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Issues And Remedies For Thalassemia- In Affected Pregnant Mothers

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Abstract:

Advancements in the treatment of thalassemia have significantly increased life expectancy, leading to a growing population of aging thalassemic patients with reproductive aspirations. Historically, only women with thalassemia intermedia were considered capable of achieving pregnancy. However, recent reports show that both thalassemia major and intermedia patients express a desire to start families.

Methodology:

This analysis reviews clinical case series and literature on pregnancy in women with β-thalassemia, focusing on the physiological demands of pregnancy, the specific complications faced by thalassemia patients, and the management strategies adopted to support maternal and fetal health.

Result:

Pregnancy induces complex systemic changes and elevates oxidative stress, which pose heightened risks for thalassemia patients. Women with β-thalassemia major, who are typically transfusion-dependent, frequently experience cardiac, hepatic, endocrine, and metabolic disorders due to chronic anoxia and iron overload. In contrast, women with thalassemia intermedia, often non-transfused, are more susceptible to thromboembolic events. These conditions make pregnancy inherently high-risk for both mother and fetus.

Conclusion:

Successful pregnancy outcomes in women with thalassemia are attainable through comprehensive, multidisciplinary care. Continuous preconception planning, antenatal monitoring, and postpartum management by specialists in thalassemia are critical for optimizing maternal and fetal health.

Keywords: thalassemia, pregnancy, chelation, transfusion, iron.

I. Introduction

About 7% of people worldwide are carriers of hemoglobinopathies, which are among the most prevalent hereditary illnesses. Every year, between 300,000 and 500,000 children are born with a severe hemoglobin abnormality. They are categorized based on the globin chains that are affected and whether the condition results in an aberrant tertiary structure of globin chains or a decreased generation of normal chains. The genes of chromosomes 11 (the β-gene cluster, which includes the globin chains γ, ε, β, and δ) and 16 (the α-gene cluster, which includes the α- and ζ-globin chains) code for the exact structure of the globin chains. Hemoglobin needs to be properly trimmed and have the right structure so that the number of α-chains exactly equals the number of β-chains. Hemoglobin in adulthood is composed of remnants of HbF (α2γ2), less than 3% HbA2 (α2δ2), and roughly 98% HbA (α2β2). Thalassemia is a term used to describe hemoglobinopathies that result in reduced hemoglobin concentration, microcytosis, and anemia. These disorders are caused by missense/nonsense mutations (single-base substitutions) or frameshift mutations of the genes governing the structure of the hemoglobin-protein chains in one or both "allelic" globin genes, which partially or totally suppress the synthesis of one of the two types of polypeptide chains (α or β). A number of thalassemia kinds have been identified, with α-, β/δ-, and β-thalassemia being the most prevalent and clinically significant. These types vary according to the genes impacted, the deficiency that results, and the related impact on the globin chain.

The pathophysiology and genetic foundation of thalassemias

Reduced or suppressed production of α-globin chains is the hallmark of α-thalassemia, the most common inherited hemoglobin disorder. It is most common in populations from sub-Saharan Africa, the Mediterranean region, the Middle East, the Indian subcontinent, and East and Southeast Asia. Globally, there are about 1,000,000 patients with different α-thalassemia syndromes, and nearly 5% of the population is a carrier. Fetal life is when the α-globin chain synthesis starts. The four genes in question are located in two distinct regions on chromosome 16. Phenotype varies on the number of genes damaged. α-thalassemia is caused by gene deletion or, less frequently, mutation. In homozygous α-thalassemia, when all four genes are impacted , fetal α-chain synthesis is impossible, resulting in an excess of γ-chains and the formation of unstable Bart's hemoglobin (γ4), which is unable to exchange oxygen. Serious anemia, cardiomegaly, hydrops fetalis, and eventually intrauterine or neonatal death are all experienced by the afflicted fetuses. There is minimal α-chain production when three genes are impacted. As a result, extra β-chains create the unstable HbH (β4). Based on the kind of mutation, the phenotype of HbH illness varies, ranging from transfusion-dependent anemia to moderate anemia caused by chromosome 16 deletions. The manifestation of moderate hypochromic microcytic anemia is caused by the presence of two α-genes (α-thalassemia trait). Iron overload and hemolysis result from the continued imbalance in globin production. When two genes are deleted, they belong to the same allele in α0-thalassemia, which is common in Asian and Eastern Mediterranean populations. In contrast, when α+-thalassemia is common in Africans, the deleted genes belong to distinct homologous chromosomes. In "silent" carriers, only one

α-gene is impacted; the other three are functioning and can produce hemoglobin normally.

