Royal College of Obstetricians & Gynaecologists

Management of Beta Thalassaemia in Pregnancy

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This is the first edition of this guideline.

1. Purpose and scope

The purpose of this guideline is to produce evidence-based guidance on the management of women with beta (β) thalassaemia major and intermedia in pregnancy. In this guideline, thalassaemia major women are those who require more than seven transfusion episodes per year and thalassaemia intermedia women are those needing seven or fewer transfusion episodes per year or those who are not transfused. Women who are thalassaemia carriers do not require transfusion. It will include preconceptual, antenatal, intrapartum and postnatal management and contraception in both primary and secondary care settings. It will not cover screening as the British Committee for Standards in Haematology has published guidelines for screening and diagnosis of thalassaemias.[1]

2. Introduction and background epidemiology

Haemoglobinopathies are one of the most common inherited disorders. More than 70 000 babies are born with thalassaemia worldwide each year[2] and there are 100 million individuals who are asymptomatic thalassaemia carriers. The basic defect in the thalassaemia syndromes is reduced globin chain synthesis with the resultant red cells having inadequate haemoglobin content. The pathophysiology of thalassaemia syndromes is characterised by extravascular haemolysis due to the release into the peripheral circulation of damaged red blood cells and erythroid precursors because of a high degree of ineffective erythropoiesis.[3] Thalassaemia major (homozygous β thalassaemia) results from the inheritance of a defective β globin gene from each parent. This results in a severe transfusion-dependent anaemia. The heterozygous state, β thalassaemia trait (thalassaemia minor) causes mild to moderate microcytic anaemia with no significant detrimental effect on overall health.

Thalassaemia intermedia is defined as a group of patients with β thalassaemia whose disease severity varies. At the severe end of the clinical spectrum of thalassaemia intermedia, patients are usually diagnosed between the ages of two and six years and, although they survive without regular blood transfusions, growth and development are impaired. At the other end of the spectrum, there are patients who are completely asymptomatic until adulthood, when they present with mild anaemia and splenomegaly often found by chance during haematological examinations or family studies. The diagnosis is dependent on the patient maintaining a satisfactory haemoglobin (Hb) level at the time of diagnosis without the need for regular blood transfusions. Patients with severe forms of β thalassaemia intermedia and those patients with thalassaemia major who had poor access to blood were previously offered splenectomy to help reduce transfusion requirements. Splenectomy is no longer the mainstay of treatment for these conditions but a considerable number of both thalassaemia major and intermedia patients have undergone splenectomy.[2,4]

The cornerstones of modern treatment in β thalassaemia are blood transfusion and iron chelation therapy.[5] Multiple transfusions cause iron overload resulting in hepatic, cardiac and endocrine dysfunction. The anterior pituitary is very sensitive to iron overload and evidence of dysfunction is common.[6] Puberty is often delayed and incomplete, resulting in low bone mass.[7] Most of these women are subfertile due to hypogonadotrophic hypogonadism and therefore require ovulation induction therapy with gonadotrophins to achieve a pregnancy.[8–10] Cardiac failure is the primary cause of death in over 50% of cases.[11] Improved transfusion techniques and effective chelation protocols have improved the quality of life and survival of individuals with thalassaemia.[12,13] The mortality from cardiac iron overload has reduced significantly since the development of magnetic resonance imaging (MRI) methods for monitoring cardiac (cardiac T2*) and hepatic iron overload (liver T2*) and FerriScan® liver iron assessment (FerriScan®, Resonance Health, Australia). These methods are now available in most large centres looking after patients with haemoglobinopathies.

