REVIEW ARTICLE

Hemoglobinopathies in Perinatal Medicine: Challenges in Management

Aliyu Labaran Dayyabu

Received on: 14 July 2022; *Accepted on:* 05 August 2022; *Published on:* 18 October 2022

Abstract

Introduction: Hemoglobinopathies are a group of genetic disorders of hemoglobin (Hb) structure or synthesis. They are among the most common inherited diseases. Approximately 7% of the global population is a carrier, and 300,000–500,000 children are born with a severe Hb disorder annually. They are classified according to the impaired globin chains and whether the disorder leads to reduced production of a normal chain or an abnormal tertiary structure of globin chains. There are two types of hemoglobinopathies, sickle cell disease (SCD), and thalassemia. For years, these diseases impair the quality of life of those afflicted. Impairment in the quality of life can be due to the disease, its complications or even as a result of its treatment. Mortality and morbidity from these diseases are staggering, and many of those affected do not survive to adulthood. However, as medical science develops, the etiology and treatment of the disease are now almost completely unraveled. These have enabled the provision of quality care to those affected with concomitant improvement in quality of life and survival for those affected. Those that get pregnant now constitute a high-risk cohort who require meticulous quality prenatal, intrapartum, and postpartum care to survive. Such care is widely available in developed countries; however, in developing countries where the burden of the disease is highest, such care is scarce, and maternal and perinatal morbidity and mortality remain high.

Methods: This review is done through extensive literature search from various sources. It first discusses sickle disease and then the thalassemias.

Aims: The review is aimed at summarizing the disease and its management in pregnancy with the hope that physicians will use the acquired knowledge of the disease and the various strategies to improve the quality of life and survival of patients and their fetuses in pregnancy and postpartum.

Conclusion: Hemoglobinopathies are a group of genetic disorders of hemoglobin (Hb) structure or synthesis. There are two types of hemoglobinopathies, sickle cell disease (SCD), and thalassemia. Mortality and morbidity from these diseases are staggering, and many of those affected do not survive until adulthood. Those that get pregnant now constitute a high-risk cohort who require meticulous quality prenatal, intrapartum, and postpartum care to survive. The aim of the review is to provide current overview of the disease and its management with the hope that physicians will use the knowledge to improve the quality of life and survival of pregnant women afflicted with the disease to go through pregnancy safely.

Keywords: Challenges, Hemoglobinopathies, Management, Medicine, Perinatal.

Donald School Journal of Ultrasound in Obstetrics and Gynecology (2022): 10.5005/jp-journals-10009-1936

The Chapter is now converted to a Journal article to facilitate wider access and dissemination. This does not contravene publication ethics, more so as the book publisher is also the publisher of Journal.

Introduction

Hemoglobinopathies are a group of genetic disorders of Hb structure or synthesis. They are among the commonest inherited diseases.[1] Approximately 7% of the global population is a carrier, and 300,000–500,000 children are born with a severe Hb disorder annually.[2] They are classified according to the impaired globin chains and whether this disorder leads to reduced production of a normal chain or an abnormal tertiary structure of globin chains.[3]

Department of Obstetrics and Gynaecology, Aminu Kano Teaching Hospital; Fetal Medicine Unit, Bayero University Kano, Kano State, Nigeria

Corresponding Author: Aliyu Labaran Dayyabu, Department of Obstetrics and Gynaecology, Aminu Kano Teaching Hospital; Fetal Medicine Unit, Bayero University Kano, Kano State, Nigeria, Phone: +234 8037054199, e-mail: zainalabidinaliyu@yahoo.com

How to cite this article: Dayyabu AL. Hemoglobinopathies in Perinatal Medicine: Challenges in Management. Donald School J Ultrasound Obstet Gynecol 2022;16(3):222–237.

Source of support: Nil

Conflict of interest: None

The precise structure of the globin chains is coded by genes of chromosomes 16 (the α-gene cluster, comprising α-, and ζ-globin chains) and 11 (the β-gene cluster), comprising the globin chains γ, ε, β, and δ).[3] Hb must have the correct structure and be trimmed in such a way that the number of α-chains precisely matches that of the β-chains.[3] These Hb diseases impair the quality of life of those affected as a result of the disease and its complications and sometimes even as a result of their treatment. Mortality and morbidity from hemoglobinopathies are staggering; however, as medical science develops, the mystery of the underlying etiology of these diseases is now almost completely unraveled. This has enabled physicians to provide better quality medical care to those affected, which concomitantly led to a significant reduction in morbidity and mortality arising from these diseases.

The debilitating effects of hemoglobinopathies are compounded when those affected become pregnant or when they plan to get pregnant. Thus, pregnancy outcome, both maternal and fetal, is impacted negatively. It is therefore important for physicians to understand these diseases and their management in a way that maternal and fetal outcomes will be optimized.

Two major types of diseases have been identified; SCD and thalassemias, both of which pose challenges in management. This chapter will discuss hemoglobinopathies in pregnancy and the challenges and prospects in light of current scientific information to improve the quality of life of those affected and make pregnancy safer for such patients.

Sickle Cell Disease

Sickle cell disease (SCD) refers to sickling disorders in which the sickling gene is present with another abnormal gene affecting the production (quantitative) or the structure (qualitative) of Hb.[4] The clinical syndrome of SCD was first described in 1910[5] and, in 1949, was the first condition to be identified as having a molecular basis by Pauling et al.[6,7] It is a genetic disorder that appeared as an isolated mutation in equatorial Africa and spread to some parts of the Arabian Peninsula, Southern Europe, and the Americas as a result of population movement.[8] It is also found in parts of Southern India. It is the most common inherited condition worldwide. About 300,000 children with SCD are born each year,[9,10] two-thirds of these are in Africa.[11] About 25% of people of African stock carry the sickle cell gene; however, only 2–3% suffer from SCD.[12] In the UK, it is estimated that there are 12,000–15,000 affected individuals, and over 300 infants are born with SCD in the UK each year as part of the neonatal screening program.[13] There are approximately 100–200 pregnancies in women with SCD/year in the UK.[14] In the US, approximately 2000 infants with SCD are identified annually by neonatal screening programs.[15,16]

Mortality among SCD patients used to be very high. It is only in the last half of the 20th century that women with SCD have survived to childbearing age in significant numbers.[14] This improved survival is seen in virtually all geographical locations where SCD exists and is attributed to the improved medical care available to those afflicted with the disease. Early experience with SCD in pregnancy was a cause for pessimism. In SCD patients with pulmonary hypertension, pregnancy mortality is as high as 30–50%, and pregnancy is thus considered to be contraindicated. The first report of a successful pregnancy in a woman with SCD was in 1931.[17] The first major review in 1941 reported a 50% fetal loss.[18] Other adverse pregnancy outcomes include; acute painful crises during pregnancy;[19–21] infection, thromboembolic events,[22] and antepartum hemorrhage.[23] An increased risk of preeclampsia and pregnancy-induced hypertension has been described in some studies,[20,21] but not in others.[19,24] Others are premature labor,[19–21,25] fetal growth restriction,[19–21,25,26–28] an increase in spontaneous miscarriage,[27] delivery by cesarean section,[28] and antenatal hospitalization.[29]

On account of the enormous risk of death and other serious complications that pregnant women with the sickle disease and their unborn fetuses face perinatal, physicians need to familiarize themselves with the pathophysiological origins of SCD. This will provide the basis for rational and comprehensive management strategies that will make pregnancy safe for women with SCD.

Normal Hb Structure

Normal Hb is composed of four subunits, with a single heme group (which binds to and subsequently releases oxygen) and four species-specific globin chains. The heme comprises an iron (Fe) molecule attached to four pyrrole rings. Two pairs of globin chains (2α and 2β) attach to the pyrrole rings and form Hb. The function of Hb is determined by; the integrity of the heme moiety, an amino acid sequence that determines the structure of the globin chains, and the interaction between the four subunits of Hb.

In a normal human, at 6 months of age, 95–97% of the total Hb is HbA. The two pairs of globin chains in its molecule are referred to as α and β chains. The remaining Hb consists of HbA_2, 2% (which has 2α and 2δ globin chains), fetal Hb, and 1.5% (2α and 2γ). The amino acid sequences of these four different polypeptide chains have been determined, the α-chain (identical in each of these three types of Hb molecule) has 141 amino acid residues, and its genetic loci are on chromosome 16 while β, δ, and γ chains each have 146 residues and their genetic loci reside on chromosome 11.[10]

Sickle Hemoglobinopathy

Sickle cell disease (SCD) is inherited as a single gene autosomal recessive disorder caused by the "sickle" gene, which affects Hb structure. SCD is a classic example of a disease in which a genetic aberration leads to the production of an abnormal protein which in turn results in the phenotypic manifestations of the disease in the affected individual.

There are over a hundred variants of Hb described in the literature, and many of them are not pathological. The most common include sickle cell anemia (HbSS), HbSC, and Hbβ-thalassemia. Others are Hb-O-Arab, Hb-Punjab,

Hb-Mulweeki, etc. In HbSS at position 6 in the β chain valine, a neutral amino acid replaces glutamic acid, a negatively charged amino acid. This occurs as a result of a point mutation. The codon for glutamic acid is GAG which is replaced by GUG, which leads to the insertion of valine at position 6 of the β chain from the N-terminus. In HbSC, the GAG is replaced by the codon AAG, and this result in the insertion of lysine at position 6 of the β chain. The consequence of this is the synthesis of an abnormal protein (Hb). In the deoxy form, the overall structure of the HbS molecule is such that the mutant valine can form new hydrophobic bonds with leucine and phenylalanine residues in positions 85 and 88 of an adjacent β chain of another HbS molecule. Only the valine residue of one of the two β chains in each HbS molecule in the polymer is involved in such linkage. Thus the abnormal Hb forms liquid crystals (solubility 1/50th that of HbA[30]) which alter the shape of the red blood cells (RBCs) from discoid to a sickle shape. These sickle cells become rigid and fragile and thus break easily. Their life span decreases from 120 days to just 17 days. Normal RBCs with a diameter of 8 μm, because of their flexible nature, can pass through narrow capillaries with a diameter of 2 μm, whereas sickle cells cannot pass because they are rigid and nonflexible. These lead to tissue infarction, stasis, and hypoxia distal to the affected sites. Consequently, there is a switch from aerobic metabolism (Krebs cycle) to anaerobic metabolism (Embden–Meyerhof pathway), the end product of which is lactic acid (lactic acidosis). By nature, lactic acid is hydrophilic and therefore draws water to the affected site resulting in local tissue edema. These changes cumulatively result in the clinical manifestations of the disease.

Pathophysiology of SCD

The above discussion highlights the processes which lead to the clinical picture of SCD. Chronic anemia and vascular occlusion, which leads to acute and chronic end organ damage basically characterized the disease.

