Fertility and pregnancy in thalassaemia and sickle cell disease.
The UK guidelines

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Abstract

Progressive improvements in the health and survival of patients with thalassaemia and sickle cell disease have increased the reproductive prospects of affected individuals. However, pregnancy in these disorders is associated with significant maternal and fetal risks and expert management is required to ensure good outcomes. In the United Kingdom, it is recognised that the patchy geographical distribution of these conditions poses challenges for access to specialist care, including specialist obstetric services. Guidelines on the pregnancy management of thalassaemia and sickle cell disease in the UK have been published by the Royal College of Obstetricians and Gynaecologists. These guidelines describe the preconceptual, antenatal, intrapartum and postpartum aspects of care. They highlight the high-risk status of pregnancy in these conditions and emphasise the vital importance of specialist multidisciplinary care to the achievement of favourable maternal and fetal outcomes. The guidelines are a valuable resource to healthcare professionals, especially those working in low prevalence areas.

Introduction

Sickle cell disease is the most common inherited disorder in the UK, with a birth prevalence of 1 in 2,000 and an estimated 12,500-15,000 affected individuals. Thalassaemia is much less common; the estimated birth prevalence is 1:20,000-30,000 and the number of affected persons is approximately 1,000.

There is marked variation in the geographical distribution of these conditions across the UK. Approximately 70% of babies with sickle cell disease are born in London where over 80% of the total number of patients are managed, with most of the remaining patients managed by hospitals in large cities outside of London. The geographical distribution of transfusion-dependent thalassaemia is different from that of sickle cell disease: although the areas of highest prevalence are in North and East London, the West Midlands and Yorkshire, around half of the total number of patients are managed in four hospitals with the two largest centres located in London.

Progressive improvements in the health and survival of patients with thalassaemia and sickle cell disease have increased the reproductive prospects and expectations of affected individuals of both genders. However, the low prevalence of these conditions in many parts of the UK poses significant challenges in terms of access to specialist obstetric care.

Separate guidelines on the obstetric management of sickle cell disease and β-thalassemia have been published by the Royal College of Obstetricians and Gynaecologists (RCOG) both of which are very valuable resources. Both guidelines highlight the high-risk nature of pregnancies in women with these conditions and emphasise the importance of a multidisciplinary approach to the achievement of good obstetric outcomes.

Obstetric risks in thalassaemia and sickle cell disease

Pregnancies in both thalassaemia and sickle cell disease are associated with an increased risk of maternal and fetal complications. Therefore, they should be managed as high-risk pregnancies.

In thalassaemia major, the main maternal risks relate to cardiac decompensation and endocrinopathies, particularly diabetes, as a result of iron overload of target organs. The risks of iron overload are enhanced by the discontinuation of iron chelation therapy during the pregnancy. Exacerbation of anaemia during pregnancy is common in thalassaemia intermedia, necessitating transfusion in the majority of patients, including patients who have never been previously transfused. Alloimmune haemolytic anaemia is a problem in such patients. Pregnant women with thalassaemia are also at increased risk of venous thromboembolism. The risk of thromboembolism is highest in splenectomised patients with thalassaemia intermedia who have thrombocytosis and are not receiving regular transfusions. Increased rates of IUGR, preterm delivery and caesarean section are also observed in women with thalassaemia.

In sickle cell disease, maternal complications are due to sickling, and include severe anaemia, painful vaso-occlusive crises, acute chest syndrome, thromboembolism, urinary tract infections, pre-eclampsia and increased rates of caesarean delivery. Fetal complications are due to placental insufficiency and include miscarriage, intrauterine growth restriction (IUGR), prematurity, low birth weight and stillbirth.

These complications highlight the high risk nature of pregnancy in women with thalassaemia and sickle cell disease. The ideal care stan-
Preconception care

The aim of preconception care is to individually assess the woman’s fitness for pregnancy in terms of her end organs and to establish their baseline measurements.

