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Review Articles

Pregnancy in Thalassemia

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Abstract. Therapeutic advances, including the availability of oral iron chelators and new non-invasive methods for early detection and treatment of iron overload, have significantly improved the life expectancy and quality of thalassemia patients, with a consequent increase in their reproductive potential and desire to have children. Hundreds of pregnancies have been reported so far, highlighting that women carefully managed in the preconception phase usually carry out a successful gestation and labor, both in case of spontaneous conception and assisted reproductive techniques. A multidisciplinary team including a cardiologist, an endocrinologist, and a gynecologist, under the supervision of an expert in beta-thalassemia, should be involved.
During pregnancy, a close follow-up of maternal disorders and of the baby's status is recommended. Hemoglobin should be maintained over 10 g/dL to allow normal fetal growth. Chelators are not recommended; nevertheless, it may be reasonable to consider restarting chelation therapy with desferrioxamine towards the end of the second trimester when the potential benefits outweigh the potential fetal risk.
Women with non-transfusion-dependent thalassemia who have never previously been transfused or who have received only minimal transfusion therapy are at risk of severe alloimmune anemia if blood transfusions are required during pregnancy. Since pregnancy increases the risk of thrombosis three-fold to four-fold and thalassemia is also a hypercoagulable state, the recommendation is to keep women who are at higher risk -such as those who are not regularly transfused and those splenectomised- on prophylaxis during pregnancy and the postpartum period.

Keywords: Pregnancy ; Thalassemia major ; Thalassemia intermedia ; Hemoglobin H disease ; Counselling.

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Introduction. Thalassemias are a group of hereditary blood disorders characterized by the reduced or suppressed production of synthesis of the globin chains of hemoglobin. They are classified according to the impaired globin chains resulting in variable phenotypes ranging from severe anemia to clinically asymptomatic individuals.[1]

Deletion of three α-globin genes results in Hemoglobin H (Hb H) disease. In addition to deletional forms, there are at least 70 forms of non-deletional Hemoglobin H disease which may require occasional or frequent transfusions. A clear phenotype-genotype correlation is found in terms of hemoglobin and reticulocyte values, MCV, bilirubin in children, LDH and splenomegaly. Hb H disease needs regular monitoring for early detection and treatment of possible complications, such as worsening anemia that

may require red cell transfusion, cholelithiasis, and iron overload.[2]

Patients with beta-thalassemia intermedia present after the first two years of life with moderate anemia and do not require regular transfusions. The main clinical features in these patients are hypertrophy of erythroid marrow with medullary and extramedullary haematopoiesis and its complications (osteoporosis, masses of erythropoietic tissue that primarily affect the spleen, liver, lymph nodes, chest and spine, and bone deformities and typical facial changes), gallstones, painful leg ulcers and an increased predisposition to thrombosis.[1]

Individuals with beta thalassemia major usually present within the first two years of life with severe anemia, requiring regular red blood cell transfusions for survival. The prognosis of beta thalassemia major was very grim before treatment became available. With no treatment, the natural history was for death by age five from infections and cachexia. The first advance in treatment was the initiation of episodic blood transfusions when the patient was going through a particularly bad time. With the advent of this type of therapy, survival was prolonged into the second decade, but it soon became evident that the treatment that saved lives in children caused death from cardiac disease in adolescence or early adulthood. The prognosis for individuals with beta-thalassemia major dramatically improved with the advent of desferrioxamine. However, many transfusion-dependent patients continued to develop progressive accumulation of iron, and which can lead to tissue damage and eventually death, particularly from cardiac disease.[1]

In recent years, transfusional and therapeutic advances, including the availability of oral iron chelators and new non-invasive methods for early detection and treatment of iron overload, have significantly improved the life expectancy and quality of patients with thalassemia, with a consequent increase in their reproductive potential and desire to have children.[3,4,5] Since an initial report of a successful pregnancy in a woman with thalassemia major by Walker in 1969,[6] more than 400 successful pregnancies have been described. As an example, the Thalassemia Clinical Research Network (TCRN), a consortium of thalassemia Centers from North America and the UK, reported in 2004 that pregnancies were infrequent (<8%),[4] while in 2013 they occurred in 25.1% of women with thalassemia at the same Centers.[7]

Fertility in Thalassemia. Despite the progress of iron chelation therapy in patients with thalassemia major, hypogonadism, generally attributed to pituitary siderosis disrupting the pituitary-gonadal axis, remains a common condition, affecting 40% to 90% of patients with transfusion-dependent thalassemia.[4,8,9] Pituitary iron deposition occurs in the first decade of life but accelerates dramatically in adolescence. Both pituitary iron deposition and volume loss are independently associated with hypogonadism.[10]