The degree of impairment in β-globin chain formation and the type of β-gene mutation determine the genotype and phenotype of β-thalassemia, which is highly variable. Normal or slightly subnormal hemoglobin levels, low mean cellular hemoglobin, low mean cell volume, low β:α-globin chain ratio on biosynthesis, and HbA2 ≥3.5% are the only laboratory values that are typically seen in heterozygous carriers of β-thalassemia (one affected allele), who are typically asymptomatic.

On the other hand, a broad range of phenotypes, from mild or moderate anemia (thalassemia intermedia [TI]) to transfusion-dependent thalassemia major [TM], are caused by the inheritance of two faulty β-globin genes. β0 indicates that the afflicted allele produces no β-globin at all, β+ indicates that some β-globin is still produced, and β++ indicates a very slight decrease in β-globin production. There have been reports of over 200 thalassemic mutations. The production of β-globin is moderately reduced when both parental genes have TI mutations. Up to 25% of people with β-thalassemia have TI, which spans a broad range of genotypes and clinical manifestations from transfusion-dependent thalassemia to the asymptomatic carrier state. The quality of life is not significantly impacted, and patients typically have milder anemia with a later clinical onset and no need for transfusions for survival during the first few years of life. However, if treatment is not received, the disease's multiple effects—including increased erythropoiesis with bone marrow expansion and increased intestinal iron absorption—as well as the resulting tissue hypoxia complicate the disease's clinical course.

The hallmark of β-TM, also known as Cooley's anemia (β0/β0 or β0/β+), is severe hypochromic microcytic anemia that manifests in early childhood or infancy and appears to be transfusion-dependent. The reduction in globin chain synthesis results in an imbalanced production of β/α-globin chains, which precipitate in large quantities to form erythrocyte inclusions. Damaged red blood cells, hemolysis, and the release of erythroid precursors into the peripheral circulation as a result of inefficient erythropoiesis are the hallmarks of pathophysiology. Anemia, skeletal abnormalities, growth restriction, bone marrow enlargement, and late sexual maturity are some of the phenotypes.

Advances in care, such as iron-chelation therapy and optimum blood transfusion, have improved the quality of life and survival of patients with β-thalassemia into adulthood. Because patients want to have their own family, there is now more worry about a positive reproductive outcome. A growing number of spontaneous or assisted reproductive technology conceptions in both TI and TM have been documented, despite the fact that women with TI were thought to be capable of becoming pregnant following the initial findings in the mid-1960s.

Since β-thalassemia can be a high-risk condition for both mother and baby, and intensive counseling and monitoring from the preconception stage is required, this article aims to examine the existing information documenting pregnancy in thalassemia, concentrating primarily on β-thalassemia and its necessary follow-up.

Fertility in β-thalassemia

The most common endocrinopathy in transfused individuals with TM is hypogonadotropic hypogonadism (HH), which is associated with a 51% to 66% risk of pubertal failure, sexual dysfunction, infertility, and low stature in thalassemic patients with significant hemosiderosis. Gonadotropins and growth hormone release are hampered by iron buildup in the anterior pituitary gland, a region with high transferrin receptor numbers that experiences free radical oxidative stress. Additionally, thalassemics may have iron buildup in the testes or ovaries, where oxidative stress may occur due to an imbalance between the reproductive tract's antioxidants' ability to scavenge reactive oxygen species and their production. The literature suggests that reactive oxygen species may play a significant regulatory role through a variety of signal-transduction pathways in both female infertility and the normal functioning of the reproductive system. These mechanisms impact a number of physiological processes, including oocyte maturation, fertilization, embryo development, and pregnancy. Additionally, recent research has revealed notable acute alterations in the sperm parameters and hormonal environment of patients with iron overload. 30 to 32 Given that individuals with severe underlying molecular abnormalities have higher iron loading rates and likely varied susceptibilities to free radical damage, it appears that genotype plays a role in the development of HH. The physiological function of leptin, which acts as a permissive signal permitting puberty, in sexual development and fertility is also affected and altered by HH, which is linked to iron toxicity in adipose tissue. When evaluating fertility, it is important to consider the potential impact of liver dysfunction and the existence of other endocrinopathies, such as diabetes or hypothyroidism. Chronic hypoxia appears to play a significant role, as studies have shown that gonadotropin secretion is reduced within two days of arriving at a moderate altitude, which strengthens the role of chronic anemia.

