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Fertility potential in thalassemia major women: current findings and future diagnostic tools

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Abstract

Issues of preserving fertility, preventing early menopause, and predicting reproductive ability have become crucial for many adult thalassemia major females.

LH/FSH and estardiol, commonly used for assessment of fertility potential in thalassemia, have a poor predictive value. Current reproductive practice utilizes markers of ovarian reserve testing (ORT), which were not yet studied in thalassemia women. We explored the relationship between liver iron concentration (LIC) and fertility status in 26 females (mean 30 years old). Seventeen (65%) of them experienced primary or secondary amenorrhea. Levels of LH/FSH and estradiol were low or undetectable in 48% and 35% of patients, respectively and did not correlate with age, presence of amenorrhea and LIC. This further addresses the need for utilization of current available methods for assessment of fertility capacity in thalassemia, which will also allow future correlation with pituitary iron measures by MRI as well as early intervention for fertility preservation.

Keywords

Thalassemia major; infertility in thalassemia; ovarian reserve testing (ORT)

Introduction

Hypogonadotrophic hypogogonadism and impairment of fertility due to deleterious effects of iron are well documented among women with thalassemia major (TM). Progress in management of iron overload has resulted in a lower prevalence of this endocrinopathy; however, a high frequency of hypogonadotrophic hypogogonadism, diagnosed in up to 50% of adult TM patients, is still reported.[1, 2] As long-term survival for this patient population has improved, attainment of reproductive capacity and formation of a family has become a major goal for many adult patients. In females with TM issues of preserving fertility, preventing premature menopause and obtaining data on fertility potential, are imperative.

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While significant advances in the predictive capacity for fertility and in assisted reproductive technology were made over the past decade,[3] little if any has been implemented for the care of thalassemia women.

In addition, as progress is made in the use of MRI technology for determining pituitary iron overload,[4] corresponding accurate functional studies are needed for early detection of patients who are developing hypogonadism and for a consistent correlation with these new imaging tools. Methods of Ovarian Reserve Testing (ORT), which have become routine diagnostic procedures for women with infertility problems, can provide data on the ovarian function and pituitary-gonadal axis function.[3, 5] ORT can be utilized for prediction of fertility potential and possibly for correlation with the extent of pituitary iron on MRI. These studies have not been applied yet in the thalassemia patient population.

Fertility and iron toxicity

It has been well established that the major effect of iron toxicity on the reproductive system is a direct damage to the hypothalamic/pituitary hormonal secretion; however, there is some controversy as to the ability of adequate long-term iron chelation therapy to preserve it.[1, 6, 7] In addition, there is no sufficient data on the direct effect of iron on the gonads and the role of compromised primary ovarian function in causing infertility problems in women.

Studies on female infertility suggest that oxidative stress has a major role in women's decline in reproduction potential.[8, 9] The natural mechanism of follicle aging is also thought to result from oxidative stress due to increase in reactive oxygen species (ROS) production, mitochondrial flaws, a compromised microenvironment and lower enzymatic antioxidant defense mechanisms.[10, 11] Taken together, there is a recent abundance of data linking oxidative damage and decline in fertility.

Iron induced oxidative damage has been studied in thalassemia and is thought to cause major tissue dysfunction.[12] However the impact of oxidative stress on the reproductive system has been only infrequently investigated. In males with TM, studies have shown sperm DNA damage which is thought to be a consequence of iron-induced oxidative injury.[13–15] In thalassemia females, one study has shown increased level of redox activity in the follicular fluid from a patient with TM suggesting that redox-active iron ions mediate free radical production, induce tissue injury and possibly contribute to impairment of reproduction in these patients.[16] It is reasonable to assume that in thalassemia females' chronic iron-induced oxidative damage can result in earlier or accelerated follicular aging, a mechanism thought to be the primary cause for reduced fertility and menopause in women.