Chronic Anemia

In the deoxygenated state, the solubility of HbS is markedly reduced, and liquid crystals are formed, which leads to the characteristic sickling of the erythrocytes. Reoxygenation can restore these erythrocytes to their normal shape. As cycles of oxygenation, deoxygenation, agglutination, and polymerization occur, the erythrocyte membrane becomes rigid, and eventually, the cells become irreversibly sickle. Thus these cells become permanently damaged and are cleared by the reticuloendothelial system. The life span of the RBCs decreases to 17 days. The result is chronic compensated anemia (Hb, 6.5–9.0 gm/dL). The marrow's capacity to produce new RBCs is limited, and as the RBCs are removed, their concentration falls, and this leads to reduced destruction until it balances the maximal bone marrow capacity to produce new cells. An aspirate of the bone marrow will show erythroid hyperplasia, and blood film will show sickle-shaped cells and polychromasia. Most times, there are splenomegaly and gallstones, all of which result from excessive erythrocyte destruction.

Sickle Cell Crises

The term sickle cell crises can describe many of the acute events that occur in individuals with SCD.[31] Two major types of crises are recognized, the vaso-occlusive and the hematologic crises. Most crises occur in the latter half of pregnancy, and the most common is the vaso-occlusive crisis.

Vaso-occlusive crises: The factors involved in the pathophysiology of sickle cell vaso-occlusive crises can be explained by the classical Virchow's triad.[32] First, cells with sickle Hb have an altered motion through the microvasculature because of the distorted erythrocyte membranes.[33] This leads to vascular stasis and hypoxia, which creates metabolic acidosis.[31] These adverse events further accelerate deoxygenation resulting in a cycle that increases the amount of sickling in the microvascular circulation, further aggravating tissue hypoxia and end-organ damage.[31] Second, because of the interaction of sickled erythrocytes with capillary endothelial membrane, a microvascular injury may occur, which creates a prothrombotic state resulting in infarction and ischemic necrosis of various organs.[31] Finally, stasis of the sickled cells in the microcirculation results in aggregation around phagocytic cells, which increases the blood viscosity and further aggravates the sickle crisis cycle.[31] The accumulation of these events is a painful, vaso-occlusive crisis that often results in end-organ damage.[31]

Hematologic crises: These are uncommon in obstetric practice. The most common is the aplastic crisis,[34] and the others are megaloblastic and sequestration crises. An aplastic crisis is usually a result of viral infection, notably by parvovirus (B19). It is characterized by a rapidly falling hematocrit secondary to aplastic bone marrow. It usually has a mild clinical course during pregnancy, and patients present with weakness and pallor. Without treatment, progressive anemia may lead to cardiac failure. The megaloblastic crisis, on the other hand, is precipitated by folate deficiency. Characteristically there is increased mean corpuscular volume and anemia. It is rare but common in malnourished patients and in those with multifetal pregnancies. Prophylactic administration of folic acid will reduce its incidence. Sequestration crisis is another rare form of crisis; though most common in children, it occurs in adults if splenic auto-infarction has not occurred.[35] Thus, sequestration crisis is commoner in patients with HbSC disease in whom the spleen remains intact even in adult life.

Acute Chest Syndrome (ACS)

Acute chest syndrome is a life-threatening complication of SCD. It occurs as a result of sickling in the lungs and possibly combined with infection. It is reported in 7–20% of pregnancies.[20,27,36] The patient characteristically presents with tachypnea, chest pain, cough, and shortness of breath in the presence of a new infiltrate on a chest X-ray. The signs and symptoms of ACS are the same as those of pneumonia, so both should be treated simultaneously. Acute severe infection with the H1N1 virus in pregnancy can cause a similar clinical picture,

and investigation and treatment should be instituted. Early recognition is a panacea to a good outcome. Treatment is with intravenous (IV) antibiotics, oxygen and blood transfusion, as in nonpregnant women. A top-up blood transfusion may be required if the Hb is falling, and certainly if it is <6.5 gm/dL, but in severe hypoxia, and if the Hb is maintained, an exchange transfusion will be required. Urgent hematology review is needed in suspected ACS. Critical care and respiratory support are also needed when there is hypoxia.

Pseudo Toxemia in SCD

This is another important complication in SCD in pregnancy associated with high fatality. It is commonly seen in the second half of pregnancy in a sickler with bone pain crisis. It is characterized by systolic hypertension and albuminuria. It signals imminent marrow embolism and should not be misconstrued as preeclampsia. Heparinization is urgently needed to avert mortality.

Moderating Factors in Severity of SCD

Not all forms of SCD present with the same severity. HbSC disease usually presents fewer crises compared to HbSS disease. In pregnancy, SCD may present with similar ferocity as SS disease. Another phenomenon is noted in the Eastern province of Saudi Arabia among the Shiites inhabiting the Al-Qatib and Al-Hasa oasis. HbS gene occurs in 20–30% of the population, but the disease runs a milder clinical course. HbS isolated from this group has identical β chain replacement of glutamic acid by valine at position six.[37] It is postulated that ameliorating factors in the Saudi subjects include continued production of fetal Hb into adult life and/or coexistence of α-thalassemia.[38,39] Deficiency of erythrocyte glucose-6-phosphate dehydrogenase (G6PD) is common in this area and has also been implicated as a possible modifier of SCD.[40] This is one puzzle about SCD that future research will find the answer to.

Other Complications of SCD

Other notable complications in SCD patients are infection with encapsulated bacteria such as *meningitidis*, *Streptococcus pneumonia*, and *Haemophilus influenzae*. The risk is increased in sicklers because of repeated splenic infarction, and the spleen has shrunken and its function impaired (autosplenectomy). During pregnancy, there is an increased risk of urinary tract infection because of the physiological effect of progesterone on smooth muscles, including the urinary tract. This is more so in SCD patients because studies have demonstrated an increased incidence of urinary tract infection and asymptomatic bacteriuria,[23] and this poses a serious challenge to maternal-fetal well-being.

Sickle Cell Disease and End-organ Damage

Repeated tissue infarction can cause end-organ failure in women with SCD, and if this affects endocrine organs, this may lead to endocrine diseases such as diabetes. Sicklers who had repeated blood transfusions in life are prone to Fe overload, which can lead to endocrine dysfunction. Gonadal failure, delayed puberty, diabetes, carbohydrate intolerance, and primary hypothyroidism have been documented in SCD patients. These may have a negative impact on fertility and fetal and maternal outcome in pregnancy. Sicklers who are malnourished/have no proper medical care may be stunted in growth or had avascular necrosis of the head of femur and may have dystocic labor and suffer its consequences.

Preconception Care in SCD

Women with SCD face a lot of challenges of the disease and, in some cases, challenges arising from the treatment of the disease itself. These challenges may be medical, social, or psychological and are likely to impact the safety of pregnancy in those affected and hence the need to prepare. Preconception care which is described as a set of interventions that aim to identify and modify biomedical, behavioral, and social risks to the woman's health or pregnancy outcome through prevention and management,[41] can be a means of achieving a safe and successful pregnancy in SCD patients.

This care should be provided by a team comprising; obstetricians, hematologists experienced in managing SCD, other medical specialists who can diagnose and manage all medical conditions that the woman has, and also medical counselors. The aim of preconception care is to optimize the patient's condition to a level that will allow the woman to go through pregnancy with minimal adverse effects on the woman and her fetus.

During preconception care, women with SCD should receive information on; reproductive planning and contraception, reproductive options, vaccinations/malaria prophylaxis, medications, and factors that precipitate crisis and how SCD affects pregnancy and how pregnancy affects SCD.

Effects of SCD on Pregnancy

- Increased risk of miscarriages.
- Increased urinary tract infections.
- Increased risk and severity of anemia.
- Increased risk of thromboembolism.
- Increased risk of preeclampsia/eclampsia.
- Increased risk of postpartum hemorrhage.
- Cephalopelvic disproportion and obstructed labor.
- Increased risk of anesthetic complications.
- Increased risk of operative in interventions.
- Increased risk of premature labor/prematurity.
- Increased risk of intrauterine growth restriction.
- Increased risk of fetal distress in labor.
- Increased risk of intrauterine fetal death.
- Increased risk of maternal mortality.

Effects of Pregnancy on SCD

- Increased risk of crises due to the stresses of pregnancy, labor, and puerperium.
- Dehydration from hyperemesis.

- Anorexia and starvation can also lead to acidosis.
- Dilutional anemia associated with pregnancy aggravates anemia of SCD.

Factors that Precipitate Crisis

- Extremes of temperature.
- Physical exertion/stress.
- Dehydration.
- Infections.
- Infestation (malaria).
- Acidosis.

Medications during Preconception Care

Folic acid 5 mg daily is recommended for women with SCD outside pregnancy in view of their hemolytic anemia, which puts them at risk of folate deficiency.[42] It is also recommended for pregnant sicklers to reduce the risk of neural tube defects and to compensate for increased demand in pregnancy.[43] In malaria-endemic regions, sicklers are given proguanil 100 mg daily, and this should continue during the preconception period. Hydroxycarbamide (hydroxyurea) is used to reduce the incidence of acute painful crises and ACS in individuals with severe clinical manifestations of the disease.[44] Hydroxycarbamide has been found to be teratogenic in animals, and it is advised that those on it should use effective contraception and should stop taking the drug 3 months before they conceive. However, there are published reports of women receiving hydroxycarbamide both for SCD and for other indications of becoming pregnant, some of whom have continued the medication throughout pregnancy without adverse effects on the baby.[14] If pregnancy occurs in this woman while on the drug, it should be stopped and level III ultrasound performed to look for fetal structural abnormality, but termination of pregnancy is not indicated based on exposure to hydroxycarbamide alone.[45,46] Angiotensin-converting enzyme inhibitors or angiotensin receptor blockers are used routinely in patients with SCD who have significant proteinuria (protein-creatinine ratio of >50 mg/mmol) since there is evidence that these agents reduce proteinuria and microalbuminuria.[47,48] These drugs are not safe during pregnancy and should be stopped in women who are trying to conceive.

Penicillin Prophylaxis and Vaccination during Preconception

Sickle cell disease (SCD) patients are susceptible to infection, particularly with encapsulated bacteria, for example, *N. meningitidis*, *S. pneumoniae*, and *H. influenzae*. There is clear evidence that penicillin prophylaxis is of benefit in young children with SCD,[49] but there is no randomized trial evidence in older patients or pregnant women. In the UK, however daily penicillin prophylaxis is given to all patients with SCD, in line with the guideline for all hyposplenism patients.[50,51,52] This practice may be applied in other countries because of its potential to prevent infection by these bacteria, which may be difficult to treat. Those allergic to penicillin should receive erythromycin as an alternative. In view of the danger posed by infection to the well-being of SCD patients, vaccinations against various infective agents may be a good practice. In line with this, women should be given *H. influenzae* type b (Hib) and conjugated meningococcal C vaccine in the preconception period if they were not given as part of primary vaccination. Hepatitis B vaccination is recommended, and the woman's immune status determines preconceptually. Women with SCD should also be advised to receive influenza and "swine flu" vaccine annually.[50]

Assessment of Chronic Disease and Other Complications of SCD

Sickle cell affects virtually all body systems, and the severity of this affectation determines the quality of life and ability of the individual to stand the stresses/strains of daily life. As pregnancy exerts additional challenges on women with SCD, it is of paramount importance that women should be fully assessed and managed for chronic conditions and complications of the disease to enhance their ability to go through pregnancy in a stable state. This will maximize the chances of having a live healthy mother and infant at the end of pregnancy.