There are approximately 1000 individuals affected by thalassaemia major or intermedia syndromes in the UK. The absolute number of affected individuals is unclear and is currently being assessed nationally as part of the National Haemoglobinopathy Registry. Previously, the community affected was principally from Cyprus and the Mediterranean. However, currently the Asian communities of India, Pakistan and Bangladesh account for 79% of thalassaemia births with only 7% occurring in the Cypriot population who have taken advantage of the availability of prenatal diagnosis.[14] High incidence areas include Greater London, Birmingham and Manchester. The NHS Sickle Cell and Thalassaemia Screening Programme in England during 2009/10 identified approximately 16 000 women as carriers of a haemoglobinopathy and partner testing was offered. 59% of screen positive women had partner testing and 1006 couples were identified as being at high risk of having a child with a clinically significant haemoglobinopathy (sickle cell disease or thalassaemia). 396 couples accepted the offer of prenatal diagnosis, which revealed 23 pregnancies affected by thalassaemia and 46 fetuses that were carriers of thalassaemia. The majority of pregnancies affected by thalassaemia major were terminated.[15]

3. Identification and assessment of evidence

This guideline was developed in accordance with standard methodology for producing RCOG Green-top Guidelines. Databases searched included the Cochrane Database of Systematic Reviews, DARE, EMBASE, TRIP, Medline and PubMed. Search terms included: 'beta thalassaemia', 'Cooley's anaemia', 'Mediterranean anaemia', 'hypogonadotrophic hypogonadism', 'ovulation induction', 'assisted reproduction', 'iron burden', 'serum ferritin', 'penicillin prophylaxis', 'iron chelation', 'fetal growth and measurement' and 'ultrasonography'. The search was limited to humans and the English language and from 1980 to July 2013. Exclusions were alpha thalassaemia or beta thalassaemia minor. There are no systematic reviews in this area and only small numbers of randomised controlled trials looking at particular interventions. The National Guideline Clearinghouse was also searched for relevant guidelines and reviews. Where possible, recommendations are based on available evidence. Areas lacking evidence are highlighted and annotated as 'Good Practice Points'.

4. Preconception care

4.1 What are the additional risks to the woman and baby?

Thalassaemia is associated with an increased risk to both mother and baby. In particular, there are the issues surrounding cardiomyopathy in the mother due to iron overload and the increased risk of fetal growth restriction (FGR). In addition, with around 9 months of little or no chelation, women with thalassaemia major may develop new endocrinopathies: in particular, diabetes mellitus, hypothyroidism and hypoparathyroidism due to the increasing iron burden.[7,16]

4.2 What is the optimum preconceptual care for women with thalassaemia?

At each visit with the thalassaemia team, there should be a discussion and documentation of intentions regarding pregnancy. This should include screening for end-organ damage and optimisation of complications prior to embarking on any pregnancy. D

Each Specialist Haemoglobinopathy Centre should have a guideline for the management of pregnant women with thalassaemia. ✓

Women should be advised to use contraception despite the reduced fertility associated with thalassaemia. ✓

Fertility may be reduced in transfusion-dependent individuals where chelation has been suboptimal and iron overload has occurred resulting in damage to the anterior pituitary.[8,10,17] They may require ovulation induction using injectable gonadotrophins to conceive.

Evidence level 2+

There is no contraindication to the use of hormonal methods of contraception such as the combined oral contraceptive pill, the progestogen-only pill, the Nexplanon® implant (Merck Sharp & Dohme Limited, Hoddesdon, Herts, UK) and the Mirena® intrauterine system (Bayer plc, Newbury, Berks, UK) in women with thalassaemia.[18]

Evidence level 4

Women with thalassaemia are best cared for in a multidisciplinary team setting, including an obstetrician with expertise in managing high-risk pregnancies and a haematologist. This team should provide prepregnancy counselling so that the woman is fully informed about how thalassaemia affects pregnancy and vice versa. The preconception evaluation involves a review of transfusion requirements, compliance with chelation therapy and assessment of the body iron burden. The assessment should include optimisation of management and screening for end-organ damage.

At both local and specialist centres, the woman's aspirations regarding pregnancy and contraception should be explored in consultation and discussion with the haemoglobinopathy team so that the decision making is shared. This should be done well in advance of the proposed pregnancy because a prolonged period of iron chelation therapy may be required to control iron overload prior to both induction of ovulation and pregnancy.

4.3 Are there any interventions which are beneficial at the preconceptual stage?

Aggressive chelation in the preconception stage can reduce and optimise body iron burden and reduce end-organ damage.