Pregnancies in Thalassemia

Over 400 pregnancies were reported; Skordis summarized a total of 290 pregnancies published in TM women up to 2004.[17] Others have since reported additional successful pregnancies.[18–20] More than half of the reported pregnancies occurred in females with primary or secondary amenorrhea, required ovulation induction and most report term delivery of normal infants. Despite these remarkable successes, there is lack of data on the unsuccessful attempts to conceive. There is also insufficient data on pregnancy-related

complications, specifically the incidence of premature labor, cardiac complications and the change in cardiac and liver iron loading over the course of pregnancy. A recent publication reports a 3 fold higher incidence of premature labor and growth retardation than the normal population, and a 73% incidence of cesarean section.[21] There is no data on the baseline fertility profile and ovarian reserve in thalassemia women who succeeded or failed to become pregnant.

Ovarian aging and ovarian reserve testing (ORT)

Ovarian reserve is the fertility potential as it relates to the total number and quality of the primordial follicles remaining in the ovaries. Measurement of ovarian reserve can increase understanding of women's reproductive potential and predict chances for pregnancy with or without treatment. Since menstruation is a poor surrogate for fertility, and age alone has limited value in predicting fertility, other markers for ovarian reserve have been extensively evaluated: 1. Biochemical tests for basal (early follicular) hormone levels (FSH, LH, Estradiol, Inhibin A and B and anti Mullerian hormone) 2. Ovarian stimulation tests. 3. Biophysical, ultrasound techniques for assessing the number of remaining follicles in the ovary. Several ultrasound methods have been developed; the more commonly utilized include ovarian volume and antral follicle count (AFC). Both have been shown to predict reproductive status.

Inhibin B is mainly secreted by pre-antral follicles and therefore is a direct measure of ovarian reserve. Anti Mullerian hormone (AMH) is produced by the granulose cells of the ovary and has several advantages: It is the earliest marker of change with age and it has very little intercycle and intracycle variability. It is therefore a convenient measure of ovarian reserve even when randomly obtained during the cycle.[3, 22] Sonographic measurement of AFC and ovarian volume have been shown to correlate with ovarian reserve, though some cycle differences may occur.[23] Overall a combination of basal FSH, AMH and AFC was shown useful in assessment of chances for pregnancy in women undergoing in vitro fertilization (IVF) or undergoing evaluation for assisted reproductive techniques (ART). AMH levels were found to correlate well with AFC[24] and seem to emerge as the single most useful marker to estimate ovarian reserve and well reflect time to the onset of the menopausal transition (determined by the onset of menstrual irregularities).[25, 26] Still, more longitudinal data and clinical outcomes to assess the predictive value of ORT and AMH in particular are needed.

For thalassemia females where age and menstrual cycle cannot assess fertility status, these novel measures can provide important predictive information and become a useful tool for clinical application.

Assessment of fertility in TM females: preliminary data

The hypothalamic/pituitary hormonal secretion appears to be particularly sensitive to the effects of iron loading, while data on the end-organ dysfunction is less well defined. In clinical practice, the standard assessment of failure of sexual development or fertility status

in thalassemia females involves measuring the concentration of LH and FSH. In some cases hormone stimulation tests (GnRH) are performed.[27]

We explored the relationships between total iron burden as measured by liver iron concentration (LIC), hormonal levels and ovarian reserve; the latter not included in this report. Iron status and chelation history was studied in 26 adult females with transfusion dependent thalassemia; median age 29, mean 30±6, range 17–42 years. Nineteen females entered puberty spontaneously at a mean age of 14.1 years, ten of them underwent secondary amenorrhea (mean age 19.2 years). Seven experienced primary amenorrhea resulting in primary or secondary amenorrhea in a total of 17 females (65%). A total of 7 women were on replacement hormone therapy at the time of this study. Patients were asked to report a self assessment of their compliance with chelation treatment in 5 years increments, starting at age 11 years.

Liver iron concentration (LIC) was available in all 23 females, as assessed by annual ferrtitometer spectoferritometry (SQUID), a non-invasive, accurate technique for measuring iron level.