A role of labile iron in the pathophysiology of decreased reproductive capacity was suggested by Singer et al., who also suggested that anti-Müllerian hormone could be used as a sensitive marker for ovarian reserve independently of gonadotropin effect correlated with non-transferrin-bound iron. They also suggested that ovarian reserve is preserved in the majority of TM patients under the age of thirty to thirty-five, despite a low follicle count and reduced ovarian volume. Only in the early stages of hypothalamic-pituitary damage can pulsatile gonadotropin-releasing hormone infusion be used to induce ovulation. However, since most HH patients are nonpulsatile and have functional gonads, they are more likely to benefit from the 80% success rate of human chorionic gonadotropin/human menopausal gonadotropin therapy. The Human Fertilisation and Embryology Authority (HFEA) guidelines41 state that only a specialised reproductive team should do ovulation induction, taking into account and informing women of the risk of miscarriage, multiple pregnancy, ectopic pregnancy, and hyperstimulation syndrome. The most severe cases require hospitalization due to hypovolemic shock, renal and/or respiratory insufficiency, and arterial thromboembolism. About 1% to 2% of inducted ovulation cases experience severe hyperstimulation syndrome, which causes fluid retention with bloating, breathlessness, and nausea, resulting in abdominal pain, vomiting, dyspnea, and rapid weight gain. Standard regimes are typically part of protocols for thalassemic women. IVF programs work better for patients with endometrial or fallopian tube impairment.

Male thalassemic spermatogenesis is more challenging; in patients with moderate to severe iron overload, success rates range from 10% to 15%. 40 HFEA criteria must be followed during the induction procedure, with a focus on counseling and consent. Even in oligoasthenospermic patients, micromanipulation methods like intracytoplasmic sperm injection (ICSI) have increased the rate of conception. All patients should have their sperm cryopreserved unless they are azoospermic in order to maintain fertility and increase the likelihood of pregnancy. However, the negative correlation between ferritin levels and aberrant sperm morphology points to a potential deleterious impact of iron chelators on spermatogenesis, and thalassemic patients with low sperm concentrations are more likely to have a larger degree of faulty chromatin packaging. Patients with thalassemia who are being evaluated for assisted conception techniques should receive the appropriate counseling because there appears to be a high risk of mutagenicity in these individuals, particularly following ICSI, when the natural barrier that protects against gamete selection during fertilization is removed.

Prepregnancy planning

For both spontaneous and assisted reproductive technology conceptions, pregnancy planning is crucial. When it comes to females, factors like medication review, endocrinological abnormality screening, infection control, and cardiac and liver function should be taken into account. Additionally, hemoglobinopathies should be examined in both couples.

Screening for thalassemias – genetic counseling

Finding thalassemia high-risk groups is the first step in lowering occurrence. Depending on population needs, culture, and/or ethics, screening programs may vary globally. While antenatal diagnosis is still a personal decision, policies emphasize counseling and education. There has been a campaign like this since the 1970s to raise awareness and draw attention to this hereditary condition in Greece, where carriers make up 7.5% of the general population. In the past, thalassemia was thought to be more common in communities in the Middle East, Eastern Mediterranean, India, and Africa. However, interethnic mixing and population migrations brought about by freedom of movement have changed these tendencies. But Hussein et al. claim that there aren't many randomized trials of preconception genetic risk assessment, and the evidence supporting the present policy recommendations comes only from nonrandomized studies.

The most reliable method for identifying and categorizing thalassemia is still hemoglobin electrophoresis. High-pressure liquid chromatography or electrophoresis are two methods for quantitatively assessing HbA2. Still, the latter offers the added benefit of simultaneously measuring HbF. Individuals who possess the β-thalassemia trait exhibit elevated HbA2 and HbF levels.

Genetic counseling should be carried out in order to obtain a prenatal diagnosis when both parents are carriers of the same trait (a α–α or β–β couple). The likelihood of a TM fetus (25%) should be disclosed to the couple. Either amniocentesis or chorionic villus samples are used to make the diagnosis. Some benefits of chorionic villus sample include the ability to diagnose the condition earlier in the first trimester (11th week), the ability to acquire more DNA by placental biopsy, and the possibility that it is safer to

enter the placenta than the amniotic cavity. The disadvantage of amniocentesis, on the other hand, is that it is only practical after the sixteenth week. The predicted risk of miscarriage is less than 1% and is the same for all of these invasive treatments.

Adoption is always an option, but using donor gametes that have been screened for hemoglobinopathies—preferably donor sperm, as sperm may be more readily obtained from sperm banks—seems to be the best choice when both parents have a particular hemoglobinopathy. It is necessary to propose a preimplantation genetic diagnosis if the partner of a homozygous parent is heterozygous. This includes the transfer of viable embryos, IVF/ICSI, and embryo biopsy. By biopsying the trophoblast cells, preimplantation genetic diagnosis can be made at the blastocyst stage on day five following fertilization or at the eight-cell stage (cleavage stage) on day three. Since cleavage-stage biopsy produces more viable blastocysts and provides more time for genetic testing prior to embryo transfer, it is frequently chosen. The disadvantages of cleavage-stage biopsy, namely the limited number of cells available for evaluation, have been overcome by polymerase chain-reaction techniques (nested, multiplex, and fluorescence).