Despite this, ovarian function is typically preserved in women with thalassemia, even those suffering from primary or secondary amenorrhea, as evidenced by pregnancies after hormonal stimulation.[11] Data on the frequency of failure in ovulation induction or timeline to a successful pregnancy are limited. Apart from hypogonadotropic hypogonadism, however, the other endocrine disorders particularly relevant to fertility and pregnancy are diabetes and hypothyroidism, problems that are amenable to relatively standard care, and do not pose a significant bar to pregnancy in the context of thalassemia.[12]

Anti-müllerian hormone (AMH), a sensitive marker for ovarian reserve independent of gonadotropin effect, has recently emerged as an important biomarker in the assessment of the reproductive capacity in thalassemia major, independently of the presence of hypogonadism. Singer et al. (2011)[13] suggested that ovarian reserve is preserved in the majority of thalassemia, major women < 30-35 years old, despite a low follicle count and reduced ovarian volume, while Chang et al. (2011)[14] demonstrated that the serum AMH levels in women with transfusion-dependent beta thalassemia are lower when compared with normal healthy women of a similar age. In this study, AMH correlated with non-transferrin-bound iron (NTBI), suggesting a role of labile iron in the pathogenesis of decreased reproductive capacity. However, both research groups observed that AMH levels were inversely correlated to serum ferritin levels, associating an impaired ovarian function with iron overload. Nevertheless, data from published studies have shown successful conceptions in women with ferritin levels in the range of 1000 and 9500 ng/ml.[8]

Most ovulation induction protocols use gonadotropins and clomiphene citrate to stimulate the development of the follicles, as well as hCG and LH to trigger ovulation.[15] The protocols should be tailored to the woman's response, which is evaluated by the number and size of the growing follicles. There are no data on the harmful effects of iron chelation therapy during hormonal stimulation therapy. Patients with endometrial or fallopian tube damage respond better to in vitro fertilization (IVF) programs. Luteal phase supplementation with progesterone is commonly given prior to the pregnancy test and, in the case of a positive outcome, continued until the 12th week.[16]

Induction of ovulation is always associated with the risk of ovarian hyperstimulation syndrome, a rare but life-threatening complication. It is characterized by increased vascular permeability and presents with renal and liver function abnormalities, ascites, hydrothorax, embolism, and coagulation disturbances.[17] The risks of

ovarian hyperstimulation syndrome are now low, as a result of a better understanding of the response to gonadotropins in the reproductive system of women with thalassemia and vigilant monitoring by endovaginal ultrasound scans. Nowadays, the main consequence of ovarian stimulation is a high number of twin or triplet pregnancies, which ranges from 1.6% to 18.9%,[8,16,18,19] and the potential risk associated with multiple births. However, since a lower prevalence of primary amenorrhea and hypogonadism has been observed in younger cohorts,[3,8,21,22] the number of women who need gonadotropin-induced ovulation to conceive is also likely to decrease.

In cases refractory to stimulation protocols, egg or embryo donation remain realistic options for many women and couples who wish to conceive, with pre-optimization of iron levels to maximize their chances of success. In fact, patients should be counseled as to the potential impact of iron deposition on reproductive capacity, even in cases of donation, with the potential negative impact on the endometrium, and thus implantation.[23]

