

Original Research Article

Do Iron Chelators Affect Fertility in Thalassemic Men?

Abstract

Aim: To evaluate the effect of iron chelator drugs on testicular volume, semen parameters and serum FSH, LH, and Testosterone concentrations in 62 young male patients with major and intermedia thalassemia.

Methods: Sixty two young male patients with major and intermedia thalassemia, aged 18–41 years who had different iron chelator drug using status were evaluated.

Results: At the time of the study their serum ferritin levels ranged from 182 to 11053 ng/mL (mean 2067 ng/mL). The mean volume of patients' ejaculate was 2.3 cc. The mean concentration of sperm was 61.04 million per milliliter. The mean size of right testis was 11.4 cc and the mean size of left testis was 11.7 cc. Hypogonadism and hypothyroidism were seen in 22.6% and 17.7% of patients, respectively. The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8 ng/dl. The mean level of serum ferritin was 2067 ng/dl.

Conclusion: This study suggests that in thalassemic men, concentrations of serum Testosterone, LH, FSH has significant correlation with sperm parameters and testicular volume but iron chelators mostly do not impact the elements of fertility in these patients.

Key Words: Thalassemia major, Thalassemia intermedia, Spermatogenesis, Puberty, Testicular volume, Gonadal hormones, Iron chelators

Introduction

Beta thalassemia is a hereditary hemoglobinopathy that can cause severe anemia. The life expectancy of these patients has noticeably extended by the combination use of transfusion and effective chelation therapy (Borgna-Pignatti, 2004). Transfusions can prevent mortality

26 and promote normal development, but the iron in the transfused red cells accumulates and in
27 the long run damages the liver, heart, and other organs. Involvement of different organs
28 including the endocrine system lessens the quality of thalassemic patients' lives. In fact,
29 pubertal failure, sexual dysfunction and infertility, due to hypogonadism have been reported
30 in 51% to 66% of thalassemic patients (Galanello and Origa, 2010, De Sanctis et al., 2011,
31 Soliman et al., 2012).

32 The etiologies of male infertility in general population are several though in β -thalassemia are
33 classically considered to be the result of iron deposition in the endocrine glands.⁴ The adverse
34 reactions of the drugs they use for different reasons including iron chelation could be an
35 important factor influencing thalassemia fertility (De Sanctis et al., 1986)

36 The prevalence of acquired hypogonadism in β -thalassemia has been reported to depend
37 mainly on the degree of compliance with blood transfusion and chelation programs (De
38 Sanctis et al., 2016). This means that iron chelator drugs could be a protector against iron
39 deposition in gonads but at the same time could have toxic effects on gonads and sperms.

40 The aim of this study was to evaluate the effect of iron chelator drugs on pubertal
41 development, sexual hormone status and sperm parameters in adolescent and young adult
42 males with Beta-thalassemia major and intermedia.

43 **Materials and method**

44 This prospective study was conducted between January 2001 and January 2003 at a teaching
45 hospital in Tehran, Iran. The study included 62 males with Beta-thalassemia major and
46 intermedia, whose ages ranged between 18 and 41 years. Among the patients, 52 had been
47 regularly transfused since early childhood and underwent different chelation therapies using
48 subcutaneous desferrioxamine and/or oral deferasirox and/or deferriperone.

49 The requisite of the study was that the participants being competent and cooperative.

50 Puberty was evaluated in the patients according to Tanner's classification of testicular
51 development (Tanner and Whitehouse, 1976). Testicular size ≤ 4 mL (long axis of ≤ 2.5 cm)
52 was considered stage I (prepubertal genitalia), and size ≥ 25 mL (≥ 5 cm in length) was
53 considered adult genitalia (Kauschansky et al., 2002). Testicular volumes were calculated
54 with scrotal ultrasound.

55 After overnight fasting, blood samples were collected from patients for evaluation of their
56 basal LH, FSH, and Testosterone.

57 Conventional semen analysis was carried out after an abstinence interval of 3–4 days using
58 manual procedures and light microscopy in the central hospital laboratory according to the
59 last World Health Organization guidelines (Tuck, 2005).

