Screening for and management of Sickle Cell and Thalassemia in Pregnancy

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Key Amendments

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4th June 2024	Document extended for another 12 months whilst under review	Maternity Governance
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Introduction

Haemoglobinopathies are inherited disorders of haemoglobin. They can be divided into 2 groups:

1) Sickle cell disease – disorder of the *quality* of haemoglobin

2) Thalassemia - disorder of the *quantity* of haemoglobin

These conditions require specialist multi-disciplinary team management throughout the pregnancy and post natal period, and ideally pre-conception.

The patients covered by this guideline are all patients presenting or at risk of haemoglobinopathies.

Sickle Cell Disease (HbSS, HbSC and HbSbeta thal)

The incidence varies across the UK. Sickle cell trait (HbAS) is more common and although it has implications for genetic counselling it does not affect pregnancy to the same extent as sickle cell disease (HbSS).

The clinical features of HbSS occur due to an increase in red cell rigidity and sickling which leads to an increase in blood viscosity and tissue hypoxia as the sickled cells occlude the microcirculation. Sickling of the red cells occurs particularly in response to hypoxia, acidosis and dehydration.

Clinical Features

- *Anaemia* - due to severe haemolysis, red cell aplasia or splenic sequestration
- *Vaso-occlusive crises* – Can be very painful and lead to organ damage
- *Infections* – increased risk of infections occurs partly due to loss of splenic function
- *Acute chest syndrome* – may occur secondary to infection or infarction and is characterised by fever, tachypnoea, pleuritic chest pain, leukocytosis and pulmonary infiltrates. (One of the commonest causes of acute mortality.)
- *Retinopathy* }
- *Leg ulcers* }
- *Aseptic necrosis of bone* }
- *Stroke* }
- *Renal impairment*
- *Pulmonary hypertension*
- *Gall stones*

Intravascular sickling leads to vaso-occlusion and tissue infarction with severe pain.

Diagnosis
Most women with HbSS will have been diagnosed pre-pregnancy and tend to have a chronic haemolytic anaemia. They are often well except during periods of crisis but tend to have a reduced life expectancy (approx. 48 years).

If there is any doubt, the diagnosis may be made by haemoglobin electrophoresis.

Pregnancy and sickle cell disease
As with most medical conditions, the disease can affect pregnancy and vice-versa.

Effect of pregnancy on HbSS
Maternal morbidity and mortality are increased; the latter has been estimated at 2.5%. Complications of sickle cell disease, particularly crises, are more common in pregnancy, labour and the early puerperium. Recent data suggests that crises complicate about 35% of pregnancies in women with sickle cell disease. These women are also at increased risk from infections, partly due to loss of splenic function, which also increases the risk of crises. In particular, there is an increased risk of urinary tract infection, pneumonia, puerperal sepsis and the acute chest syndrome.

Effect of HbSS on pregnancy
Women with sickle cell disease (HbSS) are anaemic and may require transfusion during pregnancy.

There is an increased incidence of miscarriage, IUGR, premature labour, pre-eclampsia (which may have an early onset and an accelerated course), fetal distress and caesarean section. Perinatal mortality is increased 4-6x.

Other features of sickle cell disease that may complicate pregnancy include splenic sequestration, retinopathy, leg ulcers, aseptic necrosis of bone, renal papillary necrosis, bone marrow embolism, venous thromboembolism and stroke.

Screening Programme

There is a National Sickle Cell and Thalassemia Screening Programme for Antenatal Women. Worcestershire is a low prevalence area and the use of the Family Origin Questionnaire at booking may detect women with a major sickle cell disease not previously known to Haematologist. The offer and screening of haemoglobinopathies should be completed by 10 weeks of pregnancy.