Echocardiography should be done to screen for pulmonary hypertension. The incidence of pulmonary hypertension is increased in patients with SCD and is associated with increased mortality.[52] A tricuspid regurgitant jet velocity of >2.5 m/second is associated with a high risk of pulmonary hypertension.[53] Blood pressure and urinalysis should be performed to identify women with hypertension and/or proteinuria. Renal and liver function tests should be done annually to identify sickle cell nephropathy and/or deranged hepatic function.[50] Proliferative retinopathy is common in SCD, especially in patients with HbSC, and can lead to loss of vision[54] hence the need for retinal screening preconceptually. Screening for Fe overload is an important component of preconception care in SCD. In women who had multiple transfusions in the past or who have a high ferritin level T_2*, cardiac magnetic resonance imaging may be helpful to assess body Fe loading. Aggressive Fe chelation preconception is advisable in women who are significantly Fe loaded. Screening for red cell antibodies is another desirable procedure. The presence of red cell antibodies may indicate an increased risk of hemolytic disease in the newborn and potential difficulty in transfusing the affected woman when the need arises.

Since maternal and paternal genotype contributes to determining the genotype of the offspring, women should be encouraged to have the Hb genotype of their partner tested. If a partner is a carrier or has a major hemoglobinopathy, the couple should be counseled concerning the risk of having an affected offspring.[55] Methods and risks of prenatal diagnosis and termination of pregnancy should be discussed with them.[56] They should also be counseled on the availability of preimplantation genetic diagnosis (PGD) and referred

where appropriate. Where a partner declines testing or are unavailable for it, women should be informed that their fetus is at high risk for hemoglobinopathy.[55] Couples considering *in vitro* fertilization (IVF) and their sperm donors should be screened for hemoglobinopathies.

In developing countries, preconception care may be difficult to carry out because of inadequate manpower, facilities for important procedures, and unfavorable socioeconomic factors. The sickle cell clinics should provide the starting point for preconception for women with SCD in those countries.

Antenatal Care in SCD

Pregnancy in patients with SCD is considered to be high risk because of the underlying hemolytic anemia, sickle cell crises, and multiorgan dysfunction associated with the disease. Antenatal care should be provided by a multidisciplinary team consisting of an obstetrician, a hematologist, and a midwife experienced in managing high-risk pregnancies. Inputs from other specialized healthcare providers may sometimes be required. Multidisciplinary care seems to be associated with improvement in maternal and fetal outcomes. The establishment of comprehensive sickle cell centers in the USA was associated with decreases in spontaneous miscarriage and perinatal death rates and incidence of preterm labor.[57] Active prenatal management in an African setting, which included providing information and education about SCD, improving nutritional status, malaria prevention, and early detection of bacterial infection, has been shown to have a positive impact on SCD-related morbidity and mortality.[58] Many women with SCD become pregnant without preconception care. This is the situation in virtually all developing countries. Such women, when they present for antenatal care, should be comprehensively reviewed as early as possible. At the first antenatal visit, a detailed medical history should be obtained with emphasis on previous crises and their pattern and relevant past obstetrics history. They should be assessed for any intercurrent medical disease and managed accordingly. Ascertain their immunization status, review Fe overload, red cell autoantibodies, and partner genotype. Educate patients on factors that precipitate crises and what to do to minimize crises. SCD patients should be counseled on early pregnancy dating and prenatal diagnosis.

Antenatal care visits should be planned, making allowance for extra visits based on the need. Every 4 weeks up to 28 weeks, every 2 weeks up to 32 weeks, and then weekly up to delivery.

Investigations required at booking: Baseline full blood count and reticulocyte count, serum ferritin level (Fe load), and liver and renal function should be obtained. Baseline oxygen saturations should be measured and further evaluated with an echocardiogram and lung function to rule out pulmonary hypertension and chronic lung disease. Screening for human immunodeficiency virus, hepatitis, and blood group antibody screen.

Admissions during the antenatal period: In some centers in developing countries, the policy is to admit patients when they first present in pregnancy for full evaluation and stabilization. The second admission is at 28 weeks for further maternal and fetal assessment and stabilization, then at 32 weeks till delivery. Patients can, however, be admitted as the need arises. Indications for admission include;

- Crises.
- Fever/pain.
- Increasing anemia.
- Chest pain or dyspnoea.
- Preeclampsia.
- Infection.
- Induction of labor.
- Labor.

Patients that remain stable should follow routine antenatal schedule visits. At each visit, obtain relevant information on her general condition and whether she has any complaints. She should then be examined. Check the patient's blood pressure and perform a urinalysis. Do a full blood count and urine microscopy culture and sensitivity every 4 weeks. At 20 weeks, perform a detailed ultrasound for fetal anomaly and screen for adverse pregnancy outcomes with umbilical artery Doppler [preeclampsia, intrauterine growth restriction (IUGR), and abruptio placentae]. Ultrasound should also be done every 4 weeks for fetal growth. At 36 weeks, discuss and counsel on; the timing, mode, and management of delivery and care of the infant after birth. Discuss analgesia and anesthesia and arrange for an anesthetic assessment. Recommend induction of labor or cesarean section between 38 and 40 weeks of gestation. Offer fetal monitoring if the woman declines delivery at 40 weeks of gestation.

Important Management Issues during Antenatal Care

Blood Transfusion

The decision for transfusion should be taken by an experienced hematologist and an obstetrician. Blood transfusion is indicated in the following circumstances;

- Hemoglobin level <7 gm/dL.
- Repeated crises.
- The crisis that does not respond after 48 hours of conservative treatment.
- 2 gm/dL fall in Hb level from the baseline.
- Previous poor obstetrics history.
- Women with a twin pregnancy.
- In the case of ACS or acute stroke.
- Where clinical judgment so indicates.

The blood to transfuse should be of genotype AA, *cytomegalovirus* free, and must be matched for the C, E, and Kell antigens. Alloimmunization (the formation of antibodies to red cell antigens) is common in SCD, occurring in 18–36%[14] of patients. Alloimmunization is clinically important as it can lead to delayed hemolytic transfusion

reactions or hemolytic disease of the newborn,[59] and can render patients untransfusable. Matching for the C, D, E, and Kell antigens will reduce this risk. The mode of transfusion can be prophylactic or exchange transfusion. Early studies recommended prophylactic transfusion during pregnancy as there was a decrease in maternal morbidity and perinatal mortality among transfused women compared with historical controls.[60,61] There are appreciable risks associated with transfusion in this heavily transfused patient cohort, alloimmunization,[36,62] delayed transfusion reactions,[62] transmissions of infection, and Fe overload. A randomized control trial[63] and a retrospective study[36] have demonstrated that prophylactic transfusion decreased the incidence of maternal painful crises but did not influence the fetal or maternal outcome. "Top-up" transfusion is indicated for women with acute anemia.[50] Acute anemia may be attributable to transient red cell aplasia, acute splenic sequestration, or the increased hemolysis and volume expansion encountered in SCD. The basis for exchange transfusion is to decrease the concentration of HbS, thus increasing the overall oxygen carrying capacity of the blood, thereby reducing sickling and hence tissue damage. Exchange transfusion is indicated in cases of women with previous serious medical, obstetrical, or fetal complications, ACS, or acute stroke. The disadvantages of exchange transfusion are transfusion reaction, alloimmunization, and exposure to infections.

Medications

Various classes are used in patients with SCD for various indications. Some are used for prophylaxis, and some for treatment. Some drugs should be stopped some months before conception because of concerns about teratogenicity. Others are introduced to reduce certain risks, yet some others are used for treatment. In malaria-endemic regions, malaria is the most common cause of pyrexia and can cause nausea and vomiting, which can aggravate the patient's condition and precipitate the crisis. For this reason, malaria prophylaxis is essential. Intermittent preventive therapy is advocated, and the drug of choice is sulfadoxine-pyrimethamine (SP). Patients with SCD are given three doses of the drugs. The first dose is administered after quickening or at 16 weeks of gestation. The second dose is administered at 28 weeks and the third dose at 32 weeks. The doses should be spread between 16 and 32 weeks, and the dosing interval should not be <4 weeks. Before giving SP, ask for sensitivity for it or other sulfur-containing drugs. Folic acid 5 mg daily is given in preconception and in pregnancy to reduce the risk of neural tube defect and to compensate for increased demand for Folate during pregnancy.[44] Fe supplementation was given before because older studies demonstrated Fe deficiency to be common in SCD. A more recent study with a small number of pregnant women with SCD, however, showed no evidence of Fe deficiency, and some of these women were Fe overloaded.[64,65] Therefore, Fe status should be assessed, and supplementation was given if there is evidence of Fe deficiency. Women who are at risk of preeclampsia are advised to take low-dose aspirin 75 mg from 12 weeks of gestation. While there is specific evidence that aspirin decreases the risk of preeclampsia in women with SCD, such women are probably at increased risk of developing preeclampsia.[66,67] SCD should be considered a "mild" risk factor for preeclampsia, and aspirin prophylaxis is recommended for them according to National Institute for Health and Care Excellence guidance.[53] Analgesics are used in the management of painful crises in SCD, but care must be taken in selecting which ones to use and at which period in gestation to avoid maternal or fetal complications. For this reason, non-steroidal anti-inflammatory drugs should only be prescribed between 12 and 28 weeks of gestation owing to concerns regarding adverse effects on fetal development.[14] Pethidine should be avoided because of the risk of toxicity and pethidine-associated seizures in patients with SCD.[68] Thromboprophylaxis with low molecular weight heparin is indicated in the following circumstances;

Following vaginal delivery before discharge and for 7 days postdischarge. It should also be administered for 6 weeks following a cesarean section.

- In SCD patients with pseudotoxemia of pregnancy to prevent marrow embolism.
- In SCD patients with ACS.
- If bone pain crisis does not resolve after 48 hours of conservative management with IV fluids, antibiotics, and analgesics.
- Sickle cell disease (SCD) patients who develop cerebrovascular accidents.

Start treatment with 10,000–15,000 international unit (IU) as the initial dose and maintain with 5,000–15,000 IU every 4–6 hours. While giving heparin, monitor clotting time and this should be >17 minutes. Keep protamine in readiness for complications.