60 Iron overload was assessed by direct and indirect methods. It was evaluated by measuring
61 serum ferritin level. Iron status was classified as mild (ferritin < 1000 ng/ml), moderate
62 (ferritin > 1000 ng/ml and < 2500 ng/ml) or severe (ferritin > 2500 ng/ml). T2* MRI of heart
63 and liver was assessed for iron overload. Standard computer program SPSS for Windows,
64 release 16.0 was used for data entry and analysis. $P \leq 0.05$ was considered statistically
65 significant.

66 The study was approved by the University's ethical Committee.

67 Patient informed consent was obtained, as appropriate, before beginning the study.

68 **Results**

69 The patients' age range was between 18 to 41 years. Their mean age was 27.2 years. Among
70 the patients, 75.8% were major and 24.2% were intermedia and totally 83.9% were
71 transfusion dependent. Among our patients, 4.8% did not use any kind of iron chelator drugs,
72 54.8% used deferoxamine, 50% used deferasirox and 21% used deferiprone. On an additional
73 glance, 14.5% had history of using both deferoxamine and deferasirox, 12.5% used

74 deferoxamine and deferiprone at the same time and 3.2% used deferasirox and deferiprone
75 simultaneously.

76 The mean volume of patients' ejaculate was 2.3 cc. Five patients (8.1%) had dry ejaculate
77 and 24.2% of patients had unacceptable ejaculate volume (<1.5 ml).

78 Having dry ejaculate significantly correlated with having the history of using deferiprone
79 ($p=0.025$). However, patients who had the history of using deferoxamine had significantly
80 lower ejaculate volume comparing with patients who did not use deferoxamine (1.7ml versus
81 2.6 ml). This was also true about the patients who had the history of using deferiprone (1.2ml
82 versus 2.3ml). But having the history of using deferasirox had not impacted ejaculate volume
83 in our study.

84 The mean concentration of sperm was 61.04 million per milliliter. Totally, 61.3% of patients
85 had acceptable sperm concentration (≥ 15 M/ml) but 21% had azospermia and 22.4% had
86 oligospermia. In patients who used deferiprone, oligospermia was significantly more
87 frequent ($P=0.04$).

88 Considering the sperm motility, respectively, in 22.4% and 34.6% of patients the number of
89 motile sperms and progressively motile sperms were less than normal. Considering the sperm
90 morphology, in 44.8% of patients the number of sperms with normal morphology were less
91 than normal. The drugs did not impact the sperms' motility and morphology in our study.

92 The mean size of right testis was 11.4 ml and the mean size of left testis was 11.7 ml. Only
93 3.2% of patients had testicular volume less than 4 ml which is indicative of the puberty
94 process not being started and this was significantly correlated with using deferiprone. This
95 means that deferiprone usage was associated with delayed puberty.

96 The mean level of FSH was 3.7 mIU/ml, LH was 4.6 mIU/ml, and Testosterone was 4.8
97 ng/dl. The frequency of hypogonadotropic hypogonadism and hypergonadotropic

98 hypogonadism was 16.1% and 6.5%, respectively. The chelator drug usage did not correlate
99 with the gonadal hormones' serum level.

100 The mean level of serum ferritin was 2067 ng/dl. Serum ferritin level correlated significantly
101 with deferoxamine and deferiprone usage and not with deferasirox usage. In 74.2% of
102 patients cardiac MRI was normal. In 21% of patients hepatic MRI was normal. Interestingly,
103 cardiac and hepatic MRI involvements did not correlate with chelators' usage. All the same,
104 no significant correlation was found between the iron overload determinants and sperm
105 parameters or having hypogonadism.