Cardiac assessment

The increased metabolic demands of both the mother and the fetus cause pregnancy-induced circulatory alterations, which manifest clinically as heart failure-like signs and symptoms. 68 The heart experiences significant structural alterations during pregnancy, including temporary left ventricular hypertrophy, to accommodate the 25%–30% increase in functional load that is required. Pregnant women generally tolerate simple left-to-right shunts and valvular incompetence better than stenosis. The enlarged uterus pushes the diaphragm forward, which causes the heart to migrate anteriorly and to the left, shifting the apex beat upward and outward. In addition, peripartum cardiomyopathy is a rare ailment that affects the heart and can develop in the final month of pregnancy or in the five months following delivery. It can cause myocardial sequelae, complete recovery, or worsening, which can result in death or heart transplantation. A cardiologist should evaluate heart function and use electrocardiography (ECG), cardiac echo, and 24-hour Holter monitoring of rhythm to look into symptoms.

Healthy women do not have impaired cardiac reserve despite the increased functional cardiac load during pregnancy and childbirth. Conversely, pregnant women with insufficient cardiac reserve and established or undiagnosed heart disease may experience ventricular failure and pulmonary edema due to the increased functional strain on the heart. About 10% of maternal obstetric deaths are caused by heart problems, and congenital heart disease may be underreported. Heart failure can cause premature labor, and the mother's New York Heart Association functional classification is closely linked to the risk of maternal or fetal death. Pregnancy should be discouraged for women with specific high-risk conditions (such as pulmonary hypertension, severe valvular abnormalities, or previous postpartum cardiomyopathy) because of their strong association with significant rates of morbidity and fatality.

Pregnancy causes changes in the way several organs, particularly the fetoplacental unit, use energy substrates and increases basal oxygen use. The placenta's vascularization and maturation cause it to become rich in mitochondria, which raises free iron and produces free radicals locally. Reduced cardiac muscular contractility and the development of congestive heart failure are the results of the mitochondrial

respiratory chain's compromised performance. The left ventricle is especially vulnerable to decompensation in TM because the damaged heart must sustain a high output across a stiff vascular bed brought on by chronic hemolysis, which is continuously overloaded with volume and pressure.

Pregnant thalassemic women who receive rigorous pregestational chelation therapy and have normal resting heart function typically have successful pregnancies and deliveries. 16–18, 22–74 It is unclear, nonetheless, if a woman with myocardial hemosiderosis or somewhat compromised heart function—which can occur in even well-chelated patients—will be able to cope with the stress of pregnancy and the associated hemodynamic alterations. It has been demonstrated that cardiac magnetic resonance imaging (MRI) is very beneficial for preconception cardiac care. It can precisely identify iron overload, which is understated when relying solely on ferritin levels or echocardiography, and direct and, if necessary, scale up chelation therapy. Although T2* ≥20 ms is the desired goal, successful pregnancies have been obtained with lower levels. Attention should be paid to T2* levels ≤10 ms since they indicate a high risk of cardiac failure. 77 Therefore, a thalassemia-specialist cardiologist should evaluate all pregnant women using an ECG, cardiac echo study, 24-hour Holter monitoring of rhythm, and MRI T2* assessment.

Infections

Increased risk of infection and a decrease in overall immune function are caused by higher gestational estrogen levels. Consequently, the prevalence of both clinical and silent infections is increased during pregnancy, with chorioamnionitis being present in around 18% of gestations that appear to be normal and 33% of preterm births. Iron overload is thought to be the primary etiologic factor that can upset the immune balance in thalassemia because free intracellular iron exacerbates inflammatory processes. This is initially boosted by inflammatory cytokines (IL-1β), which may release free iron from ferritin or mitochondria and subsequently increase ferritin synthesis. In addition, there is a significant danger of viral infections contracted through transfusions. Since thalassemics may experience infection with various strains of the cytomegalovirus and reactivation of pre-existing strains, all women should be checked for hepatitis B virus (HBV), HCV, HIV, cytomegalovirus, and human parvovirus B19, especially by the age of pregnancy. 82 Vaccinations against HBV and rubella are highly recommended and should be tested before to conception, even though the latter virus is not specifically linked to thalassemia but is a recognized teratogen. Women who have had splenectomy should take prophylactic penicillin. While HCV-positive women should begin the proper treatment to eradicate HCV RNA, HIV-positive women should be counseled to start highly active antiretroviral therapy, give birth by cesarean section (CS), and refrain from breastfeeding.

