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Short Communication

Use of deferoxamine (DFO) in transfusion-dependent β-thalassemia during pregnancy: A retrospective study

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ABSTRACT

Objective: To report cases of use of chelation therapy during pregnancy which resulted in favorable outcomes for the babies.
Materials and methods: In this retrospective cohort study, we described the evolution and outcome of 9 pregnancies in Italian thalassemic women who received deferoxamine (DFO) inadvertently during early pregnancy.
Results: The use of deferoxamine during first trimester did not lead to adverse effects on the fetus or cause major complications for the gestation, although an increase in iron burden was observed after suspending chelation therapy.
Conclusion: In our experience, iron-chelation therapy might be administrated in pregnancy where the benefits to the mother outweigh the potential risks to the baby.

Introduction

Improvements in managing β-thalassemia major (TM), including safer blood transfusions, specific monitoring of iron overload, parenteral and oral chelation along with other support therapies, have prolonged life and improved the quality of life of patients suffering from this condition [1]. These advances have meant that, although fertility may be impaired due to iron overload, women affected by β-thalassemia are currently able to conceive and give birth. Consequently, concern for the successful outcome of pregnancy in these patients has been growing.

Currently, three drugs are approved for the treatment of transfusional iron overload: deferoxamine (DFO), deferiprone (DFP), and deferasirox (DFX), alone or in combination [2].

DFO acts by binding free iron in the bloodstream with a 1:1 ratio and enhances its elimination mostly in the urine and to a lesser extent in the feces. It is administered by slow subcutaneous infusion at the usual dosage of 40–60 mg/kg 5–7 days per week [2,3]. DFP binds iron from intracellular compartment with a 3:1 ratio, mainly promoting urinal excretion. Its low molecular weight and rapid absorption allows oral administration at the usual dosage of 75–100 mg/kg three times a day [2,3]. Combination protocols with DFO and DFP are largely used, as the effect on iron balance seems to be additive for a shuttle mechanism with DFP entering cells and removing iron, which is then passed on to DFO for excretion in urine or feces. In addition, combining two drugs allows to reduce the number of subcutaneous administrations of DFO needed, thus increasing patients' compliance [3].

DFX is an orally administered selective binder of plasma iron which facilitates hepatobiliary excretion and has proven effective in decreasing ferritin and removing iron from liver and heart [1,3]. In Europe it is approved for treatment of iron overload in adults or when DFO is contraindicated and is usually used in monotherapy, as its role in combination protocols with DFO or DFP is not clear [1–3].

Iron chelators are usually not recommended during pregnancy for the lack of evidence about their effect on fetal development. In particular, as delayed ossification and skeletal anomalies were

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observed in pre-clinic studies in pregnant mice and rabbits, DFO is assigned to Food and Drug Administration (FDA) pregnancy category C, meaning there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks [4].

Generally, pregnancies in TM women are planned and often require assisted reproductive techniques. However, as TM patients tend to suffer from hypogonadotropic hypogonadism and subsequent amenorrhea due to the effects of iron deposition in the pituitary gland, there are reported cases of iron-chelation treatment administrated unintentionally during the early phase of pregnancy when women were not aware of conception [2].

In this study we describe nine successful pregnancy outcomes in five TM women who assumed DFO inadvertently during the first trimester. Our aim is to assess the efficacy and safety of DFO in pregnancy.

Materials and methods

In this retrospective cohort study, we studied nine women affected by β-thalassemia followed at the thalassemia unit of Umberto I Hospital of Rome, who became pregnant unintentionally while being treated with iron chelation therapy with DFO between 2008 and 2019.

Our protocols for treatment of iron overload include DFO 40–60 mg/kg/day or DFX 30 mg/kg/day, which are administrated after transfusion of 15 red blood cell (RBC) units or when ferritin level is $\geq$ 1000 ng/ml. Values of liver and cardiac T2* are also taken into consideration for further clinical decisions.