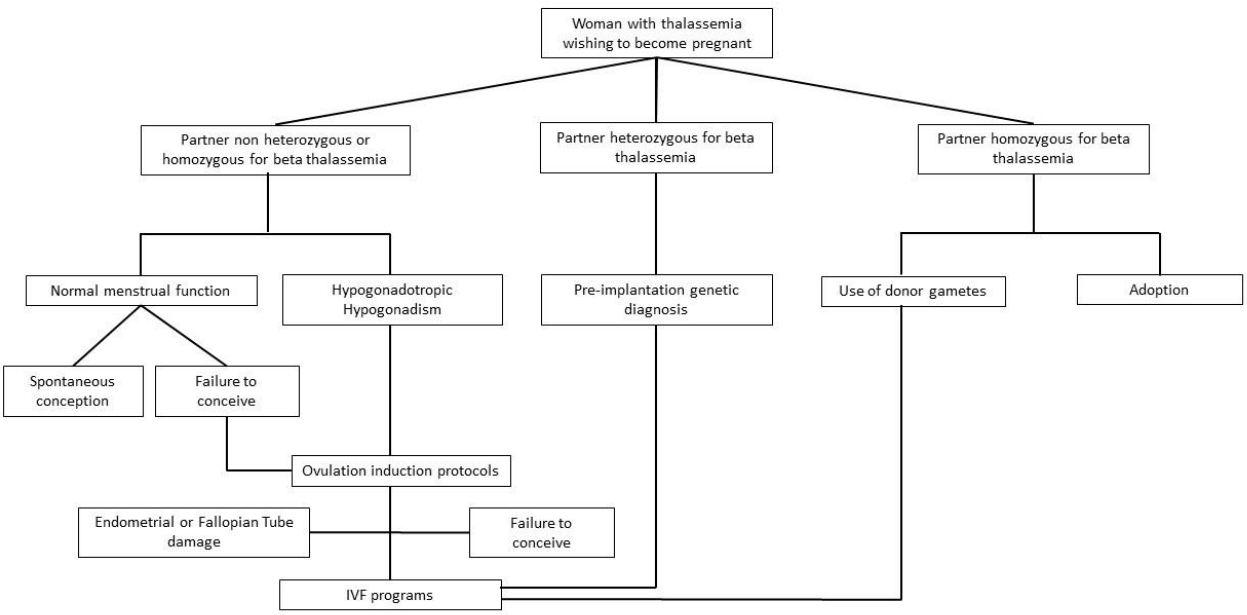
Adoption may also be a valuable alternative. Of course, the implications of these choices are complex and include ethical, emotional, cultural, financial and practical aspects (**Figure 1**).

Pre-pregnancy Counselling. A planned pregnancy is essential both in case of spontaneous conception and assisted reproductive techniques in order to minimize risks to mother and baby. A multidisciplinary team including a cardiologist, an endocrinologist, and a gynecologist, under the supervision of an expert in beta-thalassemia should be involved. Psychological support should be available if required.

The following aspects should be taken into consideration before encouraging women with thalassemia to conceive (**Table 1**):

- Partner: Screening of the partner for beta thalassemia status, with relevant genetic counseling, blood typing, and spermiogram are recommended.
- Fertility assessment: This should include analysis of gonadal function through a medical history and hormone assays, standard pelvic examination, pelvic ultrasonography and hysterosalpingography;
- Iron overload: Given the risk of a significant increase in iron overload during pregnancy, thalassemic women wishing to become pregnant should undergo complete evaluation of organ iron overload, including liver and heart magnetic resonance (MRI) T2* and/or SQUID.[8] In the case of severe hemosiderosis, pregnancy should be postponed, and an intensification of chelation therapy should be considered. Ideally, a pre-pregnancy cardiac T2* greater than or equal to 20 ms and a liver iron concentration of less than 7 mg/g dry weight should be achieved;[24]
- Heart function: Several factors can compromise heart function during pregnancy (increased blood volume, changes in blood pressure, heart rate and cardiac output, discontinuation of chelation treatment) and cardiac complications remain the primary cause of death in thalassemia.[1,25]

Figure 1. Schematic representation of the fertility options for a woman with thalassemia wishing to become pregnant.



Abbreviations: IVF, In vitro fertilization. Please note that choices concerning fertility are strictly personal and involve ethical, emotional, cultural, financial and practical aspects.

Table 1. Pre-pregnancy evaluation in women with thalassemia.

Partner	- Beta thalassemia status - Blood typing - Spermiogram
Fertility	- Menstrual history - Hormone assays (including AMH) - Standard pelvic examination - Pelvic Ultrasonography - Hysterosalpingography
Iron overload	- Serum ferritin - Heart MRI T2* - Liver MRI T2*
Heart function	- Cardiologic evaluation - Electrocardiogram (both at rest and with exercise) - 24-hour Holter monitor - Echocardiogram
Liver function	- Liver biochemical tests - Liver and gallbladder ultrasounds - Fibroscan
Endocrine function	- Thyroid function tests - Glucose metabolism tests - Vitamin D level - DEXA
Infections	- TORCH - HIV, HBV, HCV markers - Syphilis
Thrombophilia	- Personal and family history of thrombosis - Inherited thrombophilia panel - Acquired thrombophilia panel
Others	- Medication review - If not previously obtained, extended red cell phenotyping, and screen for red cell antibodies

Abbreviations: AMH, Anti-müllerian hormone; MRI, magnetic resonance; DEXA, Dual-Energy X-ray Absorptiometry; TORCH, Toxoplasmosis, Other (syphilis, varicella-zoster, parvovirus B19), Rubella, Cytomegalovirus (CMV), and Herpes infections; HIV, Human Immunodeficiency Virus; HBV, Hepatitis B virus; HCV, Hepatitis C virus.