Liver function

It is reasonable to anticipate liver function deterioration during pregnancy, which could manifest as modest symptoms. A little increase in aminotransferases may indicate potentially fatal conditions like acute fatty liver of pregnancy or HELLP (hemolysis, high liver enzyme levels, low platelet count) syndrome. Women with thalassemia may have reduced liver function as a result of iron overload, and they are more likely to develop cholelithiasis from hemolytic anemia and consequent cholecystitis. To identify liver cirrhosis,

fibrosis, and cholelithiasis, a preconception ultrasound evaluation of the liver and biliary tract should be carried out at the very least. Cholecystectomy should also be taken into consideration prior to becoming pregnant. A liver iron concentration of more than 15 mg/g dry weight is linked to a worse chance of survival in thalassemia.

Endocrine complications

Aside from HH, tissue hemochromatosis can also affect other glands. Insulin resistance, pancreatic iron overload, hereditary factors, and autoimmune are the main causes of diabetes mellitus, which is detected often. Serum fructosamine levels in those women should be maintained below 300 nmol/L for at least three months prior to conception, and they should be sent to an endocrinologist. The co-occurrence of diabetes and thalassemia is a sign that the serum fructosamine concentration should be checked every month. To prevent gestational problems (maternal and perinatal morbidity and death), thyroid function should be evaluated and treated prior to pregnancy and then reassessed at regular intervals during the pregnancy.

Medication review

Potentially teratogenic medications, such as oral hypoglycemic medicines, bisphosphonates, and ACE inhibitors, should be examined prior to actively considering pregnancy or ovulation. It is advised that women taking oral chelators (deferasirox [DFX] or deferiprone]) switch to desferrioxamine [DFO] before ovulation and spermatogenesis are induced. Ribavirin, hydroxyurea, and interferon should all be stopped at least six months before fertility treatment. To make sure they are euthyroid, hypothyroid patients undergoing thyroid replacement medication should be given higher dosages.

Antepartum management

Up to the 28th week of pregnancy, pregnant women must be evaluated monthly; beyond that, they must be evaluated every two weeks. Gestational complications can include multiple gestation pregnancies, placental ischemia disease, fetal discomfort, and preterm birth linked to poor maternal health. Gestational hypertension, gestational diabetes, placental abruption, urinary tract infections, and kidney and gallbladder stones are other often encountered obstetric problems. At 16 weeks, women should have a screening for gestational diabetes; if the results are normal, the screening should be repeated at 28 weeks. Additionally, screening for gestational diabetes should be done for pregnant women who are heterozygous thalassemic and belong to ethnic groups with high rates of diabetes mellitus. A splenectomy may be required during pregnancy or after birth due to splenomegaly's interference with the uterus's growth and its complications from hypersplenism.

Maternal transfusion

Pregnant women with thalassemia experience worsening anemia; nevertheless, some may go undetected without screening because anemia may be mild or nonexistent. As a result, their pregnancy will typically go smoothly and end normally. Preterm labor and fetal intrauterine growth restriction (IUGR) are two of the consequences of thalassemic pregnancy that are partially caused by thalassemia alone and gestational anemia, which is linked to an expanded fluid compartment of the body. In order to support proper fetal growth, the majority of facilities transfuse pregnant women with hemoglobin at the preconception objective (>10 g/dL).

Chelation during pregnancy

In order to prevent hypoxia during pregnancy, maternal hemoglobin levels should be kept within acceptable limits. However, intensive transfusion therapy can exacerbate hemosiderosis in patients who already have iron overload, increasing oxidative stress and leading to organ failure. In contrast, women who have been diagnosed with cardiac hemosiderosis or borderline left-ventricular function may experience heart complications. Thus, the function of chelation during pregnancy needs to be explained. Although DFO fetotoxicity has not yet been conclusively determined, chelation therapy will lessen iron excess and aid in free radical scavenging, hence lowering the inflammatory process. Placenta crossing is questionable because to DFO's high molecular size and charge, even though animal studies may reveal skeletal abnormalities and pharmacological teratogenic effects. In addition to a large case series of 32 TM women who chelated with DFO during the second and third trimesters with positive fetal outcomes, there are several case reports that detail its usage in the early stages of pregnancy. 20 Although subcutaneous injection may be used in the second and third trimesters for patients with a compelling rationale for treatment, experts advise against using DFO during the first trimester.

Fetal monitoring

Because these women are at a higher risk of miscarriage and multiple gestations, the first ultrasound scan should be done between weeks seven and nine of pregnancy. Serial fetal biometry scans, which focus on potential IUGR due to persistent maternal anemia and other nutritional element depletion, should be carried out monthly after the 24th gestational week in addition to first-trimester (11–14 weeks) and second-trimester (18–21 weeks) scans. As singleton and multiple pregnancies, IVF instances, and spontaneous conceptions occur, the percentage of kids with IUGR differs amongst research. Miscarriage mostly happens in fetuses with severe IUGR or those that are homozygous for thalassemia. 74 The reported frequency ranges from 9% to nearly 33%, which can be attributed to both naturally occurring and IVF-conceived pregnancies.