Ferritin is a metalloprotein that controls iron metabolism and turnover. Its plasmatic level reflects total body iron storage and it is widely used to evaluate iron load [2]. Magnetic resonance imaging (MRI) T2* measurement is a simple, noninvasive and accurate method for evaluation of tissue iron burden. It is a parameter arising principally from magnetic fields inhomogeneities and increases with iron deposition. There is an inverse correlation between T2* and tissue iron content. A cardiac T2* value of 20 ms or lower is associated with a decrease of left ventricular ejection fraction and values inferior to a higher risk of developing heart failure [5]. Similarly, low hepatic T2* values reflect high liver iron concentration and are predictive of transfusional iron burden and long-term complications [2,6].

Women usually interrupt chelation therapy when in pursuit of a pregnancy, but ferritin, cardiac and liver T2* values are strictly monitored. If ferritin is $\geq$ 1000 ng/ml or cardiac and liver T2* are <22 and 9 ms respectively, after the 20th week a chelation therapy with DFO at lower dosage (20–30 mg/kg/day) may be resumed.

In the cases we reported women were not aware of pregnancy from the beginning and accidentally assumed DFO in the first trimester. In these patients, we studied pregnancy and delivery complications and outcomes in the newborn. We also assessed maternal iron status before and after pregnancy, using serum ferritin levels and cardiac and liver T2* values.

Results

Among the patients enrolled, 7 (77.78%) had thalassemia major and 2 (22.22%) had intermediate thalassemia. As for comorbidities, 2 were positive for HCV (22.22%), 3 had hypothyroidism (33.33%) and 1 had psoriasis (11.11%). Mean age at time of conception was 31 ± 2.12. All women had spontaneous singleton pregnancy while being treated with DFO (range 40–45 mg/kg/day), which was discontinued after positivity of pregnancy test (range 6th-14th week). Pregestational mean serum ferritin was 755.89 ± 325.78 ng/ml, mean cardiac T2* was 38.4 ± 2.18 ms and hepatic T2* was 10.30 ± 4.91 ms. Patients' characteristics and pregnancies data are shown in Table 1. No cardiac, endocrinologic, thrombotic or other major complication occurred and all pregnancies resulted in live births. Three women (33.33%) resumed DFO (range 20–30 mg/kg/day) after 20th week for high ferritin values. Mean gestational age at delivery was 38 ± 2 weeks and only two patients (22.22%) had a preterm delivery for mild preeclampsia and premature rupture of membranes respectively. All women delivered by cesarean section and none of the children had any peripartum or postnatal complication. Four patients (44.44%) breastfed, and among them, two were under chelation therapy at the same time. Postpartum mean serum ferritin was 1737.0 ± 359.48 ng/ml ($p < 0.0001$), mean cardiac T2* was 31.69 ± 8.52 ms ($p = 0.03$) and hepatic T2* was 4.20 ± 2.97 ms ($p = 0.005$), all significatively higher than pregestational values. Pre and post-partum iron status data are shown in Fig. 1.

Discussion

Our study provides evidence of 9 pregnancies in which the use of DFO during early pregnancy and eventually second/third trimester did not lead to adverse effects on the fetus or cause major complications for the gestation. Several patients were able to breastfeed while assuming DFO without any major harm to the newborns' wellbeing. However, interruption of iron chelation

Table 1
Characteristic of the patients.

Characteristics	% (n)
No. patients	9
Age, year (mean ± SD)	31 ± 2.12
Type of thalassemia (%)	
Maior	77.78% (7)
Intermedia	22.22% (2)
Minor	(0)
Comorbidities (%)	
HCV infection	22.22% (2)
Hypothyroidism	33.33% (3)
Psoriasis	11.11% (1)
None	44.44% (4)
Pregestational iron status (mean ± SD)	
Serum ferritin (ng/ml)	755.89 ± 325.78
Liver T2* (ms)	10.30 ± 4.91
Cardiac T2*(ms)	38.4 ± 2.18
Chelation therapy before pregnancy (mg/kg/day - range)	DFO 40–45
Week of interruption of chelation therapy (range)	6–14
Week of delivery (mean ± SD)	38 ± 2
Type of delivery (%)	
Vaginal	0
Cesarean section	100% (9)
Preterm birth (%)	22.22% (2)
Live birth (%)	100% (9)
Weight at birth (mean ± SD)	3054.11 ± 207.31
Apgar score at birth (range)	
Minute 1	6–9
Minute 5	8–10
Complications during pregnancy (%)	
Cardiac	None
Endocrinologic	None
Thrombotic	None
Others	22.22% (2)
Preeclampsia	11.11% (1)
pPROM	11.11% (1)
Postpartum iron status (mean ± SD)	
Serum ferritin (ng/ml)	1737 ± 359.48 (p value < 0.0001; CI 95%)
Liver T2* (ms)	4.20 ± 2.97 (p value = 0.005; CI 95%)
Cardiac T2*(ms)	31.69 ± 8.52 (p value = 0.03; CI 95%)

SD = standard deviation; CI = confidence interval; DFO = deferoxamine; pPROM = preterm premature rupture of the membranes.