It is essential to stress the importance of preconception care to the patient and discuss the risks of pregnancy with her.

The principal aspects of preconception care are:
1. Assessment of fertility and treatment of subfertility where present;
2. Evaluating the woman for end-organ damage due to either iron overload or sickle cell disease;
3. Ensuring that any medical conditions are stabilised and optimised as much as possible prior to pregnancy;
4. Reviewing the woman’s medications to minimise teratogenic risk and optimise health;
5. Assessing the woman’s immune status by assessing the need for vaccinations and prophylactic antibiotics;
6. Genetic screening of the couple to assess and minimise the likelihood of an affected baby.

Assessing and managing fertility

Although spontaneous conception occurs in women with ß-thalassaemia major, subfertility is common and a significant proportion of affected women will require treatment to restore fertility. In contrast, the majority of women with ß-thalassaemia intermedia who are not receiving regular blood transfusions will achieve pregnancy spontaneously without medical intervention as will most women with sickle cell disease.

The assessment and management of thalassaemia and sickle cell patients with subfertility in the UK will generally follow national guidance published by the National Institute for Health and Care Excellence (NICE). However, there are specific issues related to thalassaemia and sickle cell disease and it is recommended that the patient is managed in a centre where there is specialist expertise in the fertility management of these conditions.

A full work-up is necessary in order to establish the precise cause(s) of the subfertility. In thalassaemia major, the main cause is hypogonadotropic hypogonadism due to iron overload of the anterior pituitary gland from repeated blood transfusions. Fortunately, most thalassaemia major women with hypogonadotropic hypogonadism will achieve pregnancy following ovulation induction therapy with gonadotrophins, although the precise treatment protocol may vary from centre to centre. Women who do not conceive following ovulation induction therapy or who have other reasons for subfertility will require assisted reproduction techniques.

Evaluating end organ damage

Thalassaemia patients should undergo a magnetic resonance imaging (MRI) and FerriScan and be reviewed by a cardiologist with the specific aim of determining whether it is safe to carry a pregnancy from the cardiac point of view. A glucose tolerance test should be done if the patient is not diabetic; patients who are already diabetic should be reviewed by a diabetic physician. The patient’s risk of VTE should be assessed and an up to date DEXA scan should be obtained.

In sickle cell disease, it is important to screen for chronic disease complications such as pulmonary hypertension, nephropathy and lung disease. Retinal screening should be undertaken to exclude sickle cell retinopathy. Multiply-transfused patients should be assessed for iron overload with FerriScan and cardiac MRI.

Pre-pregnancy medical optimisation

The patient’s health must be optimised as far as possible prior to pregnancy.

In thalassaemia major, this may involve a period of intensive chelation to reduce myocardial and total body iron. Ideally, the aim is to achieve no myocardial iron overload (heart T2* >20ms), low liver iron levels (FerriScan liver iron concentration <5mg/g dry weight) and normal left ventricular systolic function prior to pregnancy. Achieving these targets may require sustained intensive chelation treatment for several years in a severely iron overloaded patient with left ventricular dysfunction. In our unit, we have successfully managed pregnant women with heart T2* <20ms, but it should be appreciated that the risk of acute cardiac decompensation increases progressively with lower heart T2* values, and it is wise to embark on pregnancy with a heart T2* <10ms. Likewise, a reduced left ventricular ejection fraction, however modest, is a relative contraindication to pregnancy.

Strict control of diabetes is essential and the serum fructosamine should be kept consistently <300 nmol/l for at least three months before pregnancy is attempted.

Sickle cell crises become more frequent during pregnancy, even in those patients with mild disease outside of pregnancy. There is also an increased frequency of acute chest syndrome during pregnancy and in the postpartum period. Therefore sickle cell patients should be stabilised before pregnancy. Patients with clinically severe disease who are taking hydroxychloroquine may need to be switched to a transfusion programme in order to maintain optimal control of their condition before they embark on a pregnancy. Aggressive chelation is advised for patients with heavy iron overload before conception.