Medication modification

Women should be counseled to change their diet and lifestyle, abstain from alcohol and tobacco, and begin taking vitamin D, calcium, and folic acid supplements. The negative calcium-balance states of pregnancy

and lactation necessitate proper calcium and vitamin D intake, as well as the discontinuation of bisphosphonates. It is especially important to optimize vitamin D levels prior to pregnancy and thereafter keep them within the normal range for thalassemic women, who are frequently osteoporotic and vitamin D deficient. Pregnancy typically increases the demand for folate, and all thalassemic women are recommended to take folic acid supplements at a dose of 5 mg per day to prevent neural tube defects in the fetus, a marked rise in predelivery hemoglobin levels,130 and superimposed megaloblastic anemia in heterozygous cases.

Intrapartum management

Since an uncomplicated illness course should not be regarded as a suitable indication for CS, the time and route of delivery should be customized for thalassemia in general. However, the greater prevalence of cephalopelvic disproportion—primarily brought on by the mother's small stature and skeletal abnormalities mixed with normal fetal growth—is responsible for the majority of CS instances. When it comes to CS, epidural anesthetic is better than general anesthesia since significant maxillofacial deformities in TM patients, particularly those who are older, can make intubation more difficult. According to this perspective, it is critical to treat osteoporosis when necessary since spinal problems linked to TM are significant to regional blocking.

Active management of the third stage of delivery is advised if vaginal birth is chosen since it is thought to minimize blood loss. Continuous electronic fetal monitoring is advised since fetal hypoxia is common during childbirth. Unchelated transfusion-dependent women will have elevated serum levels of non-transferrin-bound iron, a toxic type of iron that can lead to cardiac dysrhythmias in addition to labor stress. For the course of labor, intravenous DFO (2 g over 24 hours) is advised.

Postpartum management

Women with thalassemia have a significant risk of venous thromboembolism during the postpartum period, thus low-molecular-weight heparin prophylaxis should be given in the hospital. This should be followed by a postdischarge regimen of either 7 days after vaginal birth or 6 weeks following CS. Due to established postpartum cardiac problems, women should be sent to a cardiologist after giving birth. Lastly, because of the possibility of transmission through breast milk, they should be encouraged to breastfeed, which is safe in all situations except for those who are HIV, hepatitis C RNA-positive, and/or HBV surface antigen-positive. While postpartum chelation using DFO appears to be safe because DFO is not absorbed orally, the necessity to resume chelation therapy with oral agents—both of which are contraindicated during breastfeeding—could account for the significantly lower rates of breastfeeding maintenance when compared to the general population. Supplements of calcium and vitamin D should be taken during breastfeeding, however bisphosphonates should be started again after breastfeeding stops.

Conclusion

For the thalassemic population, advances in chelation therapy and routine transfusions have ushered in a new era by extending life expectancy and making the attainment of reproductive capacity and starting a family a realistic objective for patients and a challenging task for qualified clinicians. Although pregnancy with TM and TI should be regarded as a high-risk pregnancy, if pregnant women adhere to strict screening and are sent to thalassemia specialists, gestation can be completed successfully for both mother and fetus. However, in order to assess and minimize potential hazards during pregnancy, a consistent management approach should be implemented for this group of pregnant women, beginning with a thorough preconception examination, as suggested by several experts.

A comprehensive examination for infectious illnesses, liver function, coagulation status, and hormonal abnormalities should be part of the evaluation. Women who are well-cared for and chelated during pregnancy typically have successful pregnancies and deliveries. Once pregnancy is confirmed, chelation must be discontinued and hemoglobin levels must be kept above 10 g/dL. Using precise MRI techniques, the two most crucial criteria to be evaluated are iron load and heart function. Given the advantages for the mother and the possible hazards to the fetus, DFO may be taken into consideration in cases of left ventricular dysfunction that develops during pregnancy, particularly after the crucial organogenesis stage. Even though CS lessens the extra stress of labor, it is often only used in situations that are comparable to those in the general population, and the delivery time and method should be customized for each patient.

Footnote:

This article is based on a review of current clinical literature and case series regarding pregnancy in β-thalassemia patients. It is intended for educational and reference purposes only. Clinical recommendations should be made in consultation with qualified healthcare providers. Key sources include recent publications in *Haematologica*, *Blood Reviews*, and *The Lancet Haematology*.

