

# Iron chelation therapy of transfusion-dependent $\beta$ -thalassemia during pregnancy in the era of novel drugs: is deferasirox toxic?

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**Abstract** The life expectancy of thalassemic patients has increased, and now approaches that of healthy individuals, thanks to improved treatment regimens. However, pregnancy in women with  $\beta$ -Thalassemia Major remains a challenging condition. Recent advances in managing this haemoglobinopathy offer the potential for safe pregnancies with favorable outcome. However, clinical data regarding the use of chelation therapy during pregnancy are limited, and it is unclear whether these agents impose any risk to the developing fetus. Successful pregnancies following unintentional treatment with deferoxamine or deferasirox have rarely been reported. Generally, chelators are not recommended during pregnancy. Regarding the new oral chelators, data on fetotoxicity are lacking. In the present study, we describe the evolution and successful outcome of nine pregnancies in six Greek thalassemic women who received deferasirox inadvertently during early pregnancy, and review the literature regarding fetal anomalies due to chelators. Use of chelation before embarking upon a non-programmed pregnancy remains a difficult and unresolved question. In our study, chelation treatment during

pregnancy did not prevent the delivery of healthy children. Nonetheless, the use of deferasirox is contraindicated in pregnant women, based on the product label. Deferasirox should only be used during pregnancy if the potential benefit outweighs the potential fetal risk.

**Keywords**  $\beta$ -Thalassemia major ( $\beta$ -TM) · Pregnancy · Chelation therapy · Deferasirox · Deferoxamine · Deferiprone

## Introduction

The life expectancy of thalassemic patients approaches that of normal people due to improvement of therapeutic strategies and to closer follow-up. This is the result of safer blood transfusions, the availability of three iron chelators, new imaging techniques, which allow specific organ assessment of the degree of iron overload and novel advances in the treatment of hepatitis, which frequently co-exists in these patients [1]. The ability to determine the amount of iron in the liver and heart using magnetic resonance imaging (MRI) allowed physicians to prescribe the most appropriate chelation agent for each patient. Recent evidence proved that by normalizing iron stores not only new morbidities are prevented, but also many complications such as cardiac failure, hypothyroidism, hypogonadism, impaired glucose tolerance and type 2 diabetes can be improved.

Today, the chelators available for thalassemic patients are deferoxamine (DFO), deferiprone (DFP) and deferasirox (DFX) [1]. Even though the three drugs are licensed for monotherapy, combinations of DFO and DFP [2] or even DFO and DFX [3] provide more effective therapy for the patients. The decision, concerning the therapy choice, must be obtained by determining the total iron load as well

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as the degree of haemosiderosis of individual organs such as heart and liver using MRI. Most patients prefer DFX due to easier administration (once orally per day) in comparison to the other drugs [4].

Furthermore, the evaluation of the iron burden is essential in order to decide when to start chelation, to select the appropriate regime and also to evaluate when to modulate or to interrupt chelation. Important parameters are the history of transfusions, type of chelation, compliance to treatment and flexibility to therapy according to the patients' needs. Generally, thalassemic patients are loaded with iron, due to blood transfusions and to chronic hemolysis, at an average rate of 0.5 mg/kg/day of body weight with a range of 0.32–0.641 [5, 6]. Ferritin has been the relatively universally available method for assessment of iron stores. Normal values of serum ferritin for men and women are 12–300 and 12–150 ng/ml, respectively. Thalassemic patients with ferritin values less than 1000 ng/ml have a better prognosis [6–8]. There is no physiological mechanism for the excretion of the excessive elemental iron from the body. The excessive accumulation of iron to the human body is associated with significant morbidity and early mortality, although the exact mechanism of the excessive iron-induced tissue damage is unknown [9].