- Consequently, all women with thalassemia should have a thorough evaluation of their cardiac function before conception, including an electrocardiogram (both at rest and under exertion), a 24-hour Holter monitor, a cardiac function evaluation by echocardiogram and an evaluation by a cardiologist. If left ventricular dysfunction or significant arrhythmias have been demonstrated, women should be strongly advised against planning a pregnancy at that time;[26]
- Liver function: Liver biochemical tests and ultrasound should be performed. The presence and the staging of liver fibrosis should be evaluated using Fibroscan and, in selected cases liver biopsy. HCV-infected women with cirrhosis should be counseled about the increased risk of adverse maternal and perinatal outcomes. In patients with evidence of sludge or gallstones, cholecystectomy may be taken into consideration before conception. In HCVRNA positive women, antiviral therapy with direct antiviral agents (DAAs) is recommended before pregnancy to reduce the risk of HCV transmission to future offspring.[27]
- Endocrine function: Given the high prevalence of osteopenia and osteoporosis in subjects with thalassemia, an assessment of bone mineral density with dual-energy x-ray absorptiometry (DEXA) is advisable. Vitamin D levels should be optimized before pregnancy and after that maintained within the normal range.[28] According to recent studies in the general population, optimal vitamin D levels may impact not only on bone health but also on the risk of gestational diabetes.[28] The administration of bisphosphonates in pregnancy should be avoided given their potentially hazardous effects on both mother and fetus. Their use should be discontinued at least six months prior to pregnancy.[29]
- Since the majority of evidence appears to support an association between overt thyroid dysfunction and an increased risk of infertility, thyroid function should be evaluated - and a potential thyroid dysfunction treated - in the pre-pregnancy phase.[30]
In patients with diabetes, blood glucose control should be optimized to prevent congenital malformations. Any improvement in fructosamine should be encouraged taking into account the risk of hypoglycemia. Women with poor glycemic control should be strongly advised to avoid pregnancy because of the associated risks. Insulin is the preferred agent for management of both type 1 and type 2 diabetes in pregnancy because it does not cross the placenta, and because oral agents are

generally insufficient to overcome the insulin resistance in type 2 diabetes and are ineffective in type 1 diabetes.[31]

Folate demand in pregnancy is normally increased, and all thalassemic women should receive folic acid supplementation to prevent fetal neural tube defects.

- Infections: Prior to pregnancy, all women should have antibodies to HIV, hepatitis B, and C and rubella checked. If the woman is not immune and is vaccinated for rubella, she should avoid becoming pregnant until four weeks after receiving the MMR vaccine and, ideally, not until her immunity is confirmed by a blood test. The HIV positive women should be advised of the usual recommendations for care, which include appropriate antiviral agents, and the HCVRNA women should be treated.[27]

Prenatal Diagnosis. Couples at risk of having children with beta-thalassemia should be informed of the risk (25%) of having a thalassemia major fetus. Diagnosis can be made either earlier during the first trimester (11th week) by chorionic villus sampling or after the 16th week by amniocentesis. The risk of miscarriage does not differ between these invasive procedures and is estimated to be less than 1%.[32,33] Preimplantation genetic diagnosis (PGD) can only be proposed in certain countries to avoid the selective abortion of affected fetuses following prenatal diagnosis.[11,32,34] The term PGD describes those procedures which involve the removal of one or more nuclei from ovocytes (polar bodies) or embryos (blastomeres of trophectoderm cells) to test for a mutation in the target gene or aneuploidy before transfer. PGD requires that couples at risk undergo in vitro fertilization even if not infertile and for this reason a multidisciplinary approach including appropriate genetic counseling and the referral to both a fertility clinic and to a highly specialized molecular genetics laboratory is mandatory.[32,34]

Pregnancy Management in Thalassemia Major.

Transfusions, Iron Overload and Chelation.