Suggested Protocol for managing Bone Pain Crisis

Carry out appropriate investigations *viz* full blood counts, urine microscopy culture and sensitivity, blood film for malaria parasite (in malaria-endemic areas), serum electrolytes and urea, and others such as blood culture, liver function tests, chest X-ray, etc. should be done if indicated.

- Keep the patient warm, if not febrile.
- Hydrate the patient (orally or intravenously, depending on the patient's condition).
- Intravenous should be selected to provide energy (glucose) provide adequate hydration and electrolytes.
- Treat malaria empirically in malaria-endemic areas.
- Treat infections with antibiotics.
- Treat pain by selecting analgesics depending on the severity of the pain.
- Oxygen by face mask.
- Heparinize if the pain persists 48 hours after the commencement of conservative treatment.
- Monitor vital signs and manage accordingly.

Intrapartum Care in SCD

There are no randomized controlled trials to indicate the appropriate time for delivery,[14] but as is the tradition, women with high-risk conditions are delivered at 38–40 weeks of gestation. This approach will forestall late pregnancy complications and associated perinatal mortality. Studies from the USA, UK, Jamaica, and Africa have highlighted increased perinatal mortality during the later stages of pregnancy, in part owing to the complications of SCD.[23,26–28,36,57] The risks of abruption, preeclampsia, peripartum cardiomyopathy, and acute sickle cell crisis are increased and are unpredictable. Based on some studies, vaginal delivery is associated with improved clinical outcomes[23,26,27,57] and is, therefore, the recommended mode of delivery. Cesarean section is based on obstetric indications. There is an increased frequency of sickle cell crisis and ACS in the intrapartum period.[14] Prolonged labor (labor >12 hours) is associated with an increased risk of painful crisis. It is for all these reasons that labor should be conducted in facilities with the capability of handling complications and offering emergency cesarean section within the shorted possible time.

Management of Labor

Sickle cell disease (SCD) is a perfect example of a condition in which active management of labor is desirable. When labor is confirmed, the anesthesiologist, the neonatologist, and the perioperative nurses should be alerted because of possible emergency interventions and the need for neonatal resuscitation. Dehydration should be avoided by giving IV fluids that maintain adequate intravascular volume and provide glucose to prevent ketosis. Input and output should be carefully monitored to avoid fluid overload. In labor, oxygen demand increases, and the use of pulse oximetry is recommended to detect maternal hypoxia. Maternal oxygen saturation should be maintained above 94%; otherwise, oxygen therapy should be instituted. Routine prophylactic antibiotic intrapartum is not supported by evidence; however, when membranes are ruptured, it is appropriate to commence broad-spectrum antibiotics. Continuous intrapartum cardiotocograph is advocated because of the increased rate of stillbirth, placental abruption, and compromised placental reserve.[69,70] For pain relief in labor, liberal epidural analgesia is encouraged. However, nitrous oxide (a mixture with 50% oxygen) *via* a face mask can be used for short-term pain without precipitating a sickling crisis.[31] Pethidine should be avoided because of the risk of seizures when administered to a woman with SCD.[68] General anesthesia should be avoided because it carries additional risks beyond the normal obstetric case and should be avoided where possible.[14] Regional anesthesia during labor may reduce the necessity of general anesthesia for delivery.[14] Shortening the second stage of labor with forceps/ventouse will reduce further stress and decrease the risk of crisis and is advocated. The third stage should be managed actively to prevent postpartum hemorrhage, which is an important complication in women with SCD. The infant should be handed over to the neonatologist for appropriate care.

Important Parameters to Monitor in Labor

The whole labor process should be monitored with the partograph. This will help in identifying problematic labor and allow for early appropriate intervention.

- Packed cell volume every 2 hours.
- Liver and spleen span every 2 hours.
- Oxygen saturation.
- Fetal heart rate (continuous cardiotocography).

Postpartum Care in SCD

The postpartum period is of critical importance in women with SCD. The woman should be kept on admission until she is judged to be stable or at least for 72 hours after delivery. The risk of sickle cell crisis remains high. During this time, there is an increased risk of infection, thromboembolism, and vaso-occlusive crises.[31] In one study, it occurred in 25% of women and was more common following general anesthesia.[71]

- Continue hydration (oral or IV-based on clinical need).
- Maintain oxygen saturation above 94%.
- Early ambulation/deterrent stocking.
- Thromboprophylaxis with low molecular heparin for 7 days after vaginal delivery and for 6 weeks following cesarean section.
- Consider antibiotics on the basis of clinical conditions.
- Packed cell volume 4 hourly.
- Liver/spleen span 4 hourly.

Contraception in SCD

Contraception is an important component in the management of women with SCD. The woman's desired family size remains a desirable consideration, but she should be counseled on the enormous risks she faces with each pregnancy. There is also the risk of genetic transmission of the disease with each pregnancy and the burden of the perpetuation of the disease within the family. Barrier methods are as safe and effective in women with SCD as in the general population.[14] There is limited safety evidence on hormonal contraception in SCD; a Cochrane review identified one randomized trial which showed that women taking intramuscular Depo-medroxyprogesterone acetate were less likely to have a painful episode.[72] A systematic review analyzing randomized and nonrandomized studies demonstrated progestogens to be effective and safe in SCD.[73] Intrauterine devices (IUDs) pose the risk of uterine and tubal infections and have a relative contraindication. They may be considered in women for whom other methods are not suitable. There is some evidence that levonorgestrel intrauterine system use is associated with a lower rate of pelvic infection than a copper IUD.[31] Barrier methods are widely used but carry a higher risk of unwanted pregnancies as compared to other methods.[31] As always, the World Health Organization

eligibility criteria should be followed in deciding the eligibility or otherwise of any contraceptive method in all women, including women with SCD.

Recent Advances

There are new methods that are aimed at preventing genetic diseases, including SCD. Other methods are devised to provide a cure for the disease. PGD is a procedure used prior to implantation to help identify genetic defects within the embryos. This can be employed to prevent SCD from being passed from couples to their offspring. The embryos used in this procedure are created during IVF. There are ethical concerns about this procedure, and as many people believe life begins at conception, the destruction of an embryo is tantamount to the destruction of a person. Other issues concern to cost and availability. Another procedure is umbilical stem cell transplantation which is reserved for those with clinically severe diseases such as stroke, frequent crises, and recurrent ACS in the hope of avoiding the development of permanent end-organ damage. Results obtained so far are promising; however, the main challenges include infection, rejection, and graft-vs-host disease. Families at high risk of passing a genetic disease can bank cord blood for the future use of a family member. Like PGD, this procedure has ethical issues to contend with. It is not universally available, and cost remains an issue.

Thalassemia in Pregnancy

The term "thalassemia" refers to hemoglobinopathies characterized by partly or completely suppressed synthesis of one of the two types of polypeptide chains (α or β) as a result of missense/nonsense mutations (single-base substitutions) or frameshift mutations of the genes controlling the structure of the Hb-protein chains in one or both "allelic" globin genes, providing decreased Hb concentrations, microcytosis, and anemia.[3] Depending on the genes affected, the resulting defect, and the corresponding effect on the globin chain, several types of thalassemia have been described, the most common types of clinical importance being α-, β/δ-, and β-thalassemia.[74–76] Thalassemia is seen commonly in sub-Saharan Africa, the Mediterranean region, the Middle East, the Indian subcontinent, and East and South East Asia.[2] Almost 5% of the world population are carriers of α-thalassemia, and approximately 1,000,000 patients are affected by various α-thalassemia syndromes worldwide.[77,78]

Genetic Basis and Pathophysiology of Thalassemias

The synthesis of α-globin starts in fetal life. The genes that are responsible are four in all, and they are situated in two genetic loci on chromosome 16. Gene deletion or, less commonly, mutation results in α-thalassemia, and the phenotype depends on the affected gene number. When all four genes are affected (–/–|–/–), the result is homozygous α-thalassemia; fetal synthesis of α-chains is impossible, leading to an excess γ-chains and forming the unstable Bart's Hb (γ_4), which is incapable of oxygen exchange. The affected fetus becomes severely anemic with cardiomegaly, suffers from hydrops fetalis, and dies *in utero* or in early neonatal life. When three genes are affected ($\alpha^{-/-/-}$), α-chain synthesis is reduced to a minimum. The β chains that exist in excess form the unstable HbH (β). HbH disease has a phenotypic variability based on mutation type, ranging from mild anemia (deletions on chromosome 16) to transfusion-dependent one.[79] The existence of two α-genes (α-thalassemia trait) is expressed as mild hypochromic microcytic anemia. Globin synthesis is not balanced by α-chain synthesis, and this result in hemolysis and Fe overload. In α^0-thalassemia, the two deleted genes belong to the same allele (–/–|α/α), and this is prevalent among Asian and Eastern Mediterranean populations, while in α^+-thalassemia, prevalent among African people, the deleted genes belong to different homologous chromosomes.[3] In "silent" carriers, only one α-gene is affected (α/–|α/α), and the three functional remaining ones are capable of normal Hb production.[80]

β-thalassemia is extremely heterogeneous in terms of both genotype and phenotype, depending on the nature of β-gene mutation and the extent of impairment in β-globin chain production.[3] As a rule, heterozygous carriers of β-thalassemia are asymptomatic and only altered laboratory values (low, normal, or slightly subnormal Hb levels, low mean cell volume, low β:α-globin chain ratio HbA_2 ≥3.5%) are observed. In contrast, inheritance of two defective β-globin genes results in a wide genotype spectrum, ranging from transfusion-dependent [thalassemia major (TM)] to mild or moderate anemia [thalassemia intermedia (TI)]. β^0 refers to the complete absence of production of β-globin on the affected allele, β^+ refers to alleles with some residual production of β-globin, and β++ to a very mild reduction in β-globin production.[3] TI mutations in both parental genes lead to a moderate reduction in β-globin production. TI represents up to a quarter of β-thalassemia patients with a wide spectrum of genotypes and a clinical phenotype ranging between transfusion-dependent thalassemia and the asymptomatic carrier state. Patients have, in general, later clinical onset, milder anemia not requiring transfusion for survival during the first few years of life, and quality of life is not severely impaired, but the clinical course of the disease, if left untreated, is complicated by multiple effects of chronic hemolytic anemia and the consequent tissue hypoxia, as well by their compensatory reactions, including increased erythropoiesis with bone marrow expansion and increased intestinal Fe absorption.[82,83] β-TM (β^0/β^0 or β^0/β^+) is characterized by severe hypochromic microcytic anemia, which becomes symptomatic at infancy or early childhood and is apparently transfusion-dependent. The reduction in globin chain synthesis leads to an unbalanced β/α-globin chain production, where the chains in abundance precipitate to form erythrocyte inclusions. The pathophysiology of β-TM is characterized by damaged RBCs, hemolysis, and erythrocyte precursor release into the peripheral circulation due to ineffective erythropoiesis.[3] The phenotype includes

anemia, bone marrow expansion, skeletal deformities, growth restriction, and late sexual maturity.[82,83]