LH and FSH levels (available in 23 of them) were low or undetectable in 11/23 females (48%) and estradiol was low or undetectable in 8 out of these 11 females. The mean levels of FSH in patients with or without amenorrhea did not differ significantly. There was a significant difference in the LH level in the 2 groups; some lack of concordance has been shown before in the secretion of FSH and LH.[28]

Age and LIC could not differentiate between those with or without hormonal deficiencies and there was also no correlation between age and LIC. This poor correlation of hypogonadotrophic hypogonadism with total body iron burden as indicated by mean LIC, confirms previous findings[29] and further highlights the distinctive and early effect of iron accumulation on the reproductive system; the anterior pituitary and likely the gonads as well.

The self-reported compliance questionnaire indicated poor average compliance in 50% of the patients (use of chelation 50–75% of the time prescribed for). There was an association of the compliance level with the range of hormonal levels, suggesting that on-going iron accumulation, most likely starting earlier than what can be detected as abnormal LIC, causes the irreversible pituitary damage, and underscores the need for more sensitive markers for declining fertility potential.

In summary, our preliminary results indicate that despite improved chelation methods, hypogonadotrphic hypogonadism and probable infertility problems still occur in a significant number of females with thalassemia. Fertility status in this cohort of patients could not be predicted from age, menstrual status or average liver iron measures. Similarly, as previously noted, transfusion or chelation parameters could not predict fertility.[27] This underscores the need for utilization of current available methods for assessment of fertility capacity, prediction of chances for pregnancy or time of menopause. We are currently applying the most successful methods of ORT and studying the levels of AMH, Inhibin B, antral follicle count (AFC) and ovarian volume in this group of women. We expect these

markers of ovarian reserve to better determine reproductive potential. Determination of ovarian reserve with such methods will also enable thalassemia women to seek assisted reproduction technologies (ART) which are continuously improving.[30]

Recent studies attempt to correlate pituitary MRI for iron deposition with LIC and cardiac iron, and develop an ability to predict hypogonadism.[4, 29] When integrated with improved measures of fertility status, it could result in improved knowledge of the reproductive status in thalassemia females. Such understanding of the relationship to iron overload and of the mechanism for declining fertility potential could result in more successful interventions for preserving fertility.

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Table 1

Patients' Fertility and Iron Overload/Chelation Characteristics.

Thalassemia type	Age (Y)	Amenorrhea (Yes/No)	Pregnancies/ live birth	Splenectomy	Average LIC (mg/gr dry wt)	Chelation score	Low LH/FSH
TM	17	Y		N	31.2	2.5	N
TM	23	Y		N	8.6	4	Y
TM	25	N		Y	6.9	3	N
TM	25	Y		Y	36.6	3	Y
E thal	26	Y	1/0	Y	34.5	1.67	N
TM	26	Y		Y	11.5	2.5	Y
TI/TM	26	Y		N	7.1	4	N
TM	26	N		Y	25.0	1.5	N
TM	26	N		N	12.7	3.5	N
TM	28	Y		Y	11.3	2.5	Y
TM	29	Y		Y	5.9	3.75	Y
TM	30	Y		Y	6.3	3.5	N
E thal	30	Y		Y	9.2	4	Y
E thal	30	Y	1/1	Y	5.9	2	Y
E thal	31	N	4/4	N	41.8	2.5	N
TM	31	N		Y	6.5	1	Y
TM	31	Y		Y	9.5	3	Y
E thal	34	Y		Y	18.3	3.4	Y
TI/TM	37	N		Y	3.2	2.4	N
TM	37	Y		Y	4.1	4	N
TM	37	Y		Y	6.6	2.75	Y
TM	41	Y		Y	9.1	3.4	N
E thal	42	N	2/2	Y	9.4	2.75	N
Total		**Y= 16 N=7**	**8/7**	**Y=18 N=5**			**Low =11 nl =12**
Mean±SD	**30±6.2**				**14±11.5**	**2.9±0.8**	

TM= Thalassemia Major; E Thal= E-beta^{0}thalassemia; TI/TM= Thalassemia intermedia transitioned to regular transfudions/chelation tretament.