B

There is evidence from clinical trials that optimising body iron reduces end-organ damage and can reverse cardiac iron loading. Longitudinal studies show that patients who have been optimally chelated are less likely to suffer from endocrinopathies or cardiac problems.[19–23]

Evidence level 1+

Due to lack of safety data, all chelation therapy should be regarded as potentially teratogenic in the first trimester. Desferrioxamine is the only chelation agent with a body of evidence for use in the second and third trimester.[24–26] The optimisation of iron burden is therefore critical as the ongoing iron accumulation from transfusion in the absence of chelation may expose the pregnant woman to a high risk of new complications related to iron overload, particularly diabetes and cardiomyopathy.

Evidence level 1-

4.3.1 Pancreas

Diabetes is common in women with thalassaemia. Women with diabetes should be referred to a diabetologist. Good glycaemic control is essential prepregnancy.

✓

Women with established diabetes mellitus should ideally have serum fructosamine concentrations < 300 nmol/l for at least 3 months prior to conception. This is equivalent to an HbA1c of 43 mmol/mol.

D

Diabetes mellitus is common in adults with thalassaemia. Diabetes is multifactorial, due to insulin resistance, iron-induced islet cell insufficiency, genetic factors and autoimmunity.[27] Similar to women with diabetes without thalassaemia, an HbA1c of less than 43 mmol/mol is associated with a reduced risk of congenital abnormalities.[28] HbA1c is not a reliable marker of glycaemic control as this is diluted by transfused blood and results in underestimation, so serum fructosamine is preferred for monitoring.[29]

Evidence level 3

4.3.2 Thyroid

Thyroid function should be determined. The woman should be euthyroid prepregnancy.

B

Hypothyroidism is frequently found in patients with thalassaemia. Untreated hypothyroidism can result in maternal morbidity, as well as perinatal morbidity and mortality. Patients should be

Evidence level 2++

assessed for thyroid function as part of the preconceptual planning and, if known to be hypothyroid, treatment initiated to ensure that they are clinically euthyroid.[30]

Evidence level 2++

4.3.3 Heart

All women should be assessed by a cardiologist with expertise in thalassaemia and/or iron overload prior to embarking on a pregnancy. ✓

An echocardiogram and an electrocardiogram (ECG) should be performed as well as T2* cardiac MRI. ✓

It is important to determine how well the cardiac status of the woman will support a pregnancy as well as the severity of any iron-related cardiomyopathy. Cardiac arrhythmias are more likely in older patients who have previously had severe myocardial iron overload and are now clear of cardiac iron.

The aim is for no cardiac iron, but this can take years to achieve so care should be individualised to the woman. Otherwise, aim for cardiac T2* > 20 ms wherever possible as this reflects minimal iron in the heart. However, pregnancies with successful maternal and fetal outcomes have occurred with lower cardiac T2* values. A T2* < 10 ms is associated with an increased risk of cardiac failure.[31] A reduced ejection fraction is a relative contraindication to pregnancy and the management should be the subject of multidisciplinary discussions involving a cardiologist with experience of cardiac pathology in pregnancy, a maternal medicine specialist, a haematologist and an obstetric anaesthetist.

Evidence level 4

4.3.4 Liver

Women should be assessed for liver iron concentration using a FerriScan® or liver T2*. Ideally the liver iron should be < 7 mg/g (dry weight) (dw). ✓

Liver and gall bladder (and spleen if present) ultrasound should be used to detect cholelithiasis and evidence of liver cirrhosis due to iron overload or transfusion-related viral hepatitis. ✓

A target liver iron of less than 7 mg/g (dw) is recommended because iron chelation is discontinued during pregnancy and therefore transfusional iron burden and the risk of iron overload-related complications increases. Anecdotally, ovulation induction is more likely to be successful when iron burden is well controlled.

If liver iron exceeds the target range, a period of intensive preconception chelation is required to optimise liver iron burden.

If liver iron exceeds 15 mg/g (dw) prior to conception, the risk of myocardial iron loading increases so iron chelation with low-dose desferrioxamine should be commenced between 20 and 28 weeks under guidance from the haemoglobinopathy team.[32]

Evidence level 3

Cholelithiasis is common in women with thalassaemia due to the underlying haemolytic anaemia and they may develop cholecystitis in pregnancy. Liver cirrhosis and active hepatitis C (HCV) may run a more complex clinical course during pregnancy. Women who are HCV RNA-positive should be reviewed by their hepatologist preconceptually. Women who have any evidence of cirrhosis, either due to previous hepatitis or as a consequence of severe hepatic iron loading, should be reviewed by a hepatologist.