Management
Pre-conception

- If identified pre-conception refer for genetic counselling and partner testing (Risk to the baby of HbSS is 50% if mother has HbSS and partner has HbAS).
- Hydroxycarbamide (hydroxyurea) is potentially teratogenic and should be discontinued in both men and women a minimum of three months pre-conception.
- Assessment of iron status: Chelation therapy should be stopped prior to conception. (Discuss with haematologists.)
- If there is evidence of significant iron overload, pregnancy should be delayed to allow for aggressive iron chelation prior to conception.
- Commence Folic acid 5mg OD.
- Discuss and review prophylactic antibiotic requirements and analgesia.
- Discuss potential risks of pregnancy with regards to Sickle cell disease (see below).
- Review Pneumovax status, serology for hepatitis viruses, HIV and immunity to rubella.
- If pregnancy occurs whilst a woman is taking hydroxycarbamide the woman should be offered counselling about the risk of possible teratogenicity and her available options.

Antenatal Screening Pathway (see appendix 1)

The antenatal screening pathway has been reviewed in line with service specification no. 18 NHS Sickle Cell and Thalassaemia Screening Programme.

- All women should be offered sickle cell and thalassemia screening in each pregnancy.
- The offer acceptance/decline should be documented in the pregnancy hand held notes and on the maternity information system (NSC leaflet Screening tests for You and Your baby will be given at the point of offer).
- Any declines for screening will be followed up by the Screening Coordinator.
- WAHT is classed as a low prevalence Trust for sickle cell and thalassaemia. Therefore, the community midwife will complete a family origin questionnaire which goes with a 5ml EDTA sample to the Laboratory by 10 weeks of pregnancy. Women at risk should be identified as early as possible in pregnancy. The Regional Haemoglobinopathy Screening Practitioner will be informed via the Lab directly. The Screening Practitioner will offer screening for the baby's Father and counselling for the family which will include a discussion regarding the potential risk to the baby.
- If the baby's Father is unavailable for testing or declines testing, pre-natal diagnosis will be offered to the Mother.
- Any pre-natal diagnosis that is required will be arranged by the Haemoglobinopathy Screening Practitioner.
- If at risk couples decline pre-natal diagnosis the Antenatal Screening Coordinator will inform the Newborn Screening Laboratory at Birmingham Children's Hospital with the couple's details. A Paediatric Alert form will also be completed.
- The Antenatal Screening Coordinator will be informed by the lab and the Haemoglobinopathy Screening Practitioner of all positive results and at risk couples.
- All results – high or low – will be documented in the pregnancy hand held notes and on the maternity information system by the Community Midwife at the next antenatal appointment.

Antenatal Care

- Collaborative care should be undertaken with lead obstetric consultant and the haematologist if required.
- A clear individualised plan of care should be documented in the woman's notes including the need to avoid factors precipitating crises and a discussion of risks.
- Woman's history of sickle cell crisis, complications and infection should be clearly noted. (Document the frequency and nature of sickle cell crises, acute and chronic complications, transfusion history, infections and routine sickle cell crisis management).
- Perform physical examination and document oxygen saturation.
- Arrange echocardiogram and retinal screening if not recently performed.
- Continue prophylactic antibiotics. (If not already on them, discuss with haematologist.)
- Folic acid (5 mg/day) should be given to all women throughout pregnancy.
- Booking bloods should include:
    - FBC
    - Hb electrophoresis to determine the level of HbF (the higher the level, the better the outcome) and HbS
    - Red cell genotype
    - Reticulocyte count
    - Ferritin
    - Folate

- Urea, Creatinine and Electrolytes
- Liver Function Tests
- Blood group
- RBC antibody screen
- CMV, Hep.C and HIV status

(A typical Hb is 6-10g/dL. A raised reticulocyte count reflects increased RBC turnover. Bilirubin levels also indicate rates of haemolysis. Red cell indices should be normal but low MCV and MCH may indicate iron deficiency or an associated thalassaemia trait and should be discussed with the haematologist. Routine blood transfusion is not usually necessary but decisions to transfuse should be made jointly with haematologist.)

- Review every 4 weeks until 28/40, or more frequently if clinically indicated. From 28/40 see every 2 weeks until 36/40 and then see weekly until term. (Some of these visits may be in the community). BP and urine must be checked at each visit.
- FBC and haematocrit should be checked monthly. (If iron deficiency suspected, confirm by iron studies before prescribing iron.)
- Follow up of red cell alloantibodies as per National Blood Service guidelines.
- Check LFT and U and E's monthly.
- Midstream urinalysis should be checked at each visit (plus MSU if indicated) and a broad spectrum antibiotic prescribed if infection is suspected until sensitivities are known.