The marked improvement in survival and the decreased morbidity in patients with  $\beta$ -Thalassemia Major ( $\beta$ -TM) permit thalassemic women to conceive and give birth to healthy children. In many cases, assisted reproduction methods with in vitro fertilization are used. In general, pregnancies in thalassemic patients are planned and iron chelation therapy is ceased before women start the in vitro fertilization procedure, due to potential toxicity of the chelators to the fetus [10–13]. However, there are reported cases, where the thalassemic women did not know that they were pregnant, because the conception was not planned. In these cases, the pregnancy was carried out successfully without complications and harmlessly for the fetus, despite the fact that the pregnant women were under chelation treatment for short time.

## Materials and methods

In this study, we would like to report the policy followed in the thalassemia units of our centers regarding iron chelation therapy and pregnancy in the era of new chelation agents in comparison and compliance with the published series.

Our usual daily clinical practice, is to initiate chelation with DFO at 30–60 mg/kg/day or DFX at 30 mg/kg/day after patients have received 15 red blood cell (RBC) units and/or when the level of ferritin is around 1000 ng/ml. Further treatment decisions are made, based on iron overload assessment with the use of Cardiac and Liver T2\* MRI and

Ferritin levels. Our goal is to maintain Liver T2\* > 9 ms and Cardiac T2\* > 22 ms to our chronically transfused patients with  $\beta$ -TM.

In our units, the thalassemic women who plan to become pregnant, replace the oral chelation with subcutaneous DFO, which is ceased when the pregnancy is confirmed. Moreover, the protocol policy of our centers—based on our clinical experience—is to recommend full cessation of DFP 6 months earlier of a programmed conception. Generally, iron chelation therapy for thalassemic women is not recommended during pregnancy in our centers.

However, six women, while being under chelation therapy with DFX, became pregnant unintentionally and all gave birth to healthy children. One of the patients had three pregnancies, while another one had two. The median age of our thalassemic cohort was 30 years (range 25–41 years) at time of conception. In total, nine successful pregnancies were completed. To the best of our knowledge, this is one of the largest studies until today investigating the role of DFX in pregnant thalassemic women who received it inadvertently.

The iron status before and after each pregnancy was determined with the use of Cardiac T2\*, Liver T2\* values and Ferritin levels. Normal ranges were Liver T2\* values >9 ms and Cardiac T2\* values >22 ms. Further classification regarding the degree of iron overload is shown on the corresponding Table, along with the data of the patients.

The women of our cohort were all negative for HBV, HCV and HIV infection, as they were screened regularly. No cardiac dysfunction, endocrine problems or glucose intolerance were diagnosed after the frequent follow-up. Moreover, biochemical data, such as transaminases, creatinine, albumin, bilirubin, CRP were unremarkable with the exception of a mild elevation of the indirect bilirubin, because of the known haemolysis, due to thalassemia. Thus, pre-existing clinical complications to our patients were absent.

We also evaluated the levels of hepatic fibrosis in 3 out of the 6 women of our study with the method of transient elastography (TE). TE is a non-invasive method accurately measuring liver stiffness (LSM), with the application of transmitting elastic shear waves to underlying tissues, such as the liver and of determining the velocity of these waves with the aid of pulse-echo ultrasound acquisitions. TE serves as a helpful tool for the assessment of the degree of fibrosis in the liver. Patients were assessed with TE (LSM in kPa) at baseline—within 35 (5–47) days after having been switched to 35 (30–40) mg/kg DFX—and reexamined with the same method by the same operator at 5 years. In clinical practice, LSM from 2.5 to 7.0 kPa indicate mild or no fibrosis. Results of kPa >8 are considered indicators of severe liver fibrosis. Values greater than 12.5 kPa are suggestive of cirrhosis. For the diagnosis of cirrhosis,

TE cutoff values have been found to be between 11.8 and 14.6 kPa [14].

## Results

The first female patient (28 years old), diagnosed with  $\beta$ -TM, was on regular transfusions with two RBC units every 2 weeks and on chelation therapy with DFX with 30 mg/kg body weight (BW) since January 2010, while her ferritin levels were 800 ng/ml and her cardiac and liver T2\* values were 50 and 6.3 ms, respectively. Her previous chelation therapy was DFO (45 mg/kg/day). While being under chelation therapy with DFX for 2 years (30 mg/kg), she became pregnant without planning it and at that time (6th week of pregnancy) she immediately stopped chelation. In September 2012, she gave birth to a healthy 3412 g boy at her 40th week by caesarian section, due to breech presentation. Her ferritin levels were 4000 ng/ml and her cardiac and liver T2\* values were 36–39 and 3.3 ms, respectively. She started the chelation therapy with DFX 40 days after the delivery (30 mg/kg) and after she had stopped breastfeeding (Table 1).