4.3.5 Bone density scan

All women should be offered a bone density scan to document pre-existing osteoporosis. ✓

Serum vitamin D concentrations should be optimised with supplements if necessary. ✓

Osteoporosis is a common finding in adults with thalassaemia.[33] The pathology is complex, but thought to be due to a variety of factors including underlying thalassaemic bone disease, chelation of calcium by chelation drugs, hypogonadism and vitamin D deficiency.[34]

Most women with thalassaemia syndromes are vitamin D deficient and often osteoporotic as well. All women should have vitamin D levels optimised before pregnancy and thereafter maintained in the normal range.[34]

Evidence level 4

4.3.6 Red cell antibodies

ABO and full blood group genotype and antibody titres should be measured. ✓

Alloimmunity occurs in 16.5% of individuals with thalassaemia.[35] Red cell antibodies may indicate a risk of haemolytic disease of the fetus and newborn.[36] If antibodies are present there may be challenges in obtaining suitable blood for transfusion.[37]

Evidence level 4

4.4 What medications should be reviewed preconceptually?

Iron chelators should be reviewed and deferasirox and deferiprone ideally discontinued 3 months before conception. D

Women with thalassaemia are often on a range of drugs, some of which may be teratogenic, e.g. deferiprone. Animal studies with deferasirox did not show teratogenicity.[38] However, there is only limited safety data on its use in pregnancy. Deferasirox and deferiprone should ideally be discontinued 3 months before conception and women converted to desferrioxamine iron chelation.

Evidence level 4

Desferrioxamine has a short half-life and is safe for infusion during ovulation induction therapy. Desferrioxamine should be avoided in the first trimester owing to lack of safety data. It has been used safely after 20 weeks of gestation at low doses.[26]

Evidence level 3

All bisphosphonates are contraindicated in pregnancy and should ideally be discontinued 3 months prior to conception in accordance with the product safety information sheet.

4.5 What is the importance of genetic screening and what procedure(s) are involved for women with thalassaemia?

If the partner is a carrier of a haemoglobinopathy that may adversely interact with the woman's genotype then genetic counselling should be offered. D

In vitro fertilisation/intracytoplasmic sperm injection (IVF/ICSI) with a pre-implantation genetic diagnosis (PGD) should be considered in the presence of haemoglobinopathies in both partners so that a homozygous or compound heterozygous pregnancy can be avoided. D

Egg and sperm donors considering IVF should be screened for haemoglobinopathies. ✓

Preconception counselling for women with thalassaemia includes partner screening and genetic counselling (Table 1) as well as the methods and risks of prenatal diagnosis and termination of pregnancy.[39] In high-risk couples PGD is an option. If the partner is unavailable, an offer of prenatal testing is appropriate. Due to the risk of a haemoglobinopathy, potential egg and sperm donors are screened for haemoglobinopathies.

Evidence level 4

Table 1: Conditions requiring counselling where the mother is affected by thalassaemia

Carrier or sufferer condition in partner	Affected offspring
Beta thalassaemia HbS HbE Delta beta thalassaemia Hb Lepore HbO Arab Hb Constant Spring	Risk of serious haemoglobinopathy applies to all
HbC Other variant haemoglobin	Risk of a mild to moderate disorder

4.6 What is the importance of immunisation and antibiotic prophylaxis in women who are at risk of transfusion-related viral infections or have had a previous splenectomy?

Hepatitis B vaccination is recommended in HBsAg negative women who are transfused or may be transfused. ✓

Hepatitis C status should be determined. ✓

All women who have undergone a splenectomy should take penicillin prophylaxis or equivalent. C

All women who have undergone a splenectomy should be vaccinated for pneumococcus and *Haemophilus influenzae* type b if this has not been done before. C

Women who are transfused regularly or intermittently are at risk of transfusion-transmitted infections. It is therefore important to ascertain infectivity and manage the common transfusion-related viral infections appropriately.[40] Evidence level 4

The majority of women with thalassaemia major will have been immunised against hepatitis B but some women with thalassaemia intermedia may not.

