uterine artery Doppler scanning should be performed at 24 weeks. This has a good negative predictive value and if normal is reassuring.[45] In view of the high incidence of fetal growth restriction, ultrasound examinations to assess fetal growth and amniotic fluid volume should be performed 4 weekly from 24 weeks gestation and more frequently if there is evidence of poor growth. This allows early detection of growth restriction and will aid decision making about early delivery if appropriate.

Blood transfusion

Blood transfusion therapy is an effective and sometimes lifesaving treatment in SCD, and there are clear clinical indications for urgent transfusion therapy which include acute anaemia, acute chest syndrome or acute stroke. Women with acute anaemia, which can be due to transient red cell aplasia, acute splenic or hepatic sequestration or increased haemolysis, often require a top up transfusion. There is no evidence for a particular level of haemoglobin acting as a trigger, but usually a haemoglobin level <6 g/dl or a fall of over 2 g/dl from baseline, especially if the woman is symptomatic of anaemia would indicate a need for transfusion. Exchange transfusion is accepted as best practice in the treatment of both acute chest syndrome or an acute stroke outside pregnancy, and whilst there is no evidence in pregnancy, it is the recommended treatment, but should be instigated by an experienced senior haematologist and obstetrician. If someone has had a complication requiring exchange transfusion during pregnancy, it is usually appropriate for them to continue to receive transfusion through the rest of pregnancy.

Some centres treat all women with SCD with prophylactic transfusion therapy throughout pregnancy, or in the later stages of pregnancy and early studies showed a decrease in maternal morbidity and mortality with transfused women compared to historical controls.[46–48] Both a randomised controlled trial and a retrospective study have shown that prophylactic blood transfusion decreased acute painful episodes during pregnancy but did not influence fetal or maternal outcome.[19,49] A systematic review has concluded that there is insufficient evidence to draw conclusions about the role of prophylactic blood transfusion in pregnancy.[50] A large retrospective study of 128 singleton pregnancies in SCD women in France which used prophylactic transfusion in all women from 22 weeks showed that despite prophylactic transfusion there was still an increase in antepartum admissions, infection rates, severe anaemia, renal failure and pre-eclampsia when compared with women without SCD and a decreased birth weight in the offspring of SS women. In addition, the sickle related complications of painful crisis and acute chest syndrome occurred despite transfusion.[22] In the randomised controlled trial the transfusions were not started until a mean gestational age of 14 weeks, and this may have been too late to have an effect on outcome in particular on fetal growth, a further randomised trial using transfusion from early in pregnancy, would be needed to answer this question fully. Prophylactic transfusion through pregnancy is indicated however for women who are on a long term transfusion regime prior to pregnancy: this is most usually for secondary stroke prevention, or for the prevention of severe disease complications.

Blood transfusion, especially in patients with SCD is not without complications and alloimmunisation (the formation of antibodies to red cell antigens) is very common in patients with SCD, occurring in up to 29% of patients.[14,49] It can be associated with delayed haemolytic transfusion reactions and haemolytic disease of the newborn.[51] The majority of red cell antibodies are to the C, E and Kell antigens, and formation of these antibodies can be diminished by giving red cells matched for these antigens.[22] Therefore all pregnant women with SCD should have red cell phenotyping performed at booking, if this has not been done already, and when blood is ordered for transfusion it is essential that the laboratory is aware that the patient has SCD and that they require C,E and Kell matched blood.

Management of acute painful episodes during pregnancy

Acute pain episodes are the most frequent complication seen during pregnancy in women with SCD. They have an incidence of between 27% and 50% in observational studies[15,16,19,21] and are associated with an increased rate of antenatal hospital admission.[11] Women often experience increased incidence of pain during pregnancy compared with their baseline pain levels which may be due to the effort of supporting the pregnancy, increased stress, dehydration or infection. A systematic review has found no randomised controlled evidence for optimal treatment in this area,[52] so treatment of acute pain in pregnancy should follow the guidelines for non-pregnant patients.[53]

Mild sickle pain can be controlled in the community with rest, fluids and simple analgesia (paracetamol, or weak opioids), but women with more severe pain should be referred to hospital for review. During pregnancy there should be a lower threshold for admitting women with sickle pain to hospital and women who are febrile, have atypical pain or chest pain should be assessed urgently in secondary care.

Women with SCD who present with acute pain should be assessed for other complications such as infection or acute chest syndrome and for other precipitating factors such as dehydration. Initial examination should include oxygen saturations and urinalysis and investigations should include full blood count, reticulocyte count and renal function with other investigations such as blood cultures and chest X-ray being done as appropriate.

Pain should be treated rapidly with effective analgesia. Most of the women will have used simple analgesia such as paracetamol and weak opioids (co-codamol, co-dydramol or dihydrocodeine) before coming to hospital, and strong opioid medication will often be necessary to control pain. Morphine or diamorphine are usually used as first line agents and can be given orally or parenterally depending on patient preference.[53] Parenteral opioids can be given subcutaneously, intra-muscularly or intravenously and can be administered by intermittent bolus or using a patient controlled analgesia device. Pethidine is not recommended because of the risk of pethidine associated fits in patients with SCD.