We also evaluated the levels of hepatic fibrosis in this patient. Thus, kPa was 7.6 at the first measurement and increased after 5 years to the levels of 8.8, indeed indicating

severe hepatic fibrosis. The latter was attributed to the fact that the patient stopped chelation treatment (DFX) during her pregnancy, resulting to the deterioration of the markers evaluating liver fibrosis.

The second patient was a 32-year-old woman diagnosed with  $\beta$ -TM and being transfused regularly with two RBC units every 2 weeks. She started taking DFX in April 2006 at a dosage of 30 mg/kg BW. Her ferritin levels were 2770 ng/ml and her cardiac and liver T2\* values were 32 and 7.75 ms, respectively. In August 2008, she found out that she was 6 weeks pregnant and she stopped chelation. Her ferritin levels were 2137 ng/ml. In April 2009, she gave birth to a 2500 g girl at her 38th week of gestation by caesarian section, due to membrane rupture and the baby was generally healthy, except from a mild pulmonary immaturity. Her ferritin levels were 2650 ng/ml and her cardiac and liver T2\* values were 40 and 4.4 ms, respectively. Her second pregnancy was in May 2012, again her being under DFX treatment (30 mg/kg). Her ferritin levels were 1850 ng/ml. She stopped the chelation and eventually she delivered a healthy girl (3160 g) at her 40th week by caesarian section. Forty days later, she started DFX at the increased dose of 40 mg/kg, as her ferritin level was 4100 ng/ml and her cardiac and liver T2\* values were 31 and 2.7 ms, respectively (Table 1).

**Table 1** Characteristics of the pregnant women and delivery data (iron status: ferritin levels in ng/ml, T2\*heart in ms, T2\*liver in ms)

Mother	Age	Mother's iron status	Week of pregnancy that DFX is ceased	Week of pregnancy upon delivery	Type of delivery	Foetus sex	Foetus weight (g)	Foetus abnormalities	Postpartum mother's iron status
1	28	800/50/6.3	6	40	Caesarian section	Boy	3412	Healthy foetus	4000/39/3.3
2A	32	2770/32/7.75	6	38	Caesarian section	Girl	2500	Mild pulmonary immaturity	2650/40/4.4
2B	35	2650/40/4.4	6	40	Caesarian section	Girl	3160	Healthy foetus	4100/31/2.7
3	41	510/43/4	10	40	Caesarian section	Girl	3000	Healthy foetus	750/37/2.4
4	32	4180/34/3.8	8	38	Caesarian section	Girl	2900	Healthy foetus	NA/NA/NA
5	25	1331/44/3	8	37	Caesarian section	Girl	2560	Healthy foetus	2022/36/2.9
6A	25	2700/NA/NA	6	36	Caesarian section	Boy	2690	Healthy foetus	6000/23.5/0.8
6B	29	2750/36.4/2.45	8	38	Caesarian section	Boy	2960	healthy foetus	4000/35.6/1.15
6C	31	2600/32.8/2.3	14	38	Caesarian section	Boy	3030	Healthy foetus	3950/33.6/1.15

T2\* heart in ms—classification: >22 = normal, 14–21 = mild hemosiderosis, 8–14 = moderate hemosiderosis, <8 = severe hemosiderosis

T2\* liver in ms—classification: >19.1 = normal, 9.1–19 = successful iron chelation, 4.1–9 = mild hemosiderosis, 1.6–4 = moderate hemosiderosis, <1.6 = severe hemosiderosis

Moreover, kPa was 5 at the initial measurement and raised after 5 years to the levels of 7.6, proving an increase to the degree of hepatic fibrosis. Between this time interval, the patient completed two successful pregnancies. However, the patient stopped chelation treatment (DFX) during her pregnancies, which resulted in an increase at the levels of liver fibrosis.