Hepatitis C is a common and often asymptomatic virus, so all women who are transfused require hepatitis C antibody testing. If a woman has a positive hepatitis C test, RNA titres should be determined with referral to a hepatologist.

Women who have undergone splenectomy are at risk of infection from encapsulated bacteria such as *Neisseria meningitidis*, *Streptococcus pneumoniae* and *Haemophilus influenzae* type b. UK guidance is that daily penicillin prophylaxis is given to all high-risk splenectomised patients.[41] Women who are allergic to penicillin should be recommended erythromycin. Evidence level 4

In addition, women should be given *Haemophilus influenzae* type b and the conjugated meningococcal C vaccine as a single dose if they have not received it as part of primary vaccination. The pneumococcal vaccine (such as Pneumovax®II, Sanofi Pasteur MSD Limited, Maidenhead, UK) should be given every 5 years.[41] Evidence level 2+

4.7 What vitamin supplements should be recommended?

Folic acid (5 mg) is recommended preconceptually to all women to prevent neural tube defects. A

Women with thalassaemia have a much higher demand for folic acid so high-dose supplementation is needed. Folic acid 5 mg daily should be commenced 3 months prior to conception.[42,43] Evidence level 1++

5. Antenatal care

5.1 How is specialist input delivered for women with thalassaemia?

Women with thalassaemia should be reviewed monthly until 28 weeks of gestation and fortnightly thereafter. The multidisciplinary team should provide routine as well as specialist antenatal care. ✓

Women with both thalassaemia and diabetes should have monthly assessment of serum fructosamine concentrations and review in the specialist diabetic pregnancy clinic. ✓

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. ✓

The multidisciplinary team should include an obstetrician, a midwife with experience of high-risk antenatal care and a haematologist with an interest in thalassaemia. A diabetologist and cardiologist may also provide additional specialist input.

The pattern of care should be individualised depending on the degree of end-organ damage and women with diabetes or cardiac dysfunction may be reviewed more frequently.

Cardiac assessment is important to determine cardiac function and possible further iron chelation as well as planning for labour.

Thyroid function should be determined periodically throughout pregnancy and if hypothyroid the dose of thyroxine altered.

5.2 What is the recommended schedule of ultrasound scanning during pregnancy?

Women should be offered an early scan at 7–9 weeks of gestation. ✓

In addition to the routine first trimester scan (11–14 weeks of gestation) and a detailed anomaly scan at 18–20^{+6} weeks of gestation, women should be offered serial fetal biometry scans every 4 weeks from 24 weeks of gestation. ✓

Women with both thalassaemia and diabetes have a higher risk of early pregnancy loss. Fertility treatment with ovulation induction is often required to achieve pregnancy so an early scan is indicated to determine viability as well as the presence of a multiple pregnancy.

Severe maternal anaemia predisposes to FGR in women with thalassaemia.[44–46] Chronic anaemia affects placental transfer of nutrients and can therefore adversely affect fetal growth. Evidence level 3

5.3 How should the transfusion regimen be managed during pregnancy in women with thalassaemia major?

All women with thalassaemia major should be receiving blood transfusions on a regular basis aiming for a pretransfusion haemoglobin of 100 g/l. ✓

Women with thalassaemia major will already be established on transfusion regimens which generally remain stable during pregnancy. In cases where lower pretransfusion thresholds have been used preconceptually, the aim is to achieve a pretransfusion haemoglobin of 100 g/l.

5.4 How should the transfusion regimen be managed during pregnancy in women with thalassaemia intermedia?

If there is worsening maternal anaemia or evidence of FGR, regular transfusions should be considered. ✓

If a woman with thalassaemia intermedia starts transfusion, haemoglobin targets are managed as for thalassaemia major. ✓

Women with thalassaemia intermedia who are asymptomatic with normal fetal growth and low haemoglobin should have a formal plan outlined in the notes with regard to blood transfusion in late pregnancy. ✓

The decision to initiate a transfusion regimen is a clinical one based on the woman's symptoms and fetal growth. If there is worsening maternal anaemia or evidence of FGR, regular transfusions should be started aiming for maintenance of pretransfusion haemoglobin concentration above 100 g/l. Initially a 2–3 unit transfusion should be administered with additional top-up transfusion if necessary the following week until the haemoglobin reaches 120 g/l.