UK Standards state that patients with acute SCD pain should be given initial analgesia within 30 minutes of arrival at hospital and that their pain should be under control by one hour.[28,53] This means that there should be rapid initial assessment and provision of analgesia and they should be frequently re-assessed, at 20 to 30 minute intervals, and further pain relief given as necessary to render them pain free. If they have received strong opioid analgesia women will usually be admitted for observation and may need ongoing analgesia. Each obstetric unit should have clear protocols for where pregnant women with sickle are assessed and admitted, and clear care pathways. They will usually be admitted to a medical ward early in pregnancy and to a level 2 obstetric bed later in pregnancy, and in both cases should be under joint care of the obstetric and haematology teams. They should be regularly assessed (every two hours, or more frequently depending on need) for pain score, sedation score and oxygen saturation using a modified obstetric early warning chart (MEOWS).

Oral fluids should be encouraged aiming for 60 ml/kg/24 hours, and if this is not possible because of nausea and vomiting or severe pain, intravenous fluids will be necessary. A careful fluid balance chart should be kept in all cases, but special care should be taken in women with PET who are at high risk of fluid overload. Oxygen saturations should be monitored and facial oxygen prescribed if they fall below 95% or >3% below baseline. Antibiotics should be prescribed if there are concerns about infection, and thromboprophylaxis should be used whilst the woman is an inpatient with acute pain. Anti-emetics, laxatives or anti-histamines may be required to treat the side effects of opioids.

Management of other acute complications in pregnancy

Acute chest syndrome (ACS) is common in SCD and is seen in 7–20% of pregnancies.[17,19,20] It is characterised by a new infiltrate on chest X-Ray in association with respiratory signs and symptoms. It is difficult to distinguish from pneumonia, can co-exist with infection, and is associated with a high morbidity and mortality. Hypoxia is an early sign of acute chest syndrome and pregnant women who develop hypoxia should be assessed for this complication by clinical examination, arterial blood gas monitoring and chest X-Ray. If ACS is suspected senior staff should be involved early, and transfer to a HDU bed should be considered. Treatment is with blood transfusion, antibiotics and respiratory support as in the non-pregnant population. Top up transfusions may be used early in the course of ACS, or if the haemoglobin is less than 6.5 g/dl, however in a deteriorating patient with severe hypoxia, or if the haemoglobin level is well maintained, an exchange transfusion should be performed. A differential diagnosis of ACS is pulmonary embolism (PE), which is also more common in pregnancy in women with SCD, and this should be considered in women presenting with chest pain and hypoxia, especially if chest X-Ray is normal. If PE is suspected therapeutic low molecular weight heparin should be used until definitive investigations have been made. D-dimers are not helpful in this situation as they are invariably raised in acute chest syndrome and in acute sickle pain.

Acute stroke, both infarctive and haemorrhagic, are increased in patients with SCD.[54] Therefore this should be considered in any woman presenting with acute neurological impairment and urgent brain imaging should be performed. Emergency exchange transfusion is vital and can decrease long term neurological disability. The haematology team and neurology team should be contacted urgently. There is no evidence that thrombolysis is of benefit in acute sickle stroke.

Other complications include splenic or hepatic sequestration, cholecystitis and acute anaemia due to parvovirus infection. This is associated with a reticulocytopenia and can be treated with top up blood transfusion, but in view of the risks of vertical transmission in pregnancy the woman should be isolated and should be reviewed by a fetal medicine specialist.

Intrapartum care

Timing of delivery

There are no randomised controlled trials providing evidence about timing of delivery. Observational studies show increased perinatal mortality particularly at the late stages of pregnancy, and there is also an increased risk of complications such as pre-eclampsia, abruption and acute sickle pain. In view of this, and high rates of fetal growth restriction, delivery by 38–40 weeks of gestation is recommended. Once women reach 38 weeks they should be monitored weekly and if there are any signs of maternal or fetal complications e.g. hypertension, proteinuria or poor fetal growth, delivery should be considered.

Most women will go into spontaneous labour, and vaginal delivery is the recommended mode of delivery. The rate of caesarean section is high ranging from 17% in Jamaica to 30–39% in recent UK data and over 60% in older data, but the indication for caesarean should be based on the usual obstetric indications.[17,24–26,55,56]

Optimal care during delivery

In view of the increased risk of complications in these women, in particular the high risk of acute sickle pain, women should be advised to give birth in units which are able to manage the complications of SCD and of high risk pregnancies. During protracted labour (over 12 hours) women may become dehydrated which may precipitate acute pain, therefore women in prolonged labour should be carefully supervised and kept well hydrated and if there is a failure to progress caesarean section should be considered.