β-thalassemia and Fertility

Advances in the management of patients with β-thalassemia, which include optimal blood transfusion and Fe chelation therapy, have significantly improved the quality of life and survival of patients. This improved quality of life and survival create a desire in affected individuals to procreate and have children of their own. Frequent transfusions create the problem of Fe overload, which adversely affects many endocrine organs which, in turn, leads to difficulty in achieving conception. When successful conception occurs, it is associated with complications making such pregnancies high risk. Hypogonadotropic hypogonadism (HH) is the most frequent endocrinopathy in transfused patients with TM. Fifty-one to sixty-six percent of thalassemic patients with marked hemosiderosis are predisposed to developing pubertal failure, sexual dysfunction, infertility, and short stature.[84,85] Fe accumulation in the anterior pituitary, a tissue with a high transferring receptor, results in free radical oxidative stress, impairing gonadotropins, and growth hormone secretion.[86] Furthermore, thalassemic may also suffer from Fe accumulation in the ovaries or testes, and oxidative stress may occur there when an imbalance between the generation of reactive oxygen species and the scavenging capacity of antioxidants in the reproductive tract is present.[87] Reactive oxygen species may have an important regulatory role through various signal-transduction pathways in the normal functioning of the reproductive system in female fertility, affecting multiple physiological processes from oocyte maturation to fertilization, embryo development, and pregnancy,[88] while recent studies have shown significant acute changes in the hormonal environment and sperm parameters of Fe overloaded patients.[89–91] It is also noted that HH is related to Fe toxicity in adipose tissue, impairing and changing the physiological role of leptin acting as a permissive signal allowing puberty in sexual maturation and fertility.[92,93] The possible role of liver dysfunction and the presence of other endocrinopathies, such as diabetes or hypothyroidism, should not be underestimated when assessing fertility.[94] Singer et al. suggested that ovarian reserve is preserved in the majority of TM patients who are <30–35 years old, despite a low follicle count and low ovarian volume, and that anti-Müllerian hormone could be used as a sensitive marker for ovarian reserve independent of gonadotropins effect correlated with nontransferrin-bound Fe, suggesting a role of labile Fe in the pathogenesis of decreased reproductive capacity.[95] Pulsatile gonadotropins-releasing hormone infusion for ovulation induction is only possible at an early stage of hypothalamic damage, but as the majority of patients with HH are nonpulsatile with functional gonads, they are more likely to benefit from chorionic gonadotropins/human menopausal gonadotropins therapy, which has an 80% success rate.[96]

Spermatogenesis in thalassemic males is more difficult; with a success rate of 10–15% in moderate to severely Fe-overloaded patients[96] Micromanipulation techniques such as intracytoplasmic sperm injection (ICSI) have improved conception rates, even in oligoasthenospermic patients[3] Sperm should be cryopreserved in all subjects unless azoospermic to preserve fertility and the chance of conception better[3] However, thalassemic patients with low sperm concentration are likely to have a higher degree of defective chromatin packaging, while the negative association between ferritin levels and abnormal sperm morphology suggests a possible detrimental effect on spermatogenesis by Fe chelators.[97] Based on the highlighted difficulties in conception for both male and female thalassemia patients, the need for proper counseling should not be neglected. Comprehensive preconception care is also needed in thalassemic patients to optimize their condition, thus enhancing successful pregnancy and delivery.

Preconception Care in Thalassemia Patients

Preconception in thalassemia is such a vital concept aimed at reducing maternal and fetal risks and thus improving the safety of pregnancy. Whether spontaneous or assisted conception is expected, there is a need for meticulous preconception care. Issues of cardiomyopathy associated with Fe overload and its detrimental effects on both the mother and fetus call for stringent chelation protocols before achieving conception. Fe overload also creates the challenge of endocrine organ damage leading to diabetes, hypothyroidism, and hypoparathyroidism, which further complicates the pregnancy. There is also a risk of liver damage as a result of Fe overload. The first step in reducing the incidence of thalassemia and other hemoglobinopathies is identifying high-risk populations for the disease. Screening thus becomes vital in this regard. Screening partners of affected women is an important first step in preconception care. If a partner is a carrier of a hemoglobinopathy that may adversely interact with the woman's genotype, then genetic counseling should be offered.[98] In IVF/ICSI with a PGD should be considered in the presence of hemoglobinopathies in both partners so that a homozygous or compound heterozygous pregnancy can be avoided.[98] Egg and sperm donors considering IVF should be screened for hemoglobinopathies.[98] Methods and risks of prenatal diagnosis and termination of affected pregnancy need to be discussed with couples.[98] In developing countries where these procedures are not commonly available premarital testing and counseling can be offered to couples. Hb electrophoresis remains the gold standard for the diagnosis and classification of thalassemia.

Like in SCD, both preconception and antenatal care are better provided by a dedicated team comprising obstetricians, hematologists, neonatologists, and midwives who specialize in managing thalassemia patients and medical counselors. Such a team should provide prepregnancy counseling so that affected women are well aware of the effect of thalassemia

on pregnancy and the effects of pregnancy on thalassemia. Preconception care should review transfusion requirements, Fe chelation therapy, and assessment of the body's Fe burden. The assessment should include optimization of management and screening for end-organ damage. There is evidence from clinical trials that optimizing body Fe reduces end-organ damage and can reverse cardiac Fe loading. Longitudinal studies show that patients who have been optimally chelated are less likely to suffer from endocrinopathies or cardiac problems.[99–101] Due to a lack of safety data, all chelation therapy should be regarded as potentially teratogenic in the first trimester.[98] Desferrioxamine is the only chelation agent with a body of evidence for use in the second and third trimester[102–104] and has a short half-life, and is safe for infusion during ovulation induction. In this regard, deferasirox and deferiprone should ideally be stopped 3 months before conception. Optimization of Fe burden is therefore critical as the ongoing Fe accumulation from transfusion in the absence of chelation may expose the pregnant woman to a high risk of new complications related to Fe overload, particularly diabetes and cardiomyopathy.[98] All bisphosphonates are contraindicated in pregnancy and should ideally be discontinued 3 months prior to conception.[98]

Diabetes mellitus is common in adults with thalassemia. Diabetes is multifactorial due to insulin resistance, Fe-induced islet cell insufficiency, genetic factors, and autoimmunity.[105] Similar to diabetes without thalassemia, an HbA1c of <43 mmol/mol is associated with a reduced risk of congenital abnormalities.[106] HbA1c is not a reliable marker of glycemic control as this is diluted by transfused blood and results in underestimation, so serum fructosamine is preferred for monitoring.[107] Hypothyroidism is frequently seen in thalassemic patients, and without treatment, it can lead to maternal morbidity, as well as perinatal morbidity and mortality. As part of preconception care, patients should have a thyroid function assessment, and if hypothyroidism is confirmed, treatment should be initiated to achieve a clinically euthyroid state.[108]

Prior to conception, the woman's cardiac status should be evaluated by performing an echocardiogram as well as a T_2* cardiac MRI. The cardiac status will indicate how well the women can safely tolerate pregnancy with little or no maternal/fetal adverse effects. Cardiomyopathy occurs in thalassemic patients because of Fe overload, and cardiac arrhythmias are more likely in older patients who previously had severe myocardial Fe overload and now clear of cardiac Fe. The aim is to achieve no cardiac Fe; however, this can take many years to achieve, so care should be individualized. Otherwise, aim for cardiac T_2* > 20 ms wherever possible as this reflects minimal Fe in the heart.[97] However, pregnancies with successful maternal and fetal outcomes have occurred with lower cardiac T_2* values. A T_2* < 10 ms is associated with increased cardiac failure.[109] A reduced ejection fraction is a relative contraindication to pregnancy, and management should involve a cardiologist.

A target liver Fe of <7 mg/gm [dry weight (DW)] is recommended because Fe chelation is discontinued during pregnancy, and therefore, transfusional Fe burden and the risk of Fe overload-related complications increases.[98] There is anecdotal evidence suggesting ovulation induction is more likely to be successful when the Fe burden is well controlled.[98] If liver Fe exceeds 15 mg/gm (DW), the risk of myocardial Fe loading increases, so Fe chelation with low dose desferrioxamine should be commenced between 20 and 28 weeks under guidance from the hemoglobinopathy team.[110] Persistent hemolysis makes cholelithiasis common in women with thalassemia and may develop cholecystitis in pregnancy. Liver cirrhosis and active hepatitis C virus (HCV) may run a more complex clinical course during pregnancy. Women with thalassemia and liver cirrhosis due to previous hepatitis or as a result of severe hepatic Fe loading and those who are HCV ribonucleic acid-positive (RNA) should be reviewed by a hepatologist during the preconception care. Adults with thalassemia are at risk of osteoporosis; this may be due to various factors, which include; hypogonadism, vitamin D deficiency, and the effect of chelation drugs that chelate Fe as well as calcium or the underlying thalassemic bone disease.[111] For this reason, all women should have vitamin D levels optimized before pregnancy and after pregnancy maintained within the normal range.[111]

Alloimmunity occurs in 16.5% of individuals with thalassemia.[112] Red cell antibodies may indicate a risk of hemolytic disease in the fetus and newborn.[113] If antibodies are present, there may be challenges in obtaining suitable blood for transfusion.[114] This scenario will enable caregivers to prepare even before conception.

Other issues relevant in preconception care include; Vaccination for Hepatitis B in HBsAg negative who are transfused or may be transfused.[98] Determining Hepatitis C status in women with thalassemia and if the woman is positive for hepatitis C, RNA titers should be determined, and the patient referred accordingly. All women who had splenectomy should take penicillin prophylaxis or equivalent.[98] Women who were splenectomized should be vaccinated for capsulated bacteria such as pneumococcus and Hib if this has not been done before.[98] Preconception folic acid supplementation of 5 mg daily should be started 3 months prior to conception because of high demand and to prevent neural tube defects.

Antenatal Care in thalassemia Patients

When pregnancy occurs in thalassemia, it should be considered high risk, and meticulous care should be provided by a multidisciplinary team comprising of an obstetrician, a hematologist, a cardiologist an endocrinology physician to take care of those with diabetes/hypothyroidism. An individualized care protocol should be adopted based on the severity of end-organ damage so that those with diabetes or cardiac dysfunction may be seen more frequently. Generally, however, women with thalassemia should be reviewed from 4 weeks until 28 weeks of gestation and fortnightly until 32 weeks, and weekly thereafter. Cardiac assessment is vital to determine the cardiac function and possible further Fe

chelation as well as planning for labor.[98] Thyroid function should be determined periodically throughout pregnancy, and women found to be hypothyroid should have their insulin dose adjusted.