The haemoglobin should be monitored after 2 to 3 weeks and a 2-unit transfusion administered if the haemoglobin has fallen below 100 g/l. Each woman's haemoglobin falls at different rates after transfusion so close surveillance of pretransfusion haemoglobin concentrations is required.

Generally, in nontransfused patients, if the haemoglobin is above 80 g/l at 36 weeks of gestation, transfusion can be avoided prior to delivery. Postnatal transfusion can be provided as necessary.

If the haemoglobin is less than 80 g/l then aim for a top-up transfusion of 2 units at 37–38 weeks of gestation.

5.5 What antenatal thromboprophylaxis is recommended?

Women with thalassaemia who have undergone splenectomy or have a platelet count greater than 600 x 10^9/l should commence or continue taking low-dose aspirin (75 mg/day). ✓

Women with thalassaemia who have undergone splenectomy and have a platelet count above 600 x 10^9/l should be offered low-molecular-weight heparin thromboprophylaxis as well as low-dose aspirin (75 mg/day). ✓

Women with thalassaemia who are not already using prophylactic low-molecular-weight heparin should be advised to use it during antenatal hospital admissions. ✓

Women with thalassaemia major or intermedia have a prothrombotic tendency due to the presence of abnormal red cell fragments, especially if they have undergone splenectomy. These red cell fragments combined with a high platelet count significantly increase the risk of venous thromboembolism. This risk is highest in splenectomised women with thalassaemia intermedia who are not receiving transfusions since a good transfusion regimen suppresses endogenous erythropoiesis.[47,48]

Evidence level 4

5.6 What is the optimum antenatal management of iron chelation therapy?

Iron chelation therapy is complex and should be tailored to the needs of the individual woman. ✓

The chelation should be managed by a haematologist with experience in iron chelation therapy particularly during pregnancy.

5.6.1 Management of women with myocardial iron

Women with myocardial iron loading should undergo regular cardiology review with careful monitoring of ejection fraction during the pregnancy as signs of cardiac decompensation are the primary indications for intervention with chelation therapy. C

Those women at highest risk of cardiac decompensation should commence low-dose subcutaneous desferrioxamine (20 mg/kg/day) on a minimum of 4–5 days a week under joint haematology and cardiology guidance from 20–24 weeks of gestation. C

Cardiac MRI is safe in pregnancy and should be undertaken in women who have not received preconceptual assessment or where there is concern about cardiac function. As the cardiac T2* value falls below 20 ms there is an increasing risk of cardiac decompensation. Those women at highest risk are those where the value is below 10 ms.[31] Evidence level 2+

Women with myocardial iron loading and T2* > 20 ms do not require desferrioxamine chelation during pregnancy unless there is severe hepatic iron overload.

Women with thalassaemia major and myocardial iron loading with T2* of < 10 ms are at high risk of cardiac decompensation which may present as increasing breathlessness, paroxysmal nocturnal dyspnoea, orthopnoea, syncope, palpitations or peripheral oedema. Presentation in the first trimester is associated with adverse clinical outcome.

If a woman describes symptoms of palpitations then a cardiac assessment is appropriate. A falling ejection fraction or increasing ventricular volumes on echocardiography will suggest increasing risk of developing heart failure. If the woman complains of palpitations then a detailed history, ECG and 24 hour ECG monitor assessment are needed to confirm a pathological cause. In either circumstance desferrioxamine infusions may be indicated if there are concerns.[22,49,50] Evidence level 2+

5.6.2 Management of women with liver iron

Women with severe hepatic iron loading should be carefully reviewed and consideration given to low-dose desferrioxamine iron chelation from 20 weeks. ✓

High concentrations of liver iron (liver iron > 15 mg/g dw as measured by MRI) are associated with an increased risk of myocardial iron and in all women with thalassaemia major the therapeutic aim is to achieve a liver iron concentration below 15 mg/g dw to reduce the risk of myocardial iron overload.[32] Evidence level 2–