106 **Discussion**

107 Iron overload in beta-thalassemia patients is the mutual outcome of multiple blood
108 transfusions and improperly increased iron absorption due to ineffective erythropoiesis.
109 Tissue iron deposition affects all organ systems, especially the cardiac, hepatic, and
110 endocrine systems. Observational records advocate that iron loading in endocrine organs may
111 precede that in the heart and liver. There is now considerable evidence on the role of iron
112 overload in endocrine morbidity in these patients (Noetzli et al., 2012, Belhoul et al., 2012).
113 Hypogonadism and delayed puberty are the most common endocrinopathy in thalassaemic
114 patients (40–91%) (Borgna-Pignatti et al., 2004, Taher et al., 2010, Vogiatzi et al., 2009). It
115 has been shown to be correlated with early onset of transfusion therapy, serum ferritin levels
116 of approximately 2000 ng/mL (Gamberini et al., 2008) and HU treatment (Taher et al., 2010)
117 in beta thalassemia patients. Iron chelation therapy could prevent long-term complications of
118 iron overload (Hershko, 2010). Chelation regimens are improving and studies show the
119 preventability and reversibility of hypogonadism by intensive combined chelation (Farmaki
120 et al., 2006). ElAlfy et al. documented that combination chelation using deferiprone and
121 desferrioxamine in a 3 year time priod in polytransfused males (>14 years) with thalassemia

122 who had good pituitary–testicular function led to progression of pubertal development;
123 meanwhile, their semen quality was still impaired (ElAlfy et al., 2013).

124 Although different chelators are being used and serum ferritin is strictly controlled, the
125 harmful effect of iron overload to the reproductive system of patients with thalassemia major
126 is still common (Al-Rimawi et al., 2005).

127 To our knowledge, no study has assessed the impact of iron chelator drugs on fertility
128 indicators. In this study we illustrated that ejaculate volume and sperm concentration in beta
129 thalassemic men could be affected by the use of iron chelator drugs.

130 The iron chelator desferrioxamine was first introduced more than 50 years ago (Moeschlin
131 and Schnider, 1963), and has been proven to prevent the iron-mediated damage of
132 parenchymal organs and to improve growth, sexual maturity, and survival time. But
133 achieving these positive effects seems to require very early and aggressive chelation therapy
134 (De Virgiliis et al., 1983) which have been confirmed to have toxic effects on acoustic and
135 visual neurosensorial pathways (Davies et al., 1983, Olivieri et al., 1986). De Virgiliis et al.
136 showed that impairment of longitudinal growth and pseudorachitic bone changes should be
137 added to the list of the negative side effects of high doses of desferrioxamine (De Virgiliis et
138 al., 1988). We found that patients who had the history of using deferoxamine had
139 significantly lower ejaculate volume comparing with patients who had not used
140 deferoxamine.

141 Deferasirox is an orally absorbed once-daily iron chelator developed for the management of
142 chronic iron overload from blood transfusions. Its safety, tolerability and efficacy in reducing
143 body iron burden have been demonstrated in patients with transfusion-dependent beta
144 thalassaemia (Cappellini et al., 2006). The most notable adverse events reported after this
145 drug usage has been transient gastrointestinal symptoms and skin rash. Mild, stable increases
146 in serum creatinine and reversible increases in liver enzymes have been noted (Jensen et al.,

2003, Mula-Abed et al., 2011). In our study, having the history of deferasirox usage did not impact sperm parameters, testicular volumes and gonadal hormones' serum levels.

Deferiprone is an orally active iron chelator which its adverse effects in clinical trials include agranulocytosis, arthropathy, gastrointestinal symptoms, increased ALT levels and progression of hepatic fibrosis (Hoffbrand et al., 1998, Bartlett et al., 1990, Agarwal et al., 1992) . In our study, patients who had the history of using deferiprone had significantly lower ejaculate volume and having dry ejaculate and oligospermia was more frequent in these patients comparing to patients who had never used deferiprone. Considering testicular volume in ultrasound assessment, in patients who used deferiprone testicular volume less than 4ml which is indicative of delayed puberty was much more frequent.

Our study has a number of limitations, including the retrospective design and the lack of dose and duration of drug usage being specified. Therefore, further prospective studies on a larger population would improve the quality of the research.

In conclusion, we observed that the fertility of male thalassemic patients is being affected by a variety of different factors including their chelator regimen. Taking into account the important role of reproduction and fatherhood in the quality of lives of these patients, we advocate the necessity of the care givers to be alert of the mentioned side effects.

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