Because of the increased risk of miscarriage and intrauterine growth restriction, obstetric ultrasound should be considered a vital part of antenatal care in women with thalassemia. Women should have an early scan at 7–9 weeks of gestation and 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 have a serial fetal biometry scan every 4 weeks from 24 weeks of gestation.[98]

Blood Transfusion

Women with thalassemia major will already be on an established blood transfusion regimen and are likely to be stable during pregnancy, and their Hb concentration should be maintained at 100 gm/L. Blood transfusion is indicated in women with TI; if they have worsening anemia or have evidence of IUGR and are started on transfusion, the target Hb will be the same as for those with thalassemia major. Generally, therefore the decision to transfuse is based on the woman's clinical symptoms or presence of IUGR. Hb concentration should be assessed at each antenatal clinical visit, and 2 units of blood should be transfused if the Hb concentration falls below 100 gm/L. In nontransfused individuals, transfusion can be withheld if the Hb concentration is 80 gm/L at 36 weeks of gestation. If the Hb concentration is <80 gm/L, then two units up should be given at 37–38 weeks of gestation.[98]

Thromboprophylaxis

Hemolysis in women with thalassemia major or intermedia releases red cell fragments predisposing them to the risk of thrombosis, most especially in those who had splenectomy hence the need for thromboprophylaxis. Therefore women with thalassemia who had splenectomy or have platelets count >600 × 10^9/L should commence or continue taking low-dose aspirin (75 mg/day).[98] Women with thalassemia who have undergone splenectomy and have a platelet count above 600 × 10^9/L should be on low-molecular-weight heparin Thromboprophylaxis as well as low-dose aspirin (75 mg/day).[98] Women with thalassemia who are not already using prophylactic low-molecular-weight heparin should be advised to use it during antenatal admissions.[98] Fe chelation therapy is complex and should be tailored to the needs of the individual patient.[98]

Antenatal Management of Women with Myocardial Fe

Cardiac MRI is safe in pregnancy and should be undertaken in women who have not received preconception assessment or where there is concern about cardiac function. As the cardiac T_2* value falls below 20 ms, there is an increasing cardiac decompensation. Those women at the highest risk are those where the value falls below 10 ms.[109] When this is seen in the first-trimester adverse pregnancy clinical outcome is likely. Women with myocardial Fe loading and T_2* values > 20 ms do not require desferrioxamine chelation during pregnancy unless there is severe hepatic Fe overload.[98] If the woman complains of palpitations, then a detailed history, electrocardiogram (ECG), and 24-hour ECG monitor assessment are needed to confirm a pathological cause. In either circumstance, desferrioxamine infusion may be indicated if there are concerns.[115–117] Women with severe hepatic Fe loading should be carefully reviewed, and consideration given to low dose desferrioxamine Fe chelation from 20 weeks.[98]

Intrapartum Care

Traditionally women with high-risk pregnancies are delivered at 38–40 weeks of gestation. The timing of delivery should be based on local guidelines for the delivery of high-risk pregnant women and maternal or fetal conditions identified during the pregnancy, such as diabetes, cardiomyopathy, or IUGR. On admission to the labor, a Hb check should be done, and if <100 gm/L, two units should cross-matched. Senior midwives, an obstetrician, a neonatologist, a hematologist, and an anesthesiologist should all be informed and should participate in the management of the labor. Labor should strictly be managed with the partograph. Women who are transfusion dependant and not on a chelating agent will have high serum concentrations of toxic Fe species known as transferrin-bound Fe. These may cause free radical damage and cardiac dysrhythmia when the woman is subjected to the stress of labor.[118] For such women, peripartum chelation therapy is recommended. For women with thalassemia, major IV desferrioxamine 2 gm over 24 hours should be administered.[98] Women with thalassemia may have low v at the time of delivery, and there is randomized control trial evidence that active management of the third stage of labor reduces blood loss.[114,119] Women with thalassemia in labor are considered to be at increased risk of operative delivery due to possible fetal hypoxia,[120] and for this reason, continuous electronic fetal monitoring is advocated. Cesarean delivery is recommended based on obstetric indications.

Postpartum Care

There is a high risk of thromboembolism due to the presence of abnormal red cells in the circulation. Women should receive low-molecular-weight heparin prophylaxis while in the hospital.[121–123] In addition, low molecular weight heparin should be administered for 7 days postdischarge following a vaginal delivery or for 6 weeks following cesarean section.[123] Women with thalassemia major who plan to breastfeed should restart desferrioxamine as soon as the initial 24-hour infusion of IV desferrioxamine finishes after delivery.[98] Desferrioxamine is secreted in breast milk but is not orally absorbed and therefore not harmful to the newborn, but there is minimal safety data from other chelators.[98] If the woman decides not to breastfeed, IV or subcutaneous desferrioxamine infusions are continued

until discharge from the hospital or until the resumption of her previous Fe chelation regimen under hematology supervision, whichever is sooner.[98]

Conclusion

Hemoglobinopathies are complex clinical diseases that limit the well-being and survival of those affected. When pregnancy is associated with hemoglobinopathy, it becomes even more complicated. The life of the woman and that of the unborn fetus become at risk due to the disease or its treatment. Because of the complexities associated as a result of multiorgan affectation, multidisciplinary care is needed to improve maternal and fetal outcomes. As management of hemoglobinopathies improves as a result of the development of new drugs and methods of care, more and more women afflicted with the disease survive to adulthood and become pregnant. These cohorts of women present a challenge to the physicians caring for them. Preconception care prepares the woman to embark on pregnancy in a relatively stable state, and with good antenatal, intrapartum, and postpartum care, the outcome for both mother and infant becomes much improved.

References

1. Aliyu Labaran Dayyabu. Haemoglobinopathies in perinatal medicine: challenges in management. In: Chervenak FA, Kupesic Plavsic S, Kurjak A. The fetus as a patient: current perspectives. Jaypee Brothers, New Delhi, 2019, pp. 1–18.
2. Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood 2010;115(22):4331–4336. DOI: 10.1182/blood-2010-01-251348
3. Petrakos G, Andriopoulos P, Tsironi M. Pregnancy in women with thalassemia: challenges and solutions. Int J Womens Health 2016;8:441–451. DOI: 10.2147/IJWH.S89308
4. Kwawukume E.Y. Sickle cell disease in Pregnancy. In: Comprehensive Obstetrics in the Tropics. First edition, Chapter 39. 2008, pp. 303–311.
5. Herrick JB. Peculiar elongated and sickle-shaped red blood corpuscles in a case of severe anemia. 1910. Yale J Biol Med 1910;74(3):179–184. DOI: 10.1001/jama.2014.11011
6. Pauling L, Itano HA, Singer SJ, et al. Sickle cell anemia, a molecular disease. Science 1949;110(2865):543–548. DOI: 10.1126/science.110.2865.54
7. Neel JV. The inheritance of sickle cell anemia. Science 1949;110(2846):64–66. DOI: 10.1126/science.110.2846.64
8. Serjeant G (1985) 'Sickle cell disease', Oxford University Press, Oxford, PP 13–19
9. Angastiniotis M, Modell B, Englezos P, et al. Prevention and control of haemoglobinopthies. Bull World Health Organ 1995;73(3):375–386.
10. Serjeant GR. Sickle cell disease. Lancet 1997;350(9079):725–730. DOI: 10.1016/S0140-6736(97)07330-3
11. Diallo D, Tchernia G. Sickle cell disease in Africa. Curr Opin Hematol 2002;9(2):111–116. DOI: 10.1097/00062752-200203000-00005
12. Agboola A. Anemia in pregnancy, sickle cell disease. Agboola A (ed). Textbook of obstetrics and gynecology for medical students. 2nd edition. Heinemann Educational Books (Nigeria) Plc. pp. 331–339.
13. Streetley A, Latinovic R, Hall K, et al. Implementation of universal newborn bloodspot screening for sickle cell disease and other clinically significant haemoglobinopthies in England: screening results for 2005–7. J Clin Pathol 2009;62(1):26–30. DOI: 10.1136/jcp.2008.058859
14. Green-top Guideline, No.61 July 2011
15. Tonniges TF. Serving the family from birth to the medical home: newborn screening: a blueprint for the future—a call for a national agenda on state newborn screening programs. Paediatrics 2000;106(2):389–422. DOI: 10.1542/peds.106.S2.389
16. The Council of Regional Networks for. Genetics Services (corn), Atlanta, December 1995
17. Tuck S, White JM. Sickle cell disease. In: JWW Studd (ed) Prog Obstet Gynaecol 1981;1:70–79. https://doi.org/10.1111/j.1471-0528.1983.tb08893.x
18. Kobak AJ, Stein PJ, Daro AF. Sickle cell anaemia in pregnancy. A review of literature and report of six cases. Am J Obstet Gynecol 1941;41(5):811–821. DOI: 10.1016/S0002-9378(41)90869-4
19. Rajab KE, Issa AA, Mohammed AM, et al. Sickle cell disease and pregnancy in Bahrain. Int J Gynaecol Obstet 2006;93(2):171–175. DOI: 10.1016/j.ijgo.2006.02.007
20. Smith JA, Espeland M, Bellevue R, et al. Pregnancy in sickle cell disease: experience of the cooperative study of sickle cell disease. Obstet Gynecol 1996;87(2):199–204. DOI: 10.1016/0029-7844(95)00367-3
21. Al Jama FE, Gasem T, Burshaid S, et al. Pregnancy outcome in patients with homozygous sickle cell disease in a university hospital, Eastern Saudi Arabia. Arc Gynecol Obstet 2009;280(5):793–797. DOI: 10.1007/s00404-009-1002-7
22. el-Shafei AM, Sandhu AK, Dhaliwal JK. Maternal mortality in Bahrain with special reference to sickle cell disease. Aust N Z J Obstet Gynaecol 1988;28(1):41–44. DOI: 10.1111/j.1479-828x.1988.tb01609.x
23. Villers MS, Jamison MG, De Castro LM, et al. Morbidity associated with sickle cell disease in pregnancy. Am J Obstet Gynecol 2008;199(2):125.e1–125.e5. DOI: 10.1016/j.ajog.2008.04.016
24. Afolabi BB, Iwuala NC, Iwuala IC, et al. Morbidity and mortality in sickle cell pregnancies in Lagos, Nigeria: a case control study. J Obstet Gynaecol 2009;29(2):104–146. DOI: 10.1080/01443610802667112
25. Tuck SM, Studd JW, White JM. Pregnancy in sickle cell disease in the UK. Br J Obstet Gynaecol 1983;90(2):112–117. DOI: 10.1111/j.1471-0528.1983.tb08893.x
26. Sun PM, Wilburn W, Raynor BD, et al. Sickle cell disease in pregnancy: twenty years experience at Grady Memorial Hospital, Atlanta, Georgia. Am J Obstet Gynecol 2001;184(6):1127–1130. DOI: 10.1067/mob.2001.115477
27. Serjeant GR, Loy LL, Crowther M, et al. Outcome of pregnancy in homozygous sickle cell disease. Obstet Gynecol 2004;103(6):1278–1285. DOI: 10.1097/01.AOG.0000127433.23611.54
28. Chakravarty EF, Khanna D, Chung L. Pregnancy outcomes in systemic sclerosis, primary pulmonary hypertension, and sickle cell disease. Obstet Gynecol 2008;111(4):927–934. DOI: 10.1097/01.AOG.0000308710.86880.a6
29. Ranney HM, Sharma V. Structure and function of haemoglobin. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ. (eds) Williams' Haematology, 5th edn. New York: McGraw-Hill, 1995;417.
30. Chernoff AI. The amino acid composition of haemoglobin: IV. The preparation of pure polypeptide chains of