6. Intrapartum care

6.1 What is the best intrapartum management for women with thalassaemia major or intermedia?

Timing of delivery should be in line with national guidance. ✓

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. ✓

Continuous intrapartum electronic fetal monitoring should be instituted. ✓

Thalassaemia in itself is not an indication for caesarean section. ✓

Active management of the third stage of labour is recommended to minimise blood loss. A

There is no specific evidence regarding the timing or mode of delivery for women with thalassaemia. The timing of delivery should be based on national guidelines dependent on any issues identified in the pregnancy (e.g. diabetes or FGR) but if otherwise uncomplicated the delivery can be planned according to local guidelines.[51]

Evidence level 4

If there are medical complications such as cardiomyopathy, a detailed management plan formulated during the pregnancy should be in the woman's notes.

Depending on the timing of the last blood transfusion, the woman may well have a low haemoglobin. If the haemoglobin is less than 100 g/l, cross-match 2 units on admission to the labour ward.

Women who are transfusion-dependent and not on a chelating agent will have high serum concentrations of a toxic iron species known as non-transferrin bound iron. These may cause free radical damage and cardiac dysrhythmia when the woman is subjected to the stress of labour.[52] Peripartum chelation therapy is therefore recommended.

Continuous electronic fetal monitoring is recommended as women with thalassaemia are considered to be at an increased risk of operative delivery due to possible fetal hypoxia.[53]

Women with thalassaemia may have a low haemoglobin at the time of delivery and there is randomised controlled trial evidence that the active management of labour reduces blood loss.[37,54]

Evidence level 1++

6.2 Postpartum care

6.2.1 What should be the optimum care post delivery?

Women with thalassaemia should be considered at high risk for venous thromboembolism. D

Breastfeeding is safe and should be encouraged. ✓

There is a high risk of venous thromboembolism due to the presence of abnormal red cells in the circulation. Women should receive low-molecular-weight heparin prophylaxis while in hospital.[47,55,56]

In addition, low-molecular-weight heparin should be administered for 7 days post discharge following vaginal delivery or for 6 weeks following caesarean section.[56]

Evidence level 4

Women with thalassaemia major who plan to breastfeed should restart desferrioxamine as soon as the initial 24-hour infusion of intravenous desferrioxamine finishes after delivery. Desferrioxamine is secreted in breast milk but is not orally absorbed and therefore not harmful to the newborn. There is minimal safety data on other iron chelators.

If a woman decides not to breastfeed, intravenous or subcutaneous desferrioxamine infusions are continued until discharge from hospital or until resumption of her previous iron chelation regimen under haematology supervision, whichever is sooner.

7. Auditable topics

Pregnancies in women with thalassaemias are relatively few in number. Audit should be approximately every 3 years and should address the following:

- preconceptual compliance with targets for liver iron, cardiac iron and fructosamine
- thalassaemia intermedia pregnancy outcomes, especially indications for transfusion, management of maternal anaemia in nontransfused patients and FGR
- compliance with prophylaxis against venous thromboembolic disease in women who have undergone splenectomy.

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Appendix I: Booking appointment

Offer information, advice and support in relation to optimising general health.
Discuss information, education and advice about how thalassaemia will affect pregnancy.
Primary care or hospital appointment – offer partner testing if not already done, review partner results if available and discuss prenatal diagnosis (chorionic villus sampling, amniocentesis or cell-free fetal DNA) if appropriate.
Take a clinical history to establish the extent of thalassaemia complications. Women with diabetes to be referred to joint diabetes pregnancy clinic with haematology input.
Review medications e.g. chelators such as deferiprone or deferasirox.
Women should be taking 5 mg folic acid.
Women who have had a splenectomy should receive antibiotic prophylaxis.
Discuss vaccinations with those women who have had a splenectomy.
Offer MRI heart and liver (T2* and FerriScan®) if these have not been performed in the previous year for thalassaemia major patients only.
Determine presence of any red cell antibodies.
Document blood pressure.
Send midstream specimen of urine for culture.
Confirm viability with ultrasound.