- Regular ultrasound assessment of fetal growth from 24/40, with 4 weekly growth parameters. Umbilical artery Doppler velocimetry assessment and two weekly USS are advised if IUGR is suspected.
- Treat any suspected infections aggressively.
- Crises should be managed as aggressively as in the non-pregnant patient with adequate pain relief, rehydration prophylactic low molecular weight heparin (unless contraindicated) and early use of antibiotics. Involve haematologists early. Keep the woman warm and well oxygenated.
- In the acute chest syndrome (one of the commonest causes of acute mortality) involve haematologists and physicians early. Heparin and antibiotics may be required.
- The role of routine exchange transfusion in pregnancy is controversial.
- An individualised labour and delivery plan should be placed in the patient's hospital records.
- Complete anaesthetic referral.
- Complete paediatric alert.
  (Note: Women with HbAS have a relatively uncomplicated pregnancy course however they do have an increased risk of renal papillary necrosis and UTI and possibly an increased risk of PET. There is also an increased risk of renal impairment. The anaesthetist should be informed and partner testing offered: *If the partner also has HbAS then 1 in 4 of the offspring will have HbSS.*)

<u>Labour and Delivery</u>

- The on call Obstetric, Anaesthetic and Haematology Consultants should be notified of admission.
- Women should be kept warm, well hydrated and well oxygenated throughout labour.
- The fetal heart rate should be monitored continuously once labour is established.
- Monitor pulse oximetry, especially in the context of high doses of opiates. Consideration should be given to care in a high dependency unit.
- Facemask oxygen should be administered if oxygen saturation falls below 97% (consider arterial blood gases).
- Intravenous fluids should be commenced at the time of admission to prevent dehydration.
- Caesarean section should only be performed for obstetric indications, but prolonged labour (>12 hours) should ideally be avoided.

- Epidural analgesia and anaesthesia is appropriate general anaesthesia should be avoided if possible, especially if the patient has not been transfused.
- Give prophylactic antibiotics if caesarean section is required

Immediate Postpartum

- Cord blood should be taken for FBC and haemoglobin electrophoresis (only if requested by parents/paediatrician as the Newborn blood spot will detect sickle cell).
- Maternal hydration and oxygenation should be maintained for 24 hours and the woman should remain on delivery suite for the first 24 hours post-delivery.
- 4 hourly observations of vital signs and oxygen saturations should continue until the woman is mobile. If chest signs or symptoms develop or oxygen saturations fall below 92% involve haematologist and anaesthetist as CPAP may be necessary.
- Prophylactic antibiotics should be given orally for 7 days (Co-amoxiclav 250mg QDS. If penicillin allergic then give Cefuroxime 250mg BD. If on long term antibiotics for functional hyposplenism, these should be continued.)
- All women with sickle cell disease should commence s/c enoxaparin 40mg daily immediately post delivery for 7 days (Intermediate Risk). This should be regardless of mode of delivery. Women with higher BMI will require higher dose as per protocol. Risk assessment should be done using risk assessment tool.

Postnatal

- The haemoglobin level should be checked two days following delivery
- Encourage early mobilisation and breastfeeding
- Advice regarding contraception should be given prior to discharge and clearly documented in the notes. Most methods are suitable although some caution should be exercised in the presence of disease complications. The combined contraceptive pill should only be used with caution.

Management of specific complications

- **Infection**
    - Most women with sickle cell disease (SS) have hyposplenism and are at increased risk of infection. They should continue their existing prophylactic antibiotics throughout the pregnancy. If their existing antibiotic is contraindicated in pregnancy, liaise with the haematologist and microbiologist for an alternative.
    - Urinary and respiratory tract infections occur in 50% of women with sickle cell disease during pregnancy.
    - Any pyrexia with or without sickling crisis require an infection screen and commencement of broad spectrum antibiotics which can be reviewed once the result of the infection screen is available.