human haemoglobins. J Chromatogr 1965;17:140–148. DOI: 10.1016/S0021-9673(00)99844-3
31. Progress in Obstetrics and Gynaecology 16
32. Jaffe RH. Die Schelzellenanamie. Virch Arch Pathol Anat 1927;265:452–471.
33. Ballas SK, Larner J, Smith ED, et al. Rheologic predictors of the severity of the painful sickle cell crises. Blood 1988;72(4):1216–1223. DOI: 10.1182/blood.V72.4.1216.1216
34. Martin Jr JN, Files J, Morrison JC. Sickle cell cell crises. In: Clark SL, Cotton DV, Hankins GDV, Phelan JP. (eds) Critical care Obstetrics, 2nd edn. Cambridge, MA: Blackwell1991;212.
35. Beutler E. The sickle cell disease related disorders. In: Beutler E, Lichtman MA, Coller BS, Kipps TJ. (eds) Williams' Haematology, 5th edn. New York: McGraw-Hill, 1995;616.
36. Howard RJ, Tuck SM, Pearson TC. Pregnancy in sickle cell disease in the UK: results of a multicentre survey of the effect of prophylactic blood transfusion on maternal and fetal outcome. Br J Obstet Gynaecol 1995;102(12):947–951. DOI: 10.1111/j.1471-0528.1995.tb10900.x
37. Perrine RP, Brown MJ, Clegg JB, et al. Benign sickle-cell anaemia. Lancet 1972;2(7788):1163–1167. DOI: 10.1016/s0140-6736(72)92592-5
38. Pembrey ME, Wood WG, Weatherall DJ, et al. Fetal haemoglobin production and the sickle gene in the oases of Eastern Saudi Arabia. Brit J Haematol 1978;40(3):415–429. DOI: 10.1111/j.1365-2141.1978.tb05813.x
39. Weatherall DJ, Clegg JB, Blankston J, et al. A new sickling disorder resulting from interaction of the genes for haemoglobin S and α-thalassemia. Brit J Haemtol 1969;17(6):517–526. DOI: 10.1111/j.1365-2141.1969.tb01402.x
40. Warsy AS. Frequency of glucose-6-phosphate dehydrogenase deficiency in sickle-cell disease. A study in Saudi Arabia. Hum Hered 1985;35(3):143–147. DOI: 10.1159/000153534
41. Johnson K, Posner SF, Biermann J, et al. Recommendation to improving preconception health and healthcare; United States. MMWR 2006;55(No. RR–06):1–23
42. Lindenbaum J, Klipstein FA. Folic acid deficiency in sickle-cell anemia. N Engl J Med 1963;269:875–882. DOI: 10.1056/NEJM196310242691701
43. Charache S, Niebyl JR. Pregnancy in sickle cell disease. Clin Haematol 1985;14(3):729–746. DOI: 10.1016/S0308-2261(21)00502-6
44. Charache S, Terrin ML, Moore RD, et al. Effect of hydroxyurea on the frequency of painful crises in sickle cell anemia. Investigators of the multicenter study of hydroxyurea in sickle cell anemia. N Engl J Med 1995;332(20):1317–1322. DOI: 10.1056/NEJM199505183322001
45. Diav-Citrin O, Hunnisett L, Sher GD, et al. Hydroxyurea use during pregnancy: a case report in sickle cell disease and a review of literature. Am J Hematol 1999;60(2):148–150. DOI: 10.1002/(sici)1096-8652(199902)60:2<148::aid-ajh12>3.0.co;2-i
46. Byrd DC, Pitts SR, Alexander CK. Hydroxyurea in two pregnant women with sickle cell anemia. Pharmacotherapy 1999;19(12):1459–1462. DOI: 10.1592/phco.19.18.1459.30901
47. Foucan L, Bourhis V, Bangou J, et al. A randomized trial of captopril for microalbuminuria in normotensive adults with sickle cell anemia. Am J Med 1998;104(4):339–342. DOI: 10.1016/s0002-9343(98)00056-4
48. McKie KT, Hanevold CD, Hernandez C, et al. Prevalence, prevention, and treatment of microalbuminuria and proteinuria in children with sickle cell disease. J Pediatr Hematol Oncol 2007;29(3):140–144. DOI: 10.1097/MPH.0b013e3180335081
49. Gaston MH, Verter JI, Woods G, et al. Prophylaxis with oral penicillin in children with sickle cell anemia. A randomized trial. N Engl J Med 1986;314(25):1593–1599. DOI: 10.1056/NEJM198606193142501
50. Sickle cell Society. Standards for the Clinical Care of Adults with Sickle Cell Disease in the UK. London: Sickle Cell Society; 2008.
51. Working party of the British committee for standards in haematology clinical haematology task force. Guidelines for the prevention and treatment of infection in patients with an absent or dysfunctional spleen. BMJ 1996;312(7028):430–434. DOI: 10.1136/bmj.312.7028.430
52. Ataga KI, Moore CG, Jones S, et al. Pulmonary hypertension in patients with sickle cell disease: a longitudinal study. Br J Haematol 2006;134(1):109–115. DOI: 10.1111/j.1365-2141.2006.06110.x
53. Gladwin MT, Sachdev V, Jison ML, et al. Pulmonary hypertension as a risk factor for death in patients with sickle cell disease. N Engl J Med 2004;350(9):886–895. DOI: 10.1056/NEJMoa035477
54. Clarkson JG. The ocular manifestation of sickle-cell disease: a prevalence and natural history study. Trns Am Opthalmol Soc 1992;90:481–504. PMID: 1494832; PMCID: PMC1298447.
55. NHS Sickle & thalassemia Screening. Programme [http;//sct.screening.nhs.uk/]
56. Royal College of Obstetricians and Gynaecologists. Amniocentesis and chorionic villus sampling. Green-top Guideline No. 8. London:RCOG;2010 [http://www.rcog.org.uk/womens-health/clinical-guidance/amniocentesis-andchorionic-villus-sampling-green-top-8]
57. Powars DR, Sandhu M, Niland-Weis J, et al. Pregnancy in sickle cell disease. Obstet Gynecol 1986;67(2):217–228. DOI: 10.1097/00006250-198602000-00012
58. Maeda T, Wakasawa T, Shima Y, et al. Role of polyamines derived from arginine in differentiation and proliferation of human blood cells. Biol Pharm Bull 2006;29(2):234–239. DOI: 10.1248/bpb.29.234
59. Tuck SM, Studd JW, White JM. Sickle cell disease in pregnancy complicated by anti-U antibody. Case report. Br J Obstet Gynaecol 1982;89(1):91–92. DOI: 10.1111/j.1471-0528.1982.tb04645.x
60. Cunningham FG, Pritchard JA, Mason R, et al. Prophylactic transfusions of normal red blood cells during pregnancies complicated by sickle cell hemoglobinopthies. Am J Obstet Gynecol 1979;135(7):994–1003. DOI: 10.1016/0002-9378(79)90825-1
61. Morrison JC, Schneider JM, Whybrew WD, et al. Prophylactic transfusion in pregnant patients with sickle hemoglobinopthies: benefit versus risk. Obstet Gynecol 1980;56(3):274–280. PMID: 7422165.
62. Tuck SM, James CE, Brewster EM, et al. Prophylactic blood transfusion in maternal sickle cell syndromes. Br J Obstet Gynaecol 1987;94(2):121–125. DOI: 10.1111/j.1471-0528.1987.tb02337.x
63. Koshy M, Burd L, Wallace D, et al. Prophylactic red-cell transfusions in pregnant patients with sickle cell disease. A randomized cooperatve study. N Engl J Med 1988;319(22):1447–1452. DOI: 10.1056/NEJM198812013192204
64. Aken'Ova YA, Adeyefa I, Okunade M. Ferritin and serum iron levels in adult patients with sickle cell anaemia at