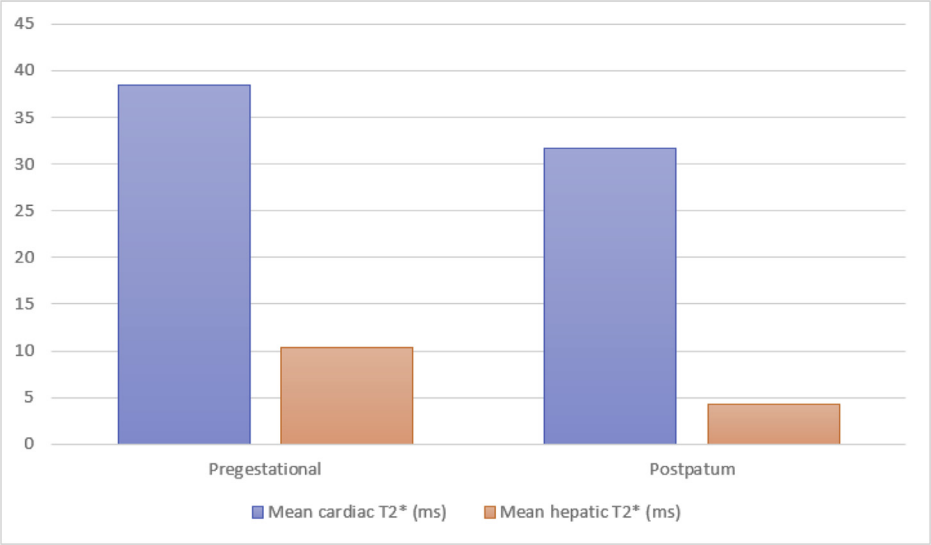

Fig. 1. Comparison between pregestational and postpartum mean cardiac and hepatic T2*.

therapy resulted in a deterioration in iron status and increase of iron burden in mothers. In fact, all women had significatively higher postpartum ferritin levels and a decrease of liver T2*, suggesting an aggravation of the degree of hepatic hemosiderosis, while mean cardiac T2*, which was also significatively diminished after delivery, was not <20 ms in any patient.

Despite concern for potential adverse effects on the developing fetus limits the use of DFO during pregnancy, review of the literature shows cases of pregnant thalassemic women who have received DFO during gestation without documented teratogenicity or toxic effect on the fetus [7–12].

McElhatton et al. [7] in 1991 suggested that an iron overload during pregnancy in the first trimester may lead to abortion or malformation and alter fetal development in second/third trimester, resulting in abnormal organ function, low birth weight, intrauterine death, or premature delivery. Treatment with DFO in second and third trimester resulted in favorable outcome in 21 patients out of 25, with no evidence of toxicity derived from chelation therapy. Singer et al. [8] described one case of talassemic pregnant woman who received DFO since 18th week, while Tampakoudis et al. [9] described one case of self-administered DFO until 8th week of gestation, both without major complication on the pregnancy. Kumar et al. [10] presented 32 cases of women chelated with DFO in second/third trimester with favorable fetal outcomes.

More recently, Pearson et al. [11] described another case of women who assumed DFO during her first pregnancy and had an elective preterm cesarean section for partial placenta previa, but overall a positive outcome. In Origa et al. [12] experience, DFO was administrated inadvertently for 2–10 weeks after conception in 31 women, without any evidence of malformation in the babies, although lack of evidence impose caution in use of iron chelation in pregnant women.

Findings of our study are in accord with data previously published in literature, although use of DFO in pregnant thalassemic women remains conflicting. Nevertheless, we acknowledge that the limits of our study are mainly represented by the retrospective setting and the small cohort.

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Declaration of Competing Interest

The authors report no conflict of interest.

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