- **Sickle cell crisis**
    - Crises may be precipitated by cold, infection, dehydration, exercise or stress and occur most commonly in the third trimester and post natal period.
    - Seek cause
    - Investigations
        - FBC
        - Reticulocyte count

- U and E
- LFT
- Blood cultures
- Arterial blood gases
- Infection screen
- Group and save

- Treatment

  - Rehydrate
  - Monitor fluid balance (may require catheter)
  - Analgesia (may require IV morphine)
  - Treat infection
  - Oxygen
  - Consider transfusion if Hb<5 g/dL (discuss with Haematologist)
  - Thromboprophylaxis unless contraindicated (s/c enoxaparin 40mg)
  - Monitor fetus

- Involve Haematologists

- **Acute anaemia**

  - If a sharp reduction in Hb occurs the differential diagnoses include blood loss, haemolysis/sickle crisis, bone marrow suppression hyperhaemolysis or splenic/hepatic sequestration
  - In splenic sequestration, blood transfusion may be lifesaving (discuss with Haematologist). These women will present with a rapidly enlarging spleen and acute abdomen
  - Check the reticulocyte count: If low or absent consider Parvovirus

- **Acute chest syndrome**

  - Present with a raised temperature, cough, pleuritic chest pain =/- severe hypoxaemia pulmonary infiltrates (although CXR changes may lag behind clinical picture) and leukocytosis
  - Treatment is the same as for a crisis
  - Careful monitoring of oxygen saturation and arterial blood gases is essential. Acute chest syndrome can develop rapidly and be rapidly progressive.
  - Often require ITU
  - Consider PE as a differential diagnosis

- **Neurological events**

  - Main concerns are CVA and seizures
  - Should be treated with exchange transfusion to reduce HbS to <30%
  - Liaise with haematologist and neurologists

Thalassaemia

Thalassaemia is a disorder of the *quantity* of haemoglobin. α globin chain synthesis is encoded by two gene alleles on each of the two chromosomes no 16.

- α-thalassaemia: 1 to 4 of the α globin genes is absent
- ß-thalassaemia: 1 or 2 of the ß globin genes is defective

α thalassaemia

Commonest in women originating from South East Asia.

There are normally 2 pairs (i.e. 4) α globin genes.

- *α trait*:
  - 1 or 2 genes missing
  - Not detected by Hb electrophoresis as no abnormal Hb is made
- *Haemoglobin H disease*:
  - Deletion of 3 α globin genes
  - Chronic haemolytic anaemia
  - Normal life expectancy
  - Detected by Hb electrophoresis
- *α-thalassaemia major: (Haemoglobin Barts Hydrops)*
  - No α chain production
  - Severe anaemia
  - Incompatible with life
  - Intrauterine hydrops

Management of α-thalassaemia trait

- Ideally counsel pre-conceptually
- Partner testing (If both woman and her partner have α-thalassaemia trait then there is a 1 in 4 risk of fetal hydrops. i.e. α-thalassaemia major)
- Iron and folate supplementation (5mg folic acid)
- Please note that parenteral iron is contraindicated

Management of Haemoglobin H disease

- Ideally counsel pre-conceptually
- Partner testing
- Folic acid (5mg daily) (from pre-conception)
- Maintain Hb. Iron supplementation +/- blood transfusion (Please note that parenteral iron is contraindicated)
- There are no specific requirements in labour although blood should be cross matched in the presence of anaemia

Management of α-thalassaemia major

- Incompatible with life but may present as fetal hydrops
- Maternal risks include increased incidence of pre-eclampsia
- Problems may occur at delivery due to a large hydropic fetus
- Post natal follow up and genetic counselling re recurrence is important

ß thalassaemia

Commonest in Cypriots and Asians.
Overall carrier rate in the UK of ß thalassaemia is 1 in 10,000 but massive geographical variations exist.