Blood consumption increase in women with thalassemia major has been reported in most studies due to the physiological changes of pregnancy (e.g., increased blood volume and hemodilution).[8,19] In an Italian multicenter experience, blood consumption rose from 132±31 to 157±49 mL of red cells per kg per year (P<0.001).[8] No differences between the amounts of blood required before pregnancy compared with those required after delivery were noted.[19]

Maternal anemia influences birthweight and preterm delivery in the general population[35] and pre-transfusional hemoglobin ≥ 10 g/dL should be maintained according to international guidelines.[36] However, while in Italy pre-transfusional hemoglobin levels were maintained during pregnancy at 9.9±0.4 g/dL to allow normal fetal growth (pre-pregnancy pre-transfusional hemoglobin 9.6±0.5 g/dL; P=0.001), there was no difference in pre-transfusional levels before, during or after pregnancy according to Toumba et al., 2008.[19]

Generally, chelators are not recommended during pregnancy. Reproductive studies in non-iron-loaded rats and rabbits have indicated that deferiprone is teratogenic and embryotoxic (decreased offspring viability and renal anomalies in male offspring) at doses leading to systemic exposures considerably lower than those observed in clinical settings.[37,38] No fetal effects were noted in a different animal model at doses equivalent to the human dose. There are no controlled data in human pregnancy.

Successful pregnancies following unintentional treatment with deferiprone or deferasirox have been reported.[8,39,40,41] Nonetheless, the use of oral iron chelators is contraindicated in pregnant women, because of the lack of controlled data.

The potential teratogenicity of desferrioxamine in humans is also based on animal studies. According to experimental models, placental transfer of deferasirox is minimal in rats.[42] Experiments in pregnant mice had shown effects on bone formation only when large doses, up to five times the maximum daily human dose, were administered.[43]

Manufacturer product information reports similar results in rabbits. However, despite this data, a review of the literature on pregnant thalassemia women shows that many dozens of them have received desferrioxamine over several weeks or months of gestation with no evidence of a toxic or teratogenic effect.[13,44,45,46] Furthermore, there is some doubt that desferrioxamine can cross the placenta due to its large molecular size and charge. Ultimately, women of childbearing age on oral chelators should be counseled to avoid getting pregnant or advised to switch to desferrioxamine if they are planning to get pregnant. However, discontinuation of iron chelation with desferrioxamine should be recommended once a pregnancy has been achieved.[8,45] Nevertheless, it may be reasonable to consider restarting chelation therapy with desferrioxamine towards the end of the second trimester in patients with severe heart and liver iron overload, when the potential benefits outweigh the potential risks to the fetus.[16,27,47] A large case series of 32 major thalassemia women chelated with desferrioxamine during the second and third trimesters with favorable fetal outcomes was described by Kumar et al. (1997).[48]

As expected, because of the increase in blood consumption and the interruption of chelation, serum ferritin increases in most pregnancies.[7,8,16,19,41,49] More specifically, Origa et al (2010)[8] reported a statistically significant increase in serum ferritin levels from

1463±1306 ng/mL to 2692±1629 ng/mL; *P*<0.001. However, a wide variability of changes in serum ferritin was noted (from 0 to 300% increase, median value 63%). In Oman, serum ferritin levels in 10 thalassemia women (15 pregnancies) went from 585.6 ng/ml (range 236-1258) to 1357.5 ng/ml (range 336-3054) [49] while in 30 thalassemia major patients (37 pregnancies) from Italy and Lebanon it increased progressively from a median of 1071 ng/ml before pregnancy (range 409-5724) to 2231 ng/ml (range 836-6918) after pregnancy (p<0.0001).[16]

Maternal Complications.

Changes in cardiac function. Changes in cardiac function and dimension may occur transiently during pregnancy remaining asymptomatic.[8,19] Transient increases in left ventricular end diastolic dimension (33±3.1/m2 before pregnancy and 34.2±3.1/m2 in the second trimester of pregnancy; P<0.01) and heart rate (75±12.6 beats/min before pregnancy and 86.7±17.4 beats/min in the second trimester of pregnancy; P<0.01) were recorded in a subgroup of patients by Origa et al. (2010).[8] Both cardiac indices returned to their pre-pregnancy levels following delivery. Overall, left ventricular ejection fraction did not change significantly during the pregnancies (from 63.4±8.1% to 61.1±5.4%; P>0.05). Myocardial complications in pregnant women with thalassemia major have been reported by some authors. One patient developed cardiac failure in Greece[50] and Tuck[12] described two maternal deaths due to cardiac failure (one ten days after delivery, one nine months after delivery) in patients with known cardiac dysfunction and symptomatic tachyarrhythmia. In addition, cardiac issues developed in 4 out of the 129 pregnant women with thalassemia described by Thompson et al. (2013).[7] A high percentage of cardiac problems during pregnancy was reported in a cohort of thalassemic women in Iran.[18] It should be noted, however, that their pre-pregnancy characteristics in terms of iron overload and clinical complications were not reported by the Authors.