The third patient was a 41-year-old woman diagnosed with thalassemia intermedia and splenectomized at the age of 12 years. Her hematological data were the following: Hb 8.5 g/dl, WBC  $15.4 \times 10^9/l$  (neutrophils  $6.78 \times 10^9/l$ , lymphocytes  $6.93 \times 10^9/l$ , nucleated red blood cells 5 %), platelets  $750 \times 10^9/l$ . Thrombocytosis was attributed to splenectomy. She was on aspirin, due to thrombocytosis.

She had started RBC transfusions regularly, two units per month, since 2 years, due to a paraspinal extramedullary mass. The incidence of extramedullary hematopoiesis (EMH) in patients with thalassemia intermedia may reach up to 20 %, because they are not transfused regularly, in comparison to poly-transfused  $\beta$ -TM patients where the incidence remains less than 1 % [15]. Transfusion independence in thalassemia intermedia increases the incidence of EMH, as the body attempts to compensate for ineffective erythropoiesis, insufficient bone marrow function and inadequate red cell replacement, leading to unsuccessful expansion of the hematopoietic tissue outside the bone marrow medulla, mainly in the form of masses [16]. Treatment in such cases to suppress these masses and/or ineffective hematopoiesis, is either the administration of hydroxycarbamide (hydroxyurea) or RBC transfusions [17]. Hydroxyurea was not chosen, because the female patient wanted to become pregnant and thus, RBC transfusions were preferred.

She had a previous unsuccessful pregnancy 3 years ago. The tests for thrombophilia factors and lupus anticoagulant were negative. Her ferritin levels were 510 ng/ml and her cardiac and liver T2\* values were 43 and 4 ms, respectively. She was on DFX for 1.5 year at a dosage of 25 mg/kg BW before she had noticed her pregnancy. She was 10 weeks pregnant when she stopped chelation. She gave birth to a healthy 3 kg girl in February 2013 at her 40th week by caesarean section. Her ferritin levels were 750 ng/ml. She has not yet started chelation, due to breastfeeding (Table 1).

The fourth patient was a 32-year-old woman diagnosed with  $\beta$ -TM and being transfused regularly every 2 weeks with two RBC units. Her ferritin levels were 4180 ng/ml and her cardiac and liver T2\* values were 34 and 3.8 ms, respectively. The patient, who showed no compliance to the iron chelation treatment with DFX (35 mg/kg) and to the follow-up program, stopped the chelation when she realized she was pregnant (8th week). She gave birth to a healthy girl at her 38th week by caesarean section, while

she was diagnosed having metastatic cancer of the liver (Table 1). The primary tumor was colorectal cancer, which infiltrated the bone marrow as well, along with hepatic dissemination. Unfortunately, she died 2 months after the caesarean section, because of her malignancy.

The fifth thalassemic woman—diagnosed with  $\beta$ -TM—aged 25, was under treatment with two RBC units every 2 weeks. She stopped DFX (30 mg/kg) after she had noticed her pregnancy. Her ferritin levels at that time were 1331 ng/ml and her cardiac and liver T2\* values were 44 and 3 ms, respectively. She delivered her daughter at the 37th week of pregnancy by caesarean section, due to positive indirect Coombs and detection of anti-Rh antibodies to her serum. The girl was healthy and weighted 2560 g. After pregnancy, her ferritin levels at that time were 2022 ng/ml and her cardiac and liver T2\* values were 36 and 2.9 ms, respectively (Table 1).

Interestingly, kPa was 5.7 at the initial measurement and decreased after 5 years to the levels of 4.5, showing that the hepatic fibrosis was less severe after 5 years. A possible explanation for this discrepancy is that she became pregnant early in the time interval of the 5 years and despite her stopping treatment with DFX at the beginning of this interval, the initiation of chelation therapy (30 mg/kg) after her labor at a larger time interval in comparison with the other patients, was enough to decrease the levels of hepatic fibrosis. In other words, she had enough time (at least 3 years) to receive DFX after her delivery (30 mg/kg), resulting to a decrease at the levels of liver fibrosis.

