Fertility and Pregnancy in Women with Transfusion-Dependent Thalassemia

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KEYWORDS

• Thalassemia major • Fertility • Pregnancy • NIPT • Iron chelation

KEY POINTS

- Hypogonadism and ovulation abnormalities are still common, ranging from 30% to 80% in adult women with transfusion-dependent thalassemia.
- Discussion of fertility preservation and the importance of optimizing chelation therapy should occur early, with the prepubescent girl and her family.
- Prenatal multidisciplinary evaluation should include assessment of fertility, iron burden, liver and cardiac function, glucose tolerance, thrombotic risk, infection screening, and extended red blood cell phenotyping.
- Pregnancy in women with transfusion-dependent thalassemia should be considered high risk, and close monitoring is needed to maintain hemoglobin over 10 g/dL, assess for gestational diabetes, and reevaluate the need for chelation therapy should cardiac symptoms or rapid increase in ferritin develop.
- The development of earlier and safer prenatal screening is under way and has the potential to open new therapeutic windows during the perinatal period.

In the not so distant past, pregnancy for women with transfusion-dependent thalassemia (TDT) was considered very high risk and often not recommended. As management of these patients has evolved, pregnancy in recent decades has proved not only possible but also increasingly safe, with marked improvements in maternal and fetal survival. What has become evident, however, is the high rate of fertility problems, mostly attributed to hypogonadism, which affects 40% to 90% of patients with TDT.[1–4] As the pathophysiology of the reproductive issues in these women is beginning to be understood, the general perception and even official recommendations seemed to have lagged behind the clinical evidence. Although many case reports depict successful pregnancies in the past 2 decades, the most recent American College of

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Obstetricians and Gynecologists recommendations from 2007 remain restrictive in terms of those for whom they recommend pregnancy.[5] Moreover, there is a disparity between the methods of expanding reproductive options available for women with infertility and the knowledge and resources accessible to TDT women striving to achieve this goal. Women with TDT have a wide array of complications beyond the reproductive axis that can affect infertility treatment outcomes and pregnancy course. These need to be addressed by a multidisciplinary approach when patients are consulted for family planning. This article reviews these topics and addresses clinical recommendations for optimizing pregnancy outcomes for women with TDT.

IRON TOXICITY AND THE FEMALE REPRODUCTIVE SYSTEM

Mechanisms

Physiologic decline in female fertility and follicle aging results from oxidative stress. Mechanisms include an increase in reactive oxygen species production, reduced enzymatic antioxidant defense mechanisms, mitochondrial flaws, a compromised microenvironment, and a decline in granulosa cell production of estradiol.[6] Iron-induced disruption of reproductive tissue in women with TDT is believed to occur via mechanisms similar to those evidenced by increased levels of redox activity in the follicular fluid and deposition of hemosiderin in endometrial glandular epithelium of iron overloaded TM women.[7,8] Extensive iron deposition may impair oocyte function and has been implicated as a cause of ovarian failure and failure of in vitro fertilization (IVF) attempts.[8,9] Furthermore, the ovarian volume in TDT women (mean age of 30.3 years) was significantly reduced to the range of that seen in postmenopausal women.[10] This effect was believed secondary to lack of gonadotropin stimulation and possible iron deposition within ovarian tissue. The pathophysiology of a compromised reproductive system in women with TDT and iron overload has been extensively reviewed by Roussou and colleagues.[8]

Despite this, ovarian function is typically preserved in women with TDT, even those suffering from primary or secondary amenorrhea, as evidenced by pregnancies after hormonal stimulation. Data on frequency of failure of ovulation induction or timeline to a successful pregnancy, however, are limited. Given the frequent successful results of ovulation induction, infertility is generally attributed to pituitary siderosis disrupting the pituitary-gonadal axis.[10,11]

Iron-induced damage to the anterior pituitary results in defective gonadotropins secretion, a condition also known to occur in patients with iron overload due to genetic hemochromatosis.[12] The anterior pituitary has increased transferrin receptor expression, perhaps making it particularly vulnerable to siderosis, and significant loading has been suggested secondary to increased gland activity during puberty.[13] Standard iron burden measures and intensity of chelation have been used for association with gonadal dysfunction; however, they cannot reliably assess pituitary hormone secretion capacity and reproductive potential.[14,15] MRI technology for pituitary iron quantitation brought about significant progress in determining the intensity of pituitary siderosis, the relation to total body iron, and detection of early-stage endocrinopathies.[16] Pituitary iron deposition was observed in TDT patients younger than 10 years of age whereas clinically significant effects and pituitary volume loss were observed during the second decade of life. Both pituitary iron overload and gland shrinkage were independently predictive of hypogonadism.[17]

Evaluation

Although luteinizing hormone/follicle-stimulating hormone and estradiol along with pubertal development can define hypogonadism in thalassemia,[3] they have