In the studies mentioned above, myocardial T2* by magnetic resonance had not been measured in any of the women who experienced cardiac deterioration during pregnancy. Among the 17 women with thalassemia who performed an MRI scan before and after the pregnancy, two (17%) with a normal global heart T2* value (>20 ms) before pregnancy showed a pathological post-partum value.[51] Similarly, Cassinerio et al. (2017)[16] reported new myocardial iron on post-pregnancy imaging in 3 out of 16 patients (19%). MRI before pregnancy showed a normal cardiac T2* (mean 35.34 ± 8.90 ms) and a mean liver iron concentration (LIC) of 3.37 ± 2.11 mg/g dry weight. Two of the three women who showed cardiac iron overload after pregnancy had a moderate liver overload before pregnancy, suggesting that hepatic iron overload can precipitate myocardial iron overload.

In addition, in both studies, there was a significant increase in MRI liver iron concentration values after pregnancy.

In conclusion, those women who have existing cardiac impairment should be strongly advised against pregnancy, and cardiac T2* should always be measured before and straight after pregnancy, and the pregnancy itself postponed in the case of organ iron overload. A regular assessment of the cardiac condition and function during pregnancy and in the postpartum period as well as a prompt resumption of chelation after delivery is mandatory.

A new appearance of diabetes mellitus or worsening of existing diabetes has been reported in several studies.[7,8] Screening for gestational diabetes at 16 weeks, and, if normal, at 28 weeks, should occur.

Risk of pregnancy-specific complications. Placental ischemic disease, placental abruption, gestational hypertension, kidney stones, cholelithiasis, and urinary tract infection, have been described during pregnancy in women with thalassemia major.[8,16,50]

However, the risk of pregnancy-specific complications in thalassemic women has not been demonstrated to be higher than in the background population.

Thrombotic Risk. Pregnancy increases the risk of thrombosis from three-fold to four-fold. Venous thromboembolism is one of the leading causes of maternal morbidity in pregnancy, and its incidence is estimated to be 0.76 to 1.72 per 1,000 gestations, while maternal death is caused prominently by pulmonary embolism.[52] Hypercoagulability, which is the basis of this phenomenon, has likely evolved to protect women against the bleedings associated with miscarriage and childbirth.[53] Thalassemia, however, is also a hypercoagulable state with an enhanced risk of thromboembolic complications especially in splenectomised patients. One of the main factors behind this risk is the procoagulant effect of anionic phospholipids on the surface of altered red cells and erythroblasts, whose number is dramatically increased by splenectomy and in non-transfused or minimally transfused patients.[54,55]

The presence of further factors, which can increase the risk of thromboembolism such as inherited and acquired thrombophilia, a history of thrombosis and pregnancy outcomes should also be assessed. [53]

Although no specific regimen or guidelines have been established, the recommendation is to keep women who are at higher risk on prophylaxis during pregnancy and the postpartum period.[56] Both acetylsalicylic acid and low molecular weight heparin have been used.[8,49,50,57,58] A recent meta-analysis on

acetylsalicylic acid in the general population has confirmed that low-dose aspirin is effective in preventing preeclampsia, preterm birth, and intrauterine growth restriction in high-risk pregnancies without posing a major safety risk to mothers or fetuses[59] and this should be taken into account in the case of non-transfusion-dependent women, a history of splenectomy or of recurrent abortions.[60]

One study recommended managing women who are at high risk with low-molecular-weight heparin for seven days after a vaginal delivery and for six weeks after a Cesarean section.[27] Interestingly, no reports of thrombotic episodes during pregnancy in thalassemia major patients are reported in the literature.[8,12,61]

Delivery, Outcomes of Pregnancies and Breast-Feeding. The percentage of abortions registered in women with thalassemia major is variable. Ansari et al. (2006)[18] reported 12 miscarriages out of 62 pregnancies, while all 37 pregnancies resulted in live births according to Cassinerio et al. (2017).[16]