References

- Weatherall DJ. The inherited diseases of hemoglobin are an emerging global health burden. Blood. 2010;115:4331–4336. doi: 10.1182/blood-2010-01-251348.
- Craig JE, Rochette J, Fisher CA, et al. Dissecting the loci controlling fetal haemoglobin production on chromosomes 11p and 6q by the regressive approach. Nat Genet. 1996;12:58–64. doi: 10.1038/ng0196-58.
- Bauer DE, Orkin SH. Update on fetal hemoglobin gene regulation in hemoglobinopathies. Curr Opin Pediatr. 2011;23:1–8. doi: 10.1097/MOP.0b013e3283420fd0.
- Old JM. Screening and genetic diagnosis of haemoglobin disorders. Blood Rev. 2003;17:43–53. doi: 10.1016/s0268-960x(02)00061-9.
- Cohen AR, Galanello R, Pennell DJ, Cunningham MJ, Vichinsky E. Thalassemia. Hematology Am Soc Hematol Educ Program. 2004;2004:14–34. doi: 10.1182/asheducation-2004.1.14.
- Harteveld CL, Higgs DR. α-Thalassaemia. Orphanet J Rare Dis. 2010;5:13. doi: 10.1186/1750-1172-5-13.
- 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.
- Chui DH, Fucharoen S, Chan V. Hemoglobin H disease: not necessarily a benign disorder. Blood. 2003;101:791–800. doi: 10.1182/blood-2002-07-1975.

- Higgs DR, Weatherall DJ. The alpha thalassaemias. Cell Mol Life Sci. 2009;66:1154–1162. doi: 10.1007/s00018-008-8529-9.
- Cao A, Galanello R. Beta-thalassemia. Genet Med. 2010;12:61–76. doi: 10.1097/GIM.0b013e3181cd68ed.
- Danjou F, Anni F, Galanello R. Beta-thalassemia: from genotype to phenotype. Haematologica. 2011;96:1573–1575. doi: 10.3324/haematol.2011.055962.
- Camaschella C, Cappellini MD. Thalassemia intermedia. Haematologica. 1995;80:58–68.
- Rund D, Rachmilewitz E. Beta-thalassemia. N Engl J Med. 2005;353:1135–1146. doi: 10.1056/NEJMra050436.
- Borgna-Pignatti C, Rugolotto S, De Stefano P, et al. Survival and complications in patients with thalassemia major treated with transfusion and deferoxamine. Haematologica. 2004;89:1187–1193.
- Nassar AH, Usta IM, Rechdan JB, Koussa S, Inati A, Taher AT. Pregnancy in patients with β-thalassemia intermedia: outcome of mothers and newborns. Am J Hematol. 2006;81:499–502. doi: 10.1002/ajh.20654.
- Toumba M, Kanaris C, Simamonian K, Skordis N. Outcome and management of pregnancy in women with thalassaemia in Cyprus. East Mediterr Health J. 2008;14:628–635.
- Tuck SM. Fertility and pregnancy in thalassemia major. Ann N Y Acad Sci. 2005;1054:300–307. doi: 10.1196/annals.1345.062.
- Aessopos A, Karabatsos F, Farmakis D, et al. Pregnancy in patients with well-treated β-thalassemia: outcome for mothers and newborn infants. Am J Obstet Gynecol. 1999;180:360–365. doi: 10.1016/s0002-9378(99)70214-0.
- Daskalakis GJ, Papageorgiou IS, Antsaklis AJ, Michalas SK. Pregnancy and homozygous beta thalassaemia major. Br J Obstet Gynaecol. 1998;105:1028–1032. doi: 10.1111/j.1471-0528.1998.tb10270.x.
- Kumar RM, Rizk DE, Khuranna A. Beta-thalassemia major and successful pregnancy. J Reprod Med. 1997;74:127–131
- Tampakoudis P, Tsatalas C, Mamopoulos M, et al. Transfusion-dependent homozygous β-thalassaemia major: successful pregnancy in five cases. Eur J Obstet Gynecol Reprod Biol. 1997;74:127–131. doi: 10.1016/s0301-2115(97)00089-4.
- Origa R, Piga A, Quarta G, et al. Pregnancy and β-thalassemia: an Italian multicenter experience. Haematologica. 2010;95:376–381. doi: 10.3324/haematol.2009.012393.
- Avila WS, Rossi EG, Ramires JA, et al. Pregnancy in patients with heart disease: experience with 1,000 cases. Clin Cardiol. 2003;26:135–142. doi: 10.1002/clc.4960260308.
- Voskaridou E, Balassopoulou A, Boutou E, et al. Pregnancy in β-thalassemia intermedia: 20-year experience of a Greek thalassemia center. Eur J Haematol. 2014;93:492–499. doi: 10.1111/ejh.12387.
- 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;17:8–18. doi: 10.4103/2230-8210.107808.
- De Sanctis V. Growth and puberty in thalassaemia. Horm Res. 2002;58:72–79. doi: 10.1159/000064766.
- Roussou P, Tsagarakis NJ, Kountouras D, Livadas S, Diamanti-Kandarakis E. β-Thalassemia major and female fertility: the role of iron and iron-induced oxidative stress. Anemia. 2013;2013:617204. doi: 10.1155/2013/617204.
- Agarwal A, Allamaneni S. Role of free radicals in female reproductive diseases and assisted reproduction. Reprod Biomed Online. 2004;9:338–347. doi: 10.1016/s1472-6483(10)62151-7.
- Al-Gubory KH, Garrel C, Faure P, Sugino N. Roles of antioxidant enzymes in corpus luteum rescue from reactive oxygen species-induced oxidative stress. Reprod Biomed Online. 2012;25:551–560. doi: 10.1016/j.rbmo.2012.08.004.
- Mahachoklertwattana P, Yimsumruay T, Poomthavorn P, Chuansumrit A, Khlairit P. Acute effects of blood transfusion on growth hormone and insulin-like growth factor-1 levels in children with thalassemia. Horm Res Paediatr. 2011;75:240–245. doi: 10.1159/000321189.
- Soliman A, Yasin M, El-Awwa A, Osman M, De Sanctis V. 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;98:638–643. doi: 10.1016/j.fertnstert.2012.05.047.