Oral hydration is usually sufficient during labour, but intravenous fluids should be considered if the woman is not able to tolerate oral fluids and fluid balance should be monitored carefully. Pulse oximetry should be used throughout labour and supplemental oxygen therapy used if necessary to maintain oxygen saturations over 94%. There is no evidence for the use of prophylactic antibiotics during labour, but antibiotic therapy should be used if there is evidence of, or high clinical suspicion of infection. Continuous fetal monitoring during labour is recommended because of the increased risk of still birth, placental abruption and poor placental reserve.[57,58]

Routine thromboprophylaxis should be given according to the RCOG guidelines which will comprise prophylactic low molecular weight heparin and anti-embolic stockings in women without additional thrombotic risk factors.[44]

Analgesia and anaesthesia

Regional anaesthesia for caesarean section is preferable to general anaesthesia in view of the higher complication rate seen with general anaesthesia in this group of patients, and women should have an anaesthetic assessment in the third trimester. Epidurals can be used if required with the same indications as in the non-SCD population. Simple analgesia and Entonox can be used, although oxygen saturations should be monitored with the latter. Pethidine should be avoided because of the risk of pethidine associated fits but other opioids can be used, as in the management of acute sickle pain.

Post partum care

Optimal care

Acute sickle pain is common, occurring in between 7 and 25%of SCD pregnancies,[19,59] and monitoring of fluid balance and oxygenation is important in the post natal period. Management of pain is the

same as in the antenatal period with paracetamol, weak opioids and then stronger opioids. Non-steroidal anti-inflammatory drugs can be used in the post partum period.

Early mobilisation should be encouraged but thromboprophylaxis with low molecular weight heparin should be given whilst the woman is in hospital, for 7 days after a vaginal delivery and for 6 weeks following a caesarean section. Breast feeding should be encouraged as in the non-SCD population.

Contraception

There is only limited evidence on the safety and effectiveness of hormonal contraception in women with sickle cell disease.[60] Progestogens are effective and safe as contraceptive agents in SCD and progestogens may decrease the frequency and severity of painful crises.[61–63] There has been a reluctance to prescribe the combined oral contraceptive pill in SCD because of its association with increased thrombosis, but there is no evidence showing that, they are associated with an increased thrombotic risk in SCD and they are recommended as second line agents.

For women not previously on contraception, or requesting alternative contraception, first line recommendations (of equal efficacy and safety) are injectable contraceptives (Depo Provera or Noristerat), Mirena coil, Implanon (implantable contraceptive), progesterone only pill or barrier methods. Second line agents include the combined oral contraceptive pill (COC), copper IUDs, the vaginal ring or the combined patch.[64] If a woman with SCD is well established on a method of contraception, including the COC, she should remain on this, as there is a high risk of accidental pregnancy if this is stopped prematurely without an alternative being commenced but its use should be reviewed annually.

Summary

Pregnant women with SCD have an increased risk of maternal and perinatal mortality and morbidity which can be reduced by effective multidisciplinary care throughout pregnancy. Pre-conceptual optimization of their SCD is advised which will include screening for chronic disease complications and medication review. Regular antenatal review is essential and ultrasound monitoring of fetal growth, at least four weekly, from 24 weeks is recommended. There is an increased risk of pre-eclampsia in SCD and the authors recommend regular antenatal low dose oral aspirin for prevention, but this needs further research. Blood transfusion should be given for women with acute anaemia, acute stroke or acute chest syndrome, but the role of prophylactic blood transfusion is not clear and further trials are needed in this area. Extended red cell phenotyping should be performed for any transfusion given. Acute painful crises are increased both in the antenatal and post partum periods and all units should have clear treatment protocols which should include the use of rapid and effective analgesia. Pethidine should not be used because of the increased risk of fits in SCD patients.

There is no clear evidence about the optimal time of delivery, but in view of the risk of fetal growth restriction and unpredictable placental disease we recommend careful monitoring after 38 weeks and delivery at 38 to 40 weeks.

Practice points

- Pregnant women with Sickle Cell Disease should be looked after by a multidisciplinary team with experience of high risk pregnancies
- They should be offered pre-conceptual partner screening and appropriate counselling
- Painful crises are the most common complication and each obstetric unit should have a clear management protocol for this and other complications of sickle cell disease based on UK Standards of Care
- The use of thromboprophylaxis with low molecular weight heparin should be based on RCOG Green Top guidelines and should be given whilst patients are in patients and in the post partum period.

Research agenda

- The role of prophylactic blood transfusion throughout pregnancy
- The optimal timing of delivery
- Aetiology of placental insufficiency in sickle cell disease in pregnancy
- The role of vitamin D in sickle cell disease in pregnancy
- The role of aspirin 75 mg in the antenatal period
- The role of omega-3 fatty acids in SCD in pregnancy
- Imaging of the feto-placental unit of SCD in pregnancy.

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