Sickle cell disease in pregnancy

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Abstract

Sickle cell disease (SCD) is a multisystem disease, in which pregnancy carries significant risks of maternal and perinatal morbidity and mortality. Women with SCD should have their pregnancies managed jointly by specialist obstetricians, midwives and haematologists. Within the UK, there is great geographical variation in the prevalence of SCD, with the highest prevalence in large urban centres. Trainee obstetricians practising outside these areas may not gain substantial experience in managing these patients and this review therefore aims to highlight the antenatal, intrapartum and postnatal management of pregnant women with SCD.

Keywords antenatal care; contraception; post-partum; pregnancy; sicklecell disease

Introduction

Sickle cell disease (SCD) has evolved into a global disease secondary to migration. The United Kingdom currently has the highest prevalence of SCD in Europe. In 1995, there were approximately 5000 cases, increasing to 15,000 by 2011 with a national birth prevalence of 1 in 2000. As a result of increased survival, more women with SCD are reaching childbearing age. There are now approximately 150–250 deliveries per year in the UK to women with SCD.

Pathophysiology

The primary genetic defect for haemoglobin S (HbS) occurs on the short arm of chromosome 11 resulting in the substitution of valine for glutamic acid on the 6th amino acid position of the β-globin chain. Clinically significant sickling disorders combine a sickle-gene defect (HbS) with another mutation on the other β-globin gene. The most common types of sickle cell disease found in the UK are:

1. HbSS
2. HbSC
3. HbSβ^0 sickle beta thalassemia zero or HbSβ^+ sickle beta thalassemia plus

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

Deoxygenation of HbS causes polymerization between haemoglobin molecules, which disrupts the architecture and flexibility of erythrocytes leading to them forming a 'sickle' shape. This results in an increase in viscosity and vaso-occlusion leading to tissue infarction and inflammation. Reperfusion generates free radical formation and subsequent oxidative damage. Damaged erythrocytes release free haemoglobin which binds to nitric oxide leading to nitric oxide deficiency and further exacerbating vasculopathy.

Clinical features

Sickle cell trait or HbAS is generally asymptomatic apart from an increased incidence of urinary tract infections (UTI). The clinical features of SCD are outlined in Box 1. Haemoglobin levels are generally low, but levels are higher in HbSC than HbSS. HbS releases oxygen to tissues more easily and therefore SCD patients are generally able to tolerate lower haemoglobin levels. Sickle cell disease most often presents in childhood with dactylitis, infection or splenic sequestration resulting in severe anaemia.

Acute painful crisis (also known as acute painful episode) is often precipitated by cold, dehydration or infection. A crisis generally presents with pain that can be generalized or local. Acute chest syndrome (ACS) is a serious complication comprising pleuritic chest pain, tachypnoea, cough and fever. ACS is thought to be caused by intrapulmonary sickling, fat emboli and/or infection. Patients initially presenting with a bony

Clinical complications of sickle cell disease

Acute complications

- Vaso-occlusive bony crisis
- Acute chest syndrome (ACS)
- Overt stroke
- Priapism
- Sequestration (spleen, liver)
- Aplastic crisis

Infection

- Osteomyelitis
- UTI
- Sepsis
- Meningitis
- Acute cholecystitis

End organ damage

- Hyposplenism
- Avascular necrosis
- Nephropathy
- Pulmonary hypertension
- Leg ulceration
- Cerebrovascular disease
- Retinopathy

Box 1

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crisis may go on to develop ACS, and therefore vigilance for this complication is mandatory.

Hyposplenism results in an increased risk of infection, particularly from encapsulated organisms such as *Streptococcus pneumonia*, *Neisseria meningitidis* and *Haemophilus influenzae*. Lifelong penicillin and vaccination prophylaxis are recommended.

Renal damage is relatively common. Microalbuminuria and proteinuria are frequent findings. Retinal damage occurs as a result of vaso-occlusion, hypoxia, and subsequent neovascularization. Proliferative retinopathy is often more severe in HbSC than HbSS. Pulmonary hypertension is an important cause of death in patients with SCD, thought to be as a result of chronic haemolysis leading to endothelial damage and impaired nitric oxide availability. Echocardiography studies have reported that approximately 30% of screened adults with SCD have an elevated tricuspid regurgitant jet velocity (TRV) $\geq$2.5 m/s which can be an indicator of pulmonary hypertension.