Review of medications

The woman’s medications should be reviewed with a two-fold purpose:
1. Potentially teratogenic drugs should be discontinued. These drugs include oral iron chelators, hydroxychloroquine and bisphosphonates; these should be stopped at least three months before conception. The timing of the discontinuation of ACE inhibitors and angiotensin receptor blockers will depend on the individual patient’s condition. Desferrioxamine may continue to be used during ovulation induction therapy but should be stopped on the day when human chorionic gonadotrophin is to be administered.
2. Drugs which are beneficial to maternal and/or fetal health should be continued or introduced. Folic acid 5 mg daily should be prescribed at least three months before conception and continued through pregnancy. Vitamin D deficiency is very common in both thalassaemia and sickle cell patients and should be corrected with supplements. Current UK guidance recommends lifelong penicillin prophylaxis for splenectomised patients and those with sickle cell disease. Penicillin allergic patients should be prescribed an appropriate macrolide.

Immunisation status

The woman’s immunisation status should be checked and updated. Women who have been splenectomised and those with sickle cell disease should be up to date with pneumococcal, *Haemophilus influenzae type B* and meningococcal C immunisations. They should also receive influenza immunisations annually. Immunisation against hepatitis B is recommended for all women with thalassaemia and sickle cell disease.

Genetic screening of the couple

It is essential that the woman’s partner is tested to determine the risk of a clinically significant haemoglobinopathy in the foetus. Ideally, this must be done preconceptionally, but failing that, it should be done as early as possible in the pregnancy and preferably no later than the 10th week...
of gestation. If the partner is a carrier of, or is affected by a major haemoglobinopathy, then the couple should be offered genetic counselling and advice with regards to their reproductive options. Egg and sperm donors should also be screened for significant haemoglobinopathies.

Antenatal care

The aim of antenatal care is to maintain maternal and fetal surveillance through a multidisciplinary approach. Among other things, it involves establishing the viability of the pregnancy, the presence of multiple pregnancy, accurate dating of the pregnancy, organising investigations, setting clinic visits, and maintaining multidisciplinary collaboration in the management of the pregnancy.

The multidisciplinary team should provide both routine and specialist antenatal care. The core of the team should always comprise an obstetrician and haematologist with a specialist interest in haemoglobinopathy and a midwife with experience of high risk antenatal care. The composition of the wider team will depend on the woman’s co-morbidities. For example, the input of a cardiologist and diabetologist will be necessary if there are cardiac and diabetic issues, and a nephrologist will be needed in women with pre-existing renal impairment.

Ideally, antenatal care must be delivered in a hospital where there is expertise in the management of haemoglobinopathies and high risk pregnancies, but this is not always practical if the woman lives far away from the specialist centre. In such cases, a robust shared care arrangement may be required; good communication between the specialist centre and the local hospital is essential for this to be successful.

Maternal surveillance

It is recommended that pregnant women with thalassaemia and sickle cell disease are booked into the antenatal clinic as early in the pregnancy as possible. The woman must be seen in the antenatal clinic monthly until the 28th week, then two-weekly thereafter.

The pattern of care should be individualised to reflect the woman’s end organ damage and more frequent routine and specialist reviews may be needed.

Rigorous glycaemic control (fructosamine <300 nmol/l) must be maintained throughout the pregnancy in diabetic patients, and other medical conditions must also be kept under good control.

Thalassaemia

Monitoring. In thalassaemia major, the cessation of iron chelation treatment during pregnancy may result in the development of new complications of iron overload such as diabetes, hypothyroidism and deterioration in cardiac function. Thus, vigilance must be maintained throughout all stages of the pregnancy. Serum fructosamine and thyroid function must be checked regularly. A cardiac MRI is advised at 28 weeks to assess cardiac function, even in patients who had normal heart T2* and normal left ventricular systolic function at the beginning of the pregnancy. Cardiac dysfunction is more likely to occur in patients with myocardial iron loading prior to pregnancy; however, patients who have a history of previous severe myocardial iron loading and/or cardiac dysfunction are also at increased risk, even when these parameters have normalised for many years before the pregnancy. In our unit, we have observed cardiac deterioration in the third trimester in such patients.