In the Italian experience, 4 out of 58 pregnancies (6.9%) resulted in spontaneous abortions and one woman (1.7%) underwent an induced abortion for personal reasons. The other pregnancies (91.4%) resulted in successful deliveries. Thus, threatened miscarriage and actual miscarriage were no more common in women with thalassemia major than in the general population.[8] Although twin or triplet pregnancies are still usual, it is likely that their number will tend to decrease over the next few years because of the increasing proportion of young women with the intact hypothalamic-pituitary-gonadal axis. Risk of fetal growth restriction was increased two-fold in some reports, however, when considering only the singleton pregnancies, the proportion of babies with intrauterine growth retardation did not differ from that reported in the general population according to Origa et al. (2010).[8]

The high prevalence of pre-term births (up to 32.7%) seems to be mostly related to multiple pregnancies and precautionary reasons.[8]

Whether thalassemia *per se* should be considered an indication for Cesarean delivery remains controversial. The most commonly reported reason for Cesarean labor is cephalopelvic disproportion, due to short stature and/or skeletal deformity. In some Centers, the policy is to support the individual patient if she chooses to attempt a vaginal delivery in the absence of risk factors.[8] A case series reported Cesarean section rates as low as 19%.[18] In the case of cesarean section, epidural anesthesia is preferable if feasible due to the risk of difficult intubation in patients with maxillofacial deformities, as well as to the risks associated with general anesthesia.[35] The placement of a spinal epidural must also be carefully considered, as scoliosis and osteoporosis are common.

Prolonged labor with acidosis may increase the risk of cardiac decompensation, and low dose intravenous desferrioxamine may be considered in these cases.[62]

Significant lower rates of breastfeeding than in the general population have been noted. Before the advent of direct antiviral agents, the most relevant reason seemed to be the unfounded belief that breastfeeding may enhance the risk of transmitting viral hepatitis.[63] More recently, the most relevant reason appears to be the need to restart chelation therapy early after delivery. Although no data are available on the presence of deferasirox or its metabolites in human milk, in animals it is known that this drug is rapidly and extensively secreted into maternal milk at higher concentrations than in maternal plasma. It is not known whether deferiprone is excreted in human milk and no prenatal and postnatal reproductive studies have been conducted in animals.

Study on desferrioxamine's transmission through breast milk is limited. However, desferrioxamine is not absorbed by the oral route and its concentrations in human milk seem to be very low. Therefore, desferrioxamine is the only chelator that seems to be safe during breastfeeding.

Pregnancy in Women with Non-Transfusion-Dependent Thalassemia.

Beta thalassemia intermedia. Pregnancy has been reported safe in most women with thalassemia intermedia under multidisciplinary management. Most successful pregnancies are conceived without assisted reproductive technologies,[8,50] and a higher proportion of women with thalassemia intermedia had pregnancies compared to women with thalassemia major according to Thompson et al. (2013).[7]

Out of 60 pregnancies, 11 abortions (18.3%) including six spontaneous (10%) and 5 (8.3%) for medical reasons were reported by Voskaridou et al. (2014).[50] No miscarriages were reported in 11 Sardinian women with thalassemia intermedia (17 pregnancies)[8] and the percentage of abortions was low (7.05%) also in 48 thalassemia intermedia patients (85 pregnancies) followed at two tertiary care centers in Lebanon and Italy.[64]

In accordance with most studies on pregnancy in thalassemia intermedia women, 60–80% of the patients need transfusions during pregnancy, although 30% of them have never had a transfusion before.[8,50,56] However, women with thalassemia intermedia who have never previously received a blood transfusion or have received a minimal quantity of blood are at risk of severe alloimmune anemia. In Origa et al. (2010)[8] one woman, who had already had a spontaneous miscarriage, developed a very difficult to manage alloimmune anemia after the first transfusion and decided to have an induced abortion. Voskaridou et al. (2014)[50] described a thalassemia intermedia patient

with worsening hemolytic anemia and progressive splenomegaly from the sixth month of pregnancy, and another who developed spastic paraparesis due to ineffective erythropoiesis masses. Moreover, out of the 48 women who had pregnancies in Lebanon and Italy, four developed alloimmune hemolytic anemia that necessitated postpartum splenectomy in two of them.[64]

In order to minimize this risk, extended genotype and antibody screening should be performed before giving any transfusions during pregnancy and, if transfusion becomes necessary, fully phenotyped matched blood should be given.[8,49,50,58] No study has evaluated obstetric outcomes based on hemoglobin levels in thalassemia intermedia, and no particular transfusion regimen can be recommended, as it should depend on the clinical profile of individual cases, with special reference to the general and cardiac maternal status and fetal growth as monitored by ultrasonography.[50,65] Nevertheless, several Authors have observed a high percentage of intrauterine growth retardation despite the administration of regular transfusion therapy, which maintained hemoglobin higher than 10 g/dL.[56,58]

Placental thrombosis and deep vein thrombosis were observed by Roumi et al.[64] in one and five pregnancies out of 85, respectively, despite the prophylactic use of aspirin in all patients and of heparin products in those who had a history of recurrent miscarriages or recurrent deep vein thrombotic events. Nevertheless, pregnant thalassemia intermedia women do not seem to have an increased risk of thromboembolic complications compared to non-pregnant women suffering from the same disease.