Finally, the sixth thalassemic woman—diagnosed with  $\beta$ -TM—aged 25, was under treatment with two RBC units every 20 days. She started receiving DFX in the beginning of 2006 at a dosage of 30 mg/kg BW. In November 2006, she found out that she was 6 weeks pregnant and she stopped chelation. Her ferritin levels were 2700 ng/ml. In June 2007, she gave birth to a 2690 g healthy boy by caesarian section at the 36th week of gestation. Her ferritin levels increased to 6000 ng/ml and her cardiac and liver T2\* values were 23.5 and 0.8 ms, respectively, showing a heavy iron overload in her liver, yet a normal amount of iron in her heart. Forty-five days later, she started DFX on a dose of 30 mg/kg. After approximately 4 years, at the age of 29, in November 2010, she found out that she was 8 weeks pregnant again. Thus, she stopped DFX. By that time, her ferritin levels were 2750 ng/ml and her cardiac and liver T2\* values were 36.4 and 2.45 ms, respectively. She eventually delivered a healthy boy (2960 g) at her 38th week by caesarian section in May 2011. Forty days later, she started DFX on a dose of 30 mg/kg, as her ferritin levels were 4000 ng/ml and her cardiac and liver T2\* values were 35.6 and 1.15 ms, respectively. In April 2013, she being 31 years old, she learned that she was pregnant

for a third time, already at her 14th week of gestation. Consequently, she stopped DFX. By that time, her ferritin levels were 2600 ng/ml and her cardiac and liver T2\* values were 32.8 and 2.3 ms, respectively. Luckily, she delivered her third son weighting 3030 g at her 38th week by caesarian section in October 2013. Thirty days later, she started DFX on a dose of 30 mg/kg, as her ferritin levels were 3950 ng/ml and her cardiac and liver T2\* values were 33.6 and 1.15 ms, respectively (Table 1). She continues receiving DFX at the same dosage until today with comparative improvement in the iron hepatic load (liver T2\* value 2.1 ms, January 2015).

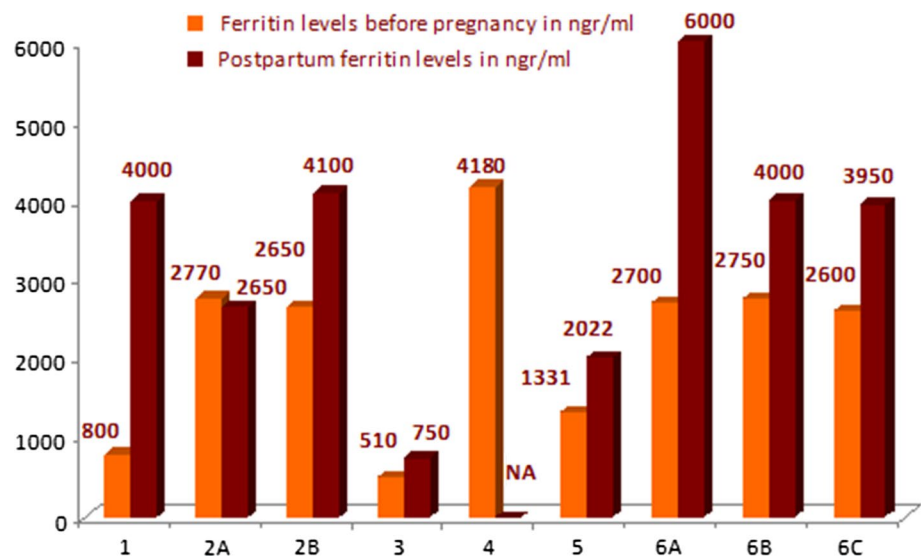
The comparison of the iron status before and after each pregnancy (Ferritin levels, Cardiac and Liver T2\* values) is shown in Figs. 1, 2 and 3.