Transfusions. In thalassaemia major, regular transfusions must continue with the aim of maintaining a pre-transfusion haemoglobin target of >100 g/l. The transfusion requirement may increase during pregnancy, but the transfusion regimen should be suitably adjusted to maintain this haemoglobin target. In thalassaemia intermedia, transfusion may not be required if the haemoglobin concentration remains >80 g/l. However, top up transfusions are commonly needed due to worsening anaemia. Transfusions are also indicated for deteriorating fetal growth.

Chelation therapy. Iron chelation therapy is advised for those judged to be at high risk of cardiac decompensation. The risk stratification should be done jointly with the cardiologist; it should be individualised and take account of the patient’s previous cardiac history and the results of the preconceptional cardiac evaluation. The main aim of chelation therapy during pregnancy is not so much to achieve reduction in tissue iron stores as to suppress non-transferrin bound iron and other toxic labile iron species. This can be achieved using a low dose desferrioxamine regimen. The oral iron chelators are contraindicated in pregnancy, but desferrioxamine can be used safely during the second and third trimesters. Patients to be considered for iron chelation during pregnancy include those with myocardial iron loading, borderline or reduced ejection fraction, severe hepatic iron overload or a history of cardiac decompensation (heart failure, significant arrhythmias). A regimen of desferrioxamine 20mg/kg/day for a minimum of 4-5 days a week from 20-24 weeks of gestation onwards is recommended.

Thromboprophylaxis. Thromboprophylaxis must be given to women at increased risk of venous thromboembolism. Aspirin 75mg daily should be prescribed for splenectomised patients or those with a platelet count >600 x10⁹/L. Splenectomised women who have a platelet count >600 x10⁹/L should receive both Aspirin 75mg daily and prophylactic low molecular weight heparin. Low molecular weight heparin should also be given to patients during inpatient episodes and to patients with other risk factors for venous thromboembolism.

Alloimmunisation. All pregnant women should be screened for clinically significant red cell alloantibodies and those with clinically significant antibodies should be followed up as stipulated in national guidelines. Referral to a fetal medicine unit is advised where the risk of haemolytic disease of the newborn (HDN) is judged to be high.

Sickle cell disease

Monitoring. Women with sickle cell disease are at increased risk of pre-eclampsia and therefore should be carefully monitored for increases in blood pressure and for proteinuria at each visit. They should also have urinalysis at each antenatal visit and monthly midstream urine culture because of their increased risk of urinary tract infections and asymptomatic bacteriuria. It is important to enquire about increased episodes of sickle cell pain at home which they may not necessarily report or be hospitalised for. A cardiac MRI at 28 weeks should be considered in heavily iron overloaded patients on regular transfusions.

Alloimmunisation. Sickle cell patients are easily alloimmunised. All pregnant sickle cell patients should be screened for clinically significant red cell alloantibodies and those with clinically significant antibodies should be followed up in accordance with national guidelines. Referral to a fetal medicine unit is recommended where the risk of HDN is judged to be high.

Transfusions. Prophylactic red cell transfusions are not routinely indicated in sickle cell patients with uncomplicated pregnancy. However, transfusion is recommended for mothers with previous serious medical, obstetric or fetal complications, those on long-term transfusion prior to becoming pregnant, women with twin pregnancies, acute anaemia, increased frequency of sickle cell crises, acute chest syndrome or stroke.

The decision to recommend transfusions should be taken by an experienced haematologist and obstetrician after a careful risk/benefit analysis.