Ibadan, Nigeria. Afr J Med Sci 1997;26(1-2):39–41. DOI: 10.1155/2015/386451
65. Akinyanju OO, Nnatu SNN, Ogedengbe OK. Antenatal iron supplementation in sickle cell disease. Int J Gynaecol Obstet 1987;25(6):433–436. DOI: 10.1016/0020-7292(87)90057-9
66. Duley L, Henderson-Smart DJ, Meher S, et al. Antiplatelet agents for preventing pre-eclampsia and its complications. Cochrane Database Syst Rev 2007;(2):CD004659. DOI: 10.1002/14651858.CD004659.pub2
67. National Institute for Health and Clinical excellence
68. Rees DC, Olujohungbe AD, Parker NE, et al. Guidelines for the management of acute painful crisis in sickle cell disease. Br J Haematol 2003;120(5):744–752. DOI: 10.1046/j.1365-2141.2003.04193.x
69. Anyaegbunam A, Morel MI, Merkatz IR. Antepartum fetal surveillance tests during sickle cell crisis. Am J Obstet Gynecol 1991;165(4):1081–1083. DOI: 10.1016/0002-9378(91)90475-7
70. Anyaegbunam A, Mikhail M, Axioitis C, et al. Placental histology and placental/fetal weight ratios in pregnant women with sickle cell disease: relationship to pregnancy outcome. J Assoc Acad Minor Phys 1994;5(3):123–125. PMID: 7949824.
71. Camous J, N'da A, Etienne-Julan M, et al. Anaesthetic management of pregnant women with sickle cell disease–effect on postnatal sickling complications. Can J Anaesth 2008;55(5):276–283. DOI: 10.1007/BF03017204
72. De Ceulaer K, Gruber C, Hayes R, et al. Medroxyprogesterone acetate and homozygous sickle-cell disease. Lancet 1982;2(8292):229–231. DOI: 10.1016/s0140-6736(82)90320-8
73. Legardy JK, Curtis KM. Progesterone-only pill use among women with sickle cell anemia: a systematic review. Contraception 2006;73(2):195–204. DOI: 10.1016/j.contraception.2005.08.010
74. Bauer DE, Orkin SH. Update on fetal hemoglobin gene regulation in hemoglobinopathies. Curr Opin Pediatr 2011;23(1):1–8. DOI: 10.1097/MOP.0b013e3283420fd0
75. Old JM. Screening and genetic diagnosis of haemoglobin disorders. Blood Rev 2003;17(1):43–53. DOI: 10.1016/s0268-960x(02)00061-9
76. Cohen AR, Galanello R, Pennell DJ, et al. Thalassemia. Hematology Am Soc Hematol Educ Program 2004;2004:14–34. DOI: 10.1182/asheducation-2004.1.14
77. Harteveld CL, Higgs DR. Alpha-thalassemia. Orphanet J Rare Dis 2010;5:13. DOI: 10.1186/1750-1172-5-13
78. Vichinsky E. Complexity of alpha thalassemia: growing health problem with new approaches to screening, diagnosis, and therapy. Ann N Y Acad Sci 2010;1202:180–187. DOI: 10.1111/j.1749-6632.2010.05572.x
79. Chui DHK, Fucharoen S, Chain V. Hemoglobin H disease: not necessarily a benign disorder. Blood 2003;101(3):791–800. DOI: 10.1182/blood-2002-07-1975
80. Higgs DR, Weatherall DJ. The alpha thalassemias. Cell Mol Life Sci 2009;66(7):1154–1162. DOI: 10.1007/s00018-008-8529-9
81. Cao A, Galanello R. Beta-thalassemia. Genet Med 2010;12(2):61–76. DOI: 10.1097/GIM.0b013e3181cd68ed
82. Danjou F, Anni F, Galanello R. Beta-thalassemia: from genotype to phenotype. Haematologica 2011;96(11):1573–1575. DOI: 10.3324/haematol.2011.055962
83. Camaschella C, Cappellini MD. Thalassemia intermedia. Haematologica 1995;80(1):58–68. DOI: 10.3324/%25x
84. De Sanctis V,Soliman AT, Elsedfy H, et al. Growth and endocrine disorders in thalassemia: the international network on endocrine complications in thalassemia (I-CET) position statement and guidelines. Indian J Endocrinol Metab 2013;17(1):8–18. DOI: 10.4103/2230-8210.107808
85. De Sanctis V. Growth and puberty and its management in thalassemia. Horm Res 2002;58(1):72–79. DOI: 10.1159/000064766
86. Roussou P, Tsagarakis NJ, Diamanti-Kandarakis E, et al. Beta-thalassemia major and female fertility: the role of iron and iron-induced oxidative stress. Anemia 2013;2013(2):617204. DOI: 10.1155/2013/617204
87. Agarwal A, Allamaneni SS. Role of free radicals in female reproductive diseases and assisted reproduction. Reprod Biomed Online 2004;9(3):338–347. DOI: 10.1016/s1472-6483(10)62151-7
88. Al-Gubory KH, Garrel C, Faure P, et al. Roles of antioxidant enzymes in corpus luteum rescue from reactive oxygen species-induced oxidative stress. Reprod Biomed Online 2012;25(6):551–560. DOI: 10.1016/j.rbmo.2012.08.004
89. Mahachoklertwattana P, Yimsumruay T, Poomthavorm P, et al. Acute effects of blood transfusion on growth hormone and insulin-like growth factor-1 levels in children with thalassemia. Horm Res Paediatr 2011;75(4):240–245. DOI: 10.1159/000321189
90. Soliman A, Yassin M, El-Awwa A, et al. Acute effects of blood transfusion on pituitary gonadal axis and sperm parameters in adolescents and young men with thalassemia major: a pilot study. Fertil Steril 2012;98(3):638–643. DOI: 10.1016/j.fertnstert.2012.05.047
91. De Sanctis V, Elsedfy H, Soliman AT, et al. Acquired hypogonadotropic hypogonadism (AHH) in thalassemia major patients: an underdiagnosed condition?. Mediterr J Haematol Infect Dis 2016;8(1):e2016001. DOI: 10.4084/MJHID.2016.001
92. Kiess W, Reich A, Meyer K, et al. A role for leptin in sexual maturation and puberty?. Horm Res 1999;51(3):55–63. DOI: 10.1159/000053163
93. Perrone L, Perrotta S, Raimondo P, et al. Inappropriate leptin secretion in thalassemia: a potential cofactor of pubertal timing derangement. J Pediatr Endocrinol Metab 2003;16(6):877–881. DOI: 10.1515/jpem.2003.16.6.877
94. De Sanctis V, D'Ascola G, Wonke B. The development of diabetes mellitus and chronic liver disease in long term chelated beta thalassemic patients. Postgrad Med J 1986;62(731):831–836. DOI: 10.1136/pgmj.62.731.831
95. Singer ST, Vichinsky EP, Gildengorin G, et al. Reproductive capacity in iron overloaded women with thalassemia major. Blood 2011;118(10):2878–2881. DOI: 10.1182/blood-2011-06-360271
96. Skordis N, Petrikkos L, Toumba M, et al. Update on fertility in thalassemia major. Pediatr Endocrinol Rev 2004;2(2):296–302.
97. De Scantis V,Perera D, Katz M, et al. Spermatozoal DNA damage in patients with B thalassemia syndromes. Pediatr Endocrinol Rev 2008;6(1):185–189.
98. Green-top Guideline No. 66 2014. DOI:10.1111/tog.12100
99. Alpendurada F, Smith GC, Carpenter JP, et al. Effects of combined deferiprone with deferoxamine on right ventricular function in thalassemia major. J Cardiovasc Magn Reson 2012;14(1):8. DOI: 10.1186/1532-429X-14-8
100. Pennell D, Porter JB, Cappellini MD, Li CK, Aydinok Y, Lee CL, et al. Efficacy and safety deferasirox (ExjadeR) in reducing cardiac iron in patients with B-thalassemia major: results from the cardiac sub-study of the EPIC trial [abstract]. Blood 2008;112(ASH Annual Meeting Abstract):Abstract,3873

[http://abstract.haematologylibrary.org/cgi/content/abstract/112/11/3873]
101. Barry M, Flynn DM, Letsky EA, et al. Long-term chelation therapy in thalassemia major: effect on liver iron concentration, liver histology, and clinical progress. Br Med J 1974;2(5909):16–20. DOI: 10.1136/bmj.2.5909.16
102. Schnebli H.P. Final Report: Preclinical evaluation of CGP 37 391(L1). Schnebli HP, editor. ERS 62/93;1993. pp. 2–30.
103. Khoury S, Odeh M, Oettinger M. Deferoxamine treatment for acute iron intoxication in pregnancy. Acta Obstet Gynecol Scand 1995;74(9):756–757. DOI: 10.3109/00016349509021190
104. Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? Am J Hematol 1999;60(1):24–26. DOI: 10.1002/(sici)1096-8652(199901)60:1
105. de Assis RA, Ribeiro AA, Kay FU, et al. Pancreatic iron stores assessed by magnetic resonance imaging (MRI) in beta thalassemic patients. Eur J Radiol 2012;81(7):1465–1470. DOI: 10.1016/j.ejrad.2011.03.077
106. National Institute for Health and Clinical Excellence. Diabetes in pregnancy: Management of diabetes and its complications from pre-conception to the postnatal period. NICE clinical guideline 63. Manchester: Nice; 2008.
107. Spencer DH, Grossman BJ, Scott MG. Red cell transfusion decreases hemoglobin A1c in patients with diabetes. Clin Chem 2011;57(2):344–346. DOI: 10.1373/clinchem.2010.157321
108. De Groot L, Abalovich M, Alexander EK, et al. Management of thyroid dysfunction during pregnancy and postpartum: an Endocrine Society clinical practice guideline. J Clin Endocrinol Metab 2012;97(8):2543–2565. DOI: 10.1210/jc.2011-2803
109. Kirk P, Roughton M, Porter JB, et al. Cardiac T2* magnetic resonance for prediction of cardiac complications in thalassemia major. Circulation 2009;120(20):196–198. DOI: 10.1161/CIRCULATIONAHA.109.874487
110. Olivieri NF, Brittenham GM. Iron-chelating therapy and the treatment of thalassemia. Blood 1997;89(3):2621.
111. Walsh JM, McGowan CA, Kilbane M, et al. The relationship between maternal and fetal vitamin D, insulin resistance, and fetal growth. Reprod Sci 2013;20(5):536–541. DOI: 10.1177/1933719112459222
112. Thompson AA, Cunningham MJ, Singer ST, et al. Red cell alloimmunization in a diverse population of transfused patients with thalassemia. Br J Haematol 2011;153(1):121–128. DOI: 10.1111/j.1365-2141.2011.08576.x
113. Royal College of Obstetricians and Gynaecologists. The management of women with red cell. Antibodies during pregnancy. Green-top Guideline No.65. London: RCOG; 2014.
114. Royal College of Obstetrician and Gynaecologists. Blood Transfus. Royal College of Obstetrician and Gynaecologists. Blood Transfusions in Obstetrics. Green-top Guideline No. 47. London: RCOG; 2007.
115. Davis BA, Porter JB. Long-term outcome of continuous 24-hour deferoxamine infusion via indwelling intravenous catheters in high-risk beta-thalassemia. Blood 2000;95(4):1229–1236. DOI: 10.1182/blood.V95.4.1229.004k32_1229_1236
116. Anderson LJ, Westwood MA, Holden S, et al. Myocardial iron clearance during reversal of siderotic cardiomyopathy with intravenous desferrioxamine: a prospective study using T2* cardiovascular magnetic resonance. Br J Haematol 2004;127(3):348–355. DOI: 10.1111/j.1365-2141.2004.05202.x
117. Davis BA, O'Sullivan C, Jarrit PH, et al. Value of sequential monitoring of left ventricular ejection fraction in the management of thalassemia major. Blood 2004;104(1):263–269. DOI: 10.1182/blood-2003-08-2841
118. Lekawanvijit S, Chattipakorn N. Iron overload thalassemic cardiomyopathy: iron status assessment and mechanisms of mechanical and electrical disturbance due to iron toxicity. Can J Cardiol 2009;25(4):213–218. DOI: 10.1016/s0828-282x(09)70064-9
119. Begley CM, Gyte GM, Devane D, et al. Active versus expectant management for women in the third stage of labor. Cochrane Database Syst Rev 2011;(11):CD007412. DOI: 10.1002/14651858.CD007412.pub3
120. National Institute for Health and Clinical Excellence. Intrapartum care: Care of healthy women and their babies during childbirth. NICE clinical guideline 55. Manchester:NICE; 2007.
121. Eldor A, Rachmilewitz EA. The hypercoagulable state in thalassemia. Blood 2002;99(1):36–43. DOI: 10.1182/blood.v99.1.36
122. Taher A, Isma'eel H, Mehio G, et al. Prevalence of thromboembolic events among 8,860 patients with thalassemia major and intermedia in the Mediterranean area and Iran. Thromb Haemost. 2006;96(4):488–491. DOI: 10.1160/TH06-05-0267
123. Royal College of Obstetrician and Gynaecologists. Reducing the Risk of Thrombosis and Embolism during Pregnancy and the Puerperium. Green-top Guideline No. 37a. London:RCOG; 2009.