## Discussion

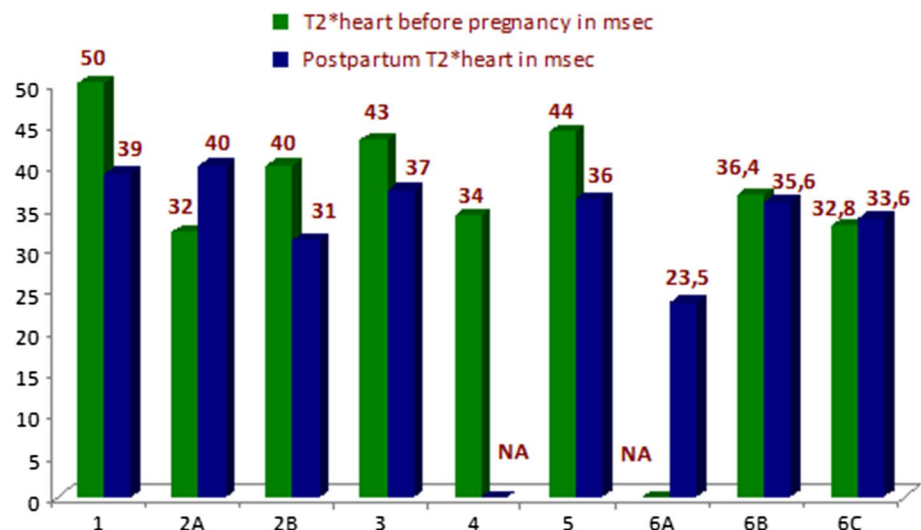
While the role of transfusion and chelation in improving survival of thalassemic patients has already been reported, there are no adequate and well-controlled studies in pregnant thalassemic women.

DFO (Desferal<sup>®</sup>), although effective in reducing the iron stores in the body, has the drawback of short pharmacological half-life and need for parenteral administration [7]. These features necessitate long-term (10–12 h) subcutaneous or intravenous (via catheter) infusions by pump daily for 5–7 days a week [8]. Thus, problems regarding compliance to DFO limit its use, particularly in the adolescents. Furthermore, conflicting data regarding skeletal anomalies in animal models have been reported [2, 13].

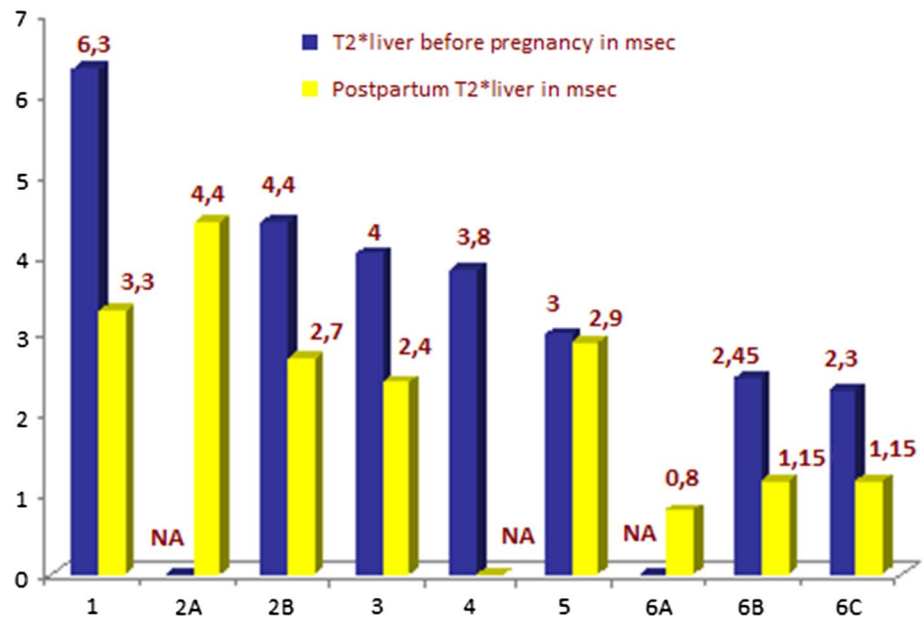
**Fig. 1** Ferritin levels before and after pregnancy in ng/ml