Management of sickle cell disease

SCD should be managed within specialist services. Each patient should have an individualized assessment and care plan that includes pregnancy advice for women and contraceptive advice for both sexes. Management approaches to pregnancy in SCD patients include supportive care, avoidance of triggers such as dehydration and cold, and prevention of infection with vaccinations and prophylactic antibiotics. Folic acid supplementation is recommended. Hydroxycarbamide is a chemotherapeutic agent that increases the production of HbF (fetal haemoglobin). It has been used for selected patients with SCD since the 1990s and has been shown to reduce crisis frequency, admissions to hospital, and transfusion. Due to concerns about teratogenicity, both men and women are advised to discontinue taking it for at least 3 months prior to attempting to conceive. Partner screening for sickle and other haemoglobin variants is encouraged at the preconception counselling stage.

Preconception counselling and contraception

Ideally all women with SCD should have preconception counselling regarding the risks from pregnancy and to the pregnancy. The purpose of preconception counselling is to undertake an individualized risk assessment for each woman and to optimize their disease management including ensuring up to date vaccinations, folic acid supplementation, and a review of medications. Hydroxycarbamide urea should be stopped at least 3 months prior to conception as should ACE inhibitors. All women should be assessed for evidence of end organ damage which should include an assessment of renal function, retinal damage and cardiac function (with an ECHO). Women with a history of multiple transfusions will need as assessment of their iron status.

Preconception counselling should also be used to develop an individualized care plan for pregnancy for women with SCD. They should be provided with information regarding the effect of nausea, vomiting and dehydration on SCD and crisis frequency and the likelihood of crises and need for transfusion. They should be informed of the increased risk of IUGR, induction of labour, fetal loss, fetal distress in labour and risk of Caesarean section.

Antenatal screening for haemoglobinopathies

All women in the UK are screened for sickle and other haemoglobin variants at the booking appointment. Those with positive results are contacted by a haemoglobinopathy counsellor, sent a letter stating their results and a leaflet of explanation, and offered an appointment for counselling. Those found to have the disease or who are carriers (sickle cell trait) are encouraged to have partner testing to enable a risk of sickle cell disease in the fetus to be determined. Women whose partners are found to be HbAA (normal adult haemoglobin) can then be reassured that no further antenatal testing of the fetal status is required. The aim of counselling is to provide information on the chances of having a child affected with SCD and the implications of this. Women who are at risk of having a child with SCD (partner is a carrier or affected) should to be referred early in the pregnancy (preferably before 11 weeks) to discuss the option of prenatal diagnosis by chorionic villus sampling (CVS) or amniocentesis, and the option of termination of pregnancy where appropriate.

Complications in pregnancy

Maternal complications

Pregnancy and labour are associated with an increased risk of sickle cell-related complications. However optimal management of patients with SCD outside of pregnancy and multidisciplinary care in pregnancy can reduce this risk. Vaso-occlusive crises are more common in pregnancy, exacerbated by nausea and vomiting in the first trimester, dehydration and stress in labour, and operative delivery. There is an increased incidence of hypertension and pre-eclampsia. There may be acceleration of end organ damage such as nephropathy and infections may be more common.

SCD increases the risk of venous thromboembolism with an incidence as high as 5.5% compared with 0.1–0.2% in pregnancies not complicated by SCD. All women should receive thromboprophylaxis in the form of low molecular weight heparin (LMWH) if admitted to hospital.

Between 2010 and 2011, the UK Obstetric Surveillance System (UKOSS) reported on the outcomes of pregnancies complicated by SCD. The incidence of painful crisis was 52% and acute chest syndrome was 6%. 24% required blood transfusion, 23% required admission to critical care, and 12% were diagnosed with a UTI. All complications were more common in HbSS than in HbSC apart from acute chest syndrome. There was also no difference in the incidence of VTE or hypertension between the two groups which is also in keeping with more recent data. Although SCD is associated with a lower systemic blood pressure than in women without haemoglobinopathy, the incidence of pre-eclampsia is higher in SCD patients, and is highest in HbSS (OR 2.43 95% CI 1.75–3.39). Women with HbSS are also more likely to have an eclamptic fit (OR 4.89 95% CI 1.97–12.16). A systematic review and meta-analysis in 2015 confirmed that the maternal mortality risk for women with HbSS was almost 6-fold higher than women without haemoglobinopathy (RR 5.98 95% CI 1.94–18.44). Pregnancy in women with pulmonary hypertension carries a mortality rate of approximately 36% and therefore all women with SCD should be screened with an echocardiogram at least once during pregnancy.