Analgesia. Women with a sickle cell crisis should be urgently assessed by the multidisciplinary team. Sickle cell crises should be managed in the same way as in the non-pregnant state; however, pethi-
dine should be avoided because it can cause seizures. Non-steroidal anti-inflammatory drugs (NSAIDs) should be given only between 12-28 weeks of gestation due to concerns about adverse effects on fetal development. Intravenous fluids and oxygen should be administered if required. Some women will be taking long-term opioids prior to becoming pregnant. In general, such drugs may be continued at the same dosage without any adverse fetal effects. Indeed abrupt cessation of opioids can result in the neonatal abstinence syndrome. There is a risk of this syndrome after birth and the input of a neonatologist is advised.

**Thromboprophylaxis.** Thromboprophylaxis should be given in line with the recommendations of the RCOG guideline for women with additional risk factors. Thromboprophylaxis should also be given to patients during inpatient episodes.

**Pre-eclampsia.** Low dose aspirin 75mg daily from 12 weeks of gestation is advised for women who are at increased risk of pre-eclampsia.

### Fetal surveillance

Both thalassaemia and sickle cell disease are associated with fetal complications as described above. Therefore, close fetal surveillance is an essential element in the management of pregnancy in these conditions.

For both conditions, the following schedule of fetal surveillance is recommended:

- an early scan at 7-9 weeks of gestation to document viability as well as the presence of a multiple pregnancy
- a routine first trimester scan at 11-14 weeks of gestation
- a detailed anomaly scan at 18-20 weeks of gestation
- serial fetal biometry scans 4-weekly from 24 weeks of gestation to monitor fetal growth, amniotic fluid volume and placental blood flow.

Such surveillance allows for early and appropriate intervention in the event of fetal complications.

### Intra-partum care

The aim of intrapartum care is a normal vaginal delivery.

Multi-disciplinary care by senior staff (midwives, obstetricians, haematologists and anaesthetists) is essential. The timing and mode of delivery should be based on obstetric reasons. Caesarean section should be performed for obstetric indications and not just because the woman has a haemoglobinopathy.

The physical environment should be made very conducive for delivery, particularly for sickle cell patients who must be kept warm and well hydrated. There should be continuous electronic fetal monitoring and a long labour should be avoided. The third stage of labour should be actively managed to minimise blood loss. Red cell units should be on standby if the woman has alloantibodies. For thalassaemia patients, chelation therapy should be resumed at delivery to mop up toxic forms of iron such as non-transferrin bound iron.

### Postpartum care

The aim of postpartum care is to continue to maintain maternal surveillance.

Ideally, the mother should be nursed in an observation area in or near the delivery suite for at least 24 hours so that close monitoring can continue. Vigilance is required. Midwives and medical staff should look out for blood loss and other complications. Blood transfusion should be given if there has been a significant fall in the haemoglobin concentration.

For sickle cell patients, sepsis, particularly urinary tract infections and endometritis, is common in the postpartum period; these must be identified and treated promptly.

For thalassaemia patients, chelation therapy should be resumed at full therapeutic doses after completion of the initial 24 hour IV infusion of desferrioxamine. The choice of chelation regimen depends on the woman’s plans with regards to breastfeeding. Desferrioxamine is safe to use in breastfeeding mothers, because although it is secreted into breast milk, it is not orally absorbed and therefore is not harmful to the infant. The summary of product characteristics for the oral iron chelators stipulate that they should not be used by breastfeeding mothers. For mothers who decide not to breastfeed, therapeutic doses of desferrioxamine should be continued until discharge from hospital or until resumption of their usual chelation therapy, whichever is sooner.

Thromboprophylaxis with low molecular weight heparin should be administered for both thalassaemia and sickle cell patients during their inpatient stay and for 7 days post discharge after vaginal delivery and 6 weeks following caesarean section.

### Conclusions

The reproductive prospects of women with thalassaemia and sickle cell disease have progressively increased due to advances in treatment. However, pregnancy in these conditions is associated with significant maternal and fetal risks. Pregnancy outcomes are usually favourable if individualised obstetric care is provided by a specialist multidisciplinary team who are working in close collaboration with each other and with the woman.

### References