Appendix II: Schedule of antenatal appointments

11–14 weeks
Midwife with high-risk obstetric experience. Review partner results and discuss prenatal diagnosis if appropriate. Confirm that all actions from first visit are complete. Continue folic acid 5 mg.
16 weeks
Midwife and multidisciplinary review (haematologist, obstetrician and diabetologist if diabetic).
20 weeks
Midwife and multidisciplinary review.
20–24 weeks
Women assessed with risks of cardiac decompensation should start on low-dose subcutaneous desferrioxamine (20 mg/kg/day) on a minimum of 4 to 5 days a week under guidance of a haematologist with experience in iron chelation.
Women with T2* > 10 but < 20 ms should be assessed for risks and consideration given to starting desferrioxamine infusions if there are concerns.
Women with T2* > 20 ms (optimal preconception result) should not be given any desferrioxamine chelation during pregnancy unless there is severe hepatic iron overload.
24 weeks
Midwife and multidisciplinary review.
Ultrasound for fetal biometry.
28 weeks
Midwife and multidisciplinary review. Ultrasound for fetal biometry.
Specialist cardiology review and formulation of delivery plan based on cardiac function.
30 weeks
Midwife for routine assessment.
32 weeks
Midwife and multidisciplinary review.
Ultrasound for biometry.
34 weeks
Midwife for routine assessment.
36 weeks
Midwife and multidisciplinary review. A care plan regarding the delivery should be formulated by the team and documented in the notes.
Ultrasound for fetal biometry.
Offer information and advice about:
Timing, mode and management of the birth
Analgesia and anaesthesia; arrange anaesthetic assessment if cardiac dysfunction
Care of baby after birth.
38 weeks
Midwife and obstetrician for routine assessment.
Offer induction of labour if the woman has diabetes.
39 weeks
Midwife for routine assessment.
40 weeks
Obstetrician for routine assessment.
41 weeks
Obstetrician for routine assessment.
For a nondiabetic woman with normal fetal growth and no complications, offer induction of labour in accordance with the NICE guideline for induction of labour.

APPENDIX III: Explanation of guidelines and evidence levels

Clinical guidelines are: 'systematically developed statements which assist clinicians and patients in making decisions about appropriate treatment for specific conditions'. Each guideline is systematically developed using a standardised methodology. Exact details of this process can be found in Clinical Governance Advice No.1 *Development of RCOG Green-top Guidelines* (available on the RCOG website at http://www.rcog.org.uk/green-top-development). These recommendations are not intended to dictate an exclusive course of management or treatment. They must be evaluated with reference to individual patient needs, resources and limitations unique to the institution and variations in local populations. It is hoped that this process of local ownership will help to incorporate these guidelines into routine practice. Attention is drawn to areas of clinical uncertainty where further research may be indicated.

The evidence used in this guideline was graded using the scheme below and the recommendations formulated in a similar fashion with a standardised grading scheme.

Classification of evidence levels

1++	High-quality meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a very low risk of bias
1+	Well-conducted meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a low risk of bias
1–	Meta-analyses, systematic reviews of randomised controlled trials or randomised controlled trials with a high risk of bias
2++	High-quality systematic reviews of case–control or cohort studies or high-quality case–control or cohort studies with a very low risk of confounding, bias or chance and a high probability that the relationship is causal
2+	Well-conducted case–control or cohort studies with a low risk of confounding, bias or chance and a moderate probability that the relationship is causal
2–	Case–control or cohort studies with a high risk of confounding, bias or chance and a significant risk that the relationship is not causal
3	Non-analytical studies, e.g. case reports, case series
4	Expert opinion

Grades of recommendations

A	At least one meta-analysis, systematic review or randomised controlled trial rated as 1++ and directly applicable to the target population; or A systematic review of randomised controlled trials or a body of evidence consisting principally of studies rated as 1+ directly applicable to the target population and demonstrating overall consistency of results
B	A body of evidence including studies rated as 2++ directly applicable to the target population, and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 1++ or 1+
C	A body of evidence including studies rated as 2+ directly applicable to the target population and demonstrating overall consistency of results; or Extrapolated evidence from studies rated as 2++
D	Evidence level 3 or 4; or Extrapolated evidence from studies rated as 2+

Good practice point

✓	Recommended best practice based on the clinical experience of the guideline development group

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The final version is the responsibility of the Guidelines Committee of the RCOG.

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