Iron overload and the consequent increase in free iron in the bloodstream, which results in organ damage, may be related to pregnancy complications in these women and optimization of antenatal iron levels may be essential to obtain an uncomplicated pregnancy in a thalassemia intermedia patient.[64]

Vaginal delivery has been reported in approximately half of the cases,[50,58,64] while a Cesarean section was performed mainly due to suboptimal fetal growth associated with low hemoglobin levels, in contrast with reports in thalassemia major where the Cesarean section accounted for more than 80% of deliveries. Even Aessopos et al. (2009),[66] who performed Cesarean delivery in all patients, encouraged physicians to individualize the mode of delivery in these patients as vaginal delivery is possible in most of them.

Hemoglobin H disease. Hydrop foetalis can be the outcome of pregnancy of mothers with Hb H disease,[67-68] and in fact, according to a report on hydrop foetalis in Thailand by Taweevisit and Thorner (2008),[69] 3.8% were related to Hb H disease. Ong et al. (1977)[70] reported that Hb H disease probably had no adverse effect on pregnancy, although Tantiweerawong et al. (2005)[71] found that Hb H disease may adversely affect maternal and fetal health, causing in particular low birth weight.

Comparing 120 Thai women with Hb H disease to 240 in a control group, Tongsong et al. (2009)[67] reported that Hb H disease places fetuses at significant risk for growth restriction, preterm birth, and low birth weight, resulting in increased perinatal mortality. The women were transfused to keep their hemoglobin levels higher than 7.0 g/dL. In this study, common obstetric complications, such as pre-eclampsia, antepartum hemorrhage, and postpartum hemorrhage, were not significantly associated with Hb H disease. Vaeusorn et al. (1988)[72] reported pre-eclampsia in 18% and congestive heart failure in 9% of 34 pregnancies among 29 Thai women, while in Italy only 5.5% had pre-eclampsia and none had heart failure.[2] Aiken et al. (2018)[73] have recently reported a case of hyperhemolysis in a pregnant patient with Hb H disease who was treated with intravenous methylprednisolone for three days, and 0.4 g kg−1 intravenous immunoglobulins for five days. After six days of post-treatment, the patient's hemoglobin gradually recovered to her pre-transfusion level of 6.8 g/dL. The pregnancy progressed uneventfully, and the patient maintained stable hemoglobin until she delivered a healthy child. In addition, a case of Hb H pregnant woman whose pregnancy was complicated with portal vein thrombosis, splenic vein thrombosis, and partial HELLP was recently reported.[74] She was treated with anticoagulation therapy, and the outcome was successful.

However, most mothers with Hb H disease can complete pregnancy without complications and give birth to normal healthy infants.[75,76] The percentage of miscarriages reported in the Sardinian experience was 11%, similar to that of the general Italian population even when threatened abortions, preterm births, and Caesarean deliveries were taken into account. While in the Italian general population the prevalence of neonates born at term with a birth weight <2.5 kg is only 2%, in the case of mothers with Hb H disease it was 5.5%, showing that Hb H disease is usually more benign in the Sardinian population than in that of south-east Asia and the Middle East and that it is possible for maternal anemia to compromise fetal growth, but only rarely.[2]

Conclusions. Healthy pregnancy outcomes have become the expectation in women with thalassemia and provided that a multidisciplinary team is available, gestation can be completely safe for both mother and child.

However, pregnancy in thalassemia should be considered high risk and should always be preceded by a complete preconception assessment. In patients with

severe myocardial or liver iron overload, conception should be delayed until after a period of intensive chelation. During pregnancy, a close follow-up of maternal disorders, as well as that of fetus status, is recommended. Pregnancy also seems to be safe in most patients with non-transfusion-dependent thalassemia, but wider and more detailed studies are needed.

Finally, topics that require further study include the possible safe use of chelation therapy during pregnancy in particular as regards oral chelators and indications regarding anticoagulation treatment and its duration both in thalassemia major and intermedia.

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