- *ß thalassaemia trait: (heterozygous state)*
    - Asymptomatic
    - Ideally counsel pre-conceptually
    - Partner testing (if partner has HbAS or ß thalassaemia trait, then the risk is 1 in 4 of the fetus having a major Haemoglobinopathy)
    - Causes hypochromic microcytic red cell indices and can lead to a misdiagnosis of iron deficiency
    - Iron should be given on the basis of haematinics rather than the FBC (a serum ferritin assay in early pregnancy will give an indication of the patient's iron stores).
    - May become anaemic in pregnancy
    - Folic acid (5mg daily) (from pre-conception)
    - Do not give parenteral iron
    - Obtain a cord sample at delivery if the woman has an at risk pregnancy
- *ß thalassaemia major: (homozygous state)*
    - Inherited defective ß globin gene from each parent
    - In the absence of regular blood transfusions these patients usually die within a few years, although children are now surviving until the second or third decade.
    - Pregnancy is uncommon in transfusion-dependent patients with thalassaemia major
    - (Patients with a milder form of thalassaemia (thalassaemia intermedia) can become profoundly anaemic during pregnancy and require regular transfusion.)
    - Ideally counsel pre-conceptually

B thalassemia major:
Antenatal care:

- The multidisciplinary team should provide routine as well as specialist antenatal care.
- Partner testing (If the partner has a relevant heterozygous condition, then the risk is 1 in 2 of the fetus having a major haemoglobinopathy)
- Folic acid (5mg daily) (from pre-conception)
- **Avoid oral and parenteral iron**
- Women with thalassaemia should be reviewed monthly until 28 weeks of gestation and fortnightly thereafter with serial growth scan
- Women with both thalassaemia and diabetes should have monthly assessment of serum fructosamine concentrations and review in the specialist diabetic pregnancy clinic. Non diabetic women with iron overload are at increased risk of gestational diabetes. Perform a GTT at16/40 and repeat at 28/40.
- All women with thalassaemia major should undergo specialist cardiac assessment at 28 weeks of gestation and thereafter as appropriate.
- Thyroid function should be monitored during pregnancy in hypothyroid patients.
- All women with thalassaemia major should be receiving blood transfusions on a regular basis aiming for a pre transfusion haemoglobin of 100 g/l.

- Consider thromboprophylaxis in women who have undergone splenectomy and/or have a platelet count greater than 600 x 10^9/l
- Women with thalassaemia who are not already using prophylactic low-molecular-weight heparin should be advised to use it during antenatal hospital admissions.
- The Iron chelation therapy should be managed by a haematologist with experience in iron chelation therapy particularly during pregnancy. Women with myocardial iron loading and severe hepatic iron loading should receive specialist input from cardiologists and haematologists regarding chelation therapy.
- Inform paediatricians: paediatric alert
- Anaesthetic referral

Intrapartum care:

- Timing of delivery should be dependent on any issues identified in the pregnancy (e.g. diabetes or Growth Restriction) but if otherwise uncomplicated, the delivery can be planned according to local guidelines
- Senior midwifery, obstetric, anaesthetic and haematology staff should be informed as soon as the woman is admitted to the delivery suite.
- In the presence of red cell antibodies, blood should be cross-matched for delivery since this may delay the availability of blood. Otherwise a group and save will suffice.
- In women with thalassaemia major intravenous desferrioxamine 2 g over 24 hours should be administered for the duration of labour. (Seek advice from Haematologist for the dose and duration of treatment and plans for post-delivery)
- Continuous intrapartum electronic fetal monitoring should be instituted.
- Thalassaemia in itself is not an indication for caesarean section.
- Obtain a cord sample at delivery
- Active management of the third stage of labour is recommended to minimise blood loss

Postpartum care:

- Appropriate thromboprophylaxis must be considered as there is a high risk of venous thromboembolism. Low-molecular-weight heparin should be administered for 7 days post discharge following vaginal delivery or for 6 weeks following caesarean section.
- Desferrioxamine is secreted in breast milk but is not orally absorbed and therefore not harmful to the Newborn. If maternal treatment is prolonged, monitor infant ferritin levels and give an oral iron supplement to the infant if required. There is minimal safety data on other iron chelators.

The National Antenatal Haemoglobinopathy Programme offers universal screening for thalassaemia to all women. Women will be referred to Haemoglobinopathy Counsellor via the Laboratory lead upon identification of carrier status. The Haemoglobinopathy Counsellor will then contact the woman and arrange screening of the father of the baby.

Appendix 1