- De Sanctis V, Elsedfy H, Soliman AT, et al. Acquired hypogonadotropic hypogonadism (AHH) in thalassaemia major patients: an underdiagnosed condition? Mediterr J Hematol Infect Dis. 2016;8:e2016001. doi: 10.4084/MJHID.2016.001.
- Skordis N, Gourni M, Kanaris C, et al. The impact of iron overload and genotype on gonadal function in women with thalassaemia major. Pediatr Endocrinol Rev. 2004;2:292–295.
- Chern JP, Lin KH, Tsai WY, et al. Hypogonadotropic hypogonadism and hematologic phenotype in patients with transfusion-dependent β-thalassemia. J Pediatr Hematol Oncol. 2003;25:880–884. doi: 10.1097/00043426-200311000-00011.
- Kiess W, Reich A, Meyer K, et al. A role for leptin in sexual maturation and puberty? Horm Res. 1999;51:55–63. doi: 10.1159/000053163.
- Perrone L, Perrotta S, Raimondo P, et al. Inappropriate leptin secretion in thalassaemia: a potential cofactor of pubertal timing derangement. J Pediatr Endocrinol Metab. 2003;16:877–881. doi: 10.1515/jpem.2003.16.6.877.
- De Sanctis V, D'Ascola G, Wonke B. The development of diabetes mellitus and chronic liver disease in long term chelated β thalassaemic patients. Postgrad Med J. 1986;62:831–836. doi: 10.1136/pgmj.62.731.831.
- Humpeler E, Skrabal F, Bartsch G. Influence of exposure to moderate altitude on the plasma concentration of cortisol, aldosterone, renin, testosterone, and gonadotropins. Eur J Appl Physiol Occup Physiol. 1980;45:167–176. doi: 10.1007/BF00421324
- Singer ST, Vichinsky EP, Gildengorin G, van Disseldorp J, Rosen M, Cedars MI. Reproductive capacity in iron overloaded women with thalassemia major. Blood. 2011;118:2878–2881. doi: 10.1182/blood-2011-06-360271.
- Skordis N, Petrikkos L, Toumba M, et al. Update on fertility in thalassaemia major. Pediatr Endocrinol Rev. 2004;2:296–302.
- Deech R. A fine conception: the experience of the Human Fertilisation and Embryology Authority (HFEA)": speech to the 13th Congress of the European Association of Gynaecologists and Obstetricians (EAGO), Jerusalem, 11 May 1998. Eur J Obstet Gynecol Reprod Biol. 1999;85:3–5. doi: 10.1016/s0301-2115(98)00274-7.
- Smith V, Osianlis T, Vollenhoven B. Prevention of ovarian hyperstimulation syndrome: a review. Obstet Gynecol Int. 2015;2015:514159. doi: 10.1155/2015/514159.
- De Sanctis V, Perera D, Katz M, Fortini M, Gamberini MR. Spermatozoal DNA damage in patients with B thalassaemia syndromes. Pediatr Endocrinol Rev. 2008;6:185–189.
- Perera D, Pizzey A, Campbell A, et al. Sperm DNA damage in potentially fertile homozygous β-thalassaemia patients with iron overload. Hum Reprod. 2002;17:1820–1825. doi: 10.1093/humrep/17.7.1820.
- Singer ST, Vichinsky EP. Deferoxamine treatment during pregnancy: is it harmful? Am J Hematol. 1999;60:24–26. doi: 10.1002/(sici)1096-8652(199901)60:1<24::aid-ajh5>3.0.co;2-c.