**Fig. 2** T2\* heart values before and after pregnancy in ms



**Fig. 3** T2\* liver values before and after pregnancy in ms



Because of the remarkable maternal toxicity of DFO, extreme caution in using this drug is recommended during pregnancy [18]. Hence, DFO has been assigned to pregnancy category C by the Food and Drug Administration (FDA), meaning that animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans until today. Nevertheless, potential benefits may warrant use of the drug in pregnant women despite potential risks. Thus, DFO should be used during pregnancy, only if the potential benefit exceeds the potential risk to the fetus [12, 19].

However, there is a study which evaluated the effect of iron overload and its treatment with DFO on the outcome of pregnancy, suggesting that iron overdose in pregnancy can be fatal and antidote treatment if appropriate should not be withheld. The majority of second and third trimester iron overdoses, treated with DFO or other antidotes had a normal pregnancy outcome. The risk of spontaneous abortion is low, but cannot be excluded [20]. Nevertheless, the possible risks for the fetus should be taken into account, especially when the drug is used at the first trimester. Thus, the decision of a possible use of DFO in pregnancies is multifactorial, always considering the existing literature data and balancing the possible risks and benefits both for the mother and the fetus. Indeed, deciding regarding the possible use of DFO in pregnant thalassemic women, is a difficult task, not only demanding vast knowledge of a continuously changing scientific landscape, but also necessitating broad clinical experience and meetings involving the corresponding medical specialties.

In contrast to DFO, DFX (Exjade®) and DFP (Ferriprox®) are oral iron chelators, administered once daily and three times a day, respectively. DFX is an

iron-chelating agent that selectively binds to plasma iron, facilitating hepatobiliary excretion. DFX is an alternative option to DFO in patients with intolerance and non-compliance [1, 21]. DFP is an agent that binds to ferric ion, creating complexes that are predominately excreted in the urine.

Moreover, there are no adequate data from the use of DFP in pregnant women [22]. Studies in animals have shown reproductive toxicity. The potential risk for the humans is unknown. No carcinogenicity studies in animals have been conducted with DFP. The genotoxic potential of DFP was evaluated in a set of in vitro and in vivo tests. DFP did not show direct mutagenic properties; however, it did display clastogenic characteristics in in vitro assays and in vivo in animals [Deferiprone Summary of Product Characteristics (SPC), preclinical safety data].

Based on the above, DFP has been assigned to pregnancy category D by the FDA, which means that there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks. Women of child-bearing potential must be advised to avoid pregnancy, due to the clastogenic and teratogenic properties of DFP. These women should be advised to take contraceptive measures and must be instructed to immediately stop taking DFP, if they become pregnant or plan to become pregnant. The protocol policy of our centers—based on our clinical experience—is to recommend full cessation of the drug 6 months earlier of a programmed conception [10, 22].

DFX has also been assigned to pregnancy category C by the FDA. Animal studies have revealed evidence of embryo fetotoxicity (i.e., decreased offspring viability, increased renal anomalies). The manufacturer recommends that DFX

should only be used during pregnancy, when the potential benefits outweigh the potential risks to the developing fetus (Deferasirox SPC, preclinical safety data). There are no adequate and well-controlled studies regarding DFX in pregnant women. We agree that DFX should be used during pregnancy, only if the potential benefit exceeds the potential risk to the fetus [23, 24].

Embryofetal developmental studies regarding DFX in animals, resulted in maternal toxicity, but no fetal harm was observed (Deferasirox SPC, preclinical safety data). The important message seems to be that teratogenic and embryo toxic effects were not noted after inadvertent iron chelation therapy with DFX in early pregnancy.

Interestingly, our study involves—among our patient cohort—2 patients having received DFX inadvertently for long-time intervals during pregnancy. Actually, they are 2 of the longest—if not the only such long intervals—reported until today: 14 and 10 weeks of inadvertent use of DFX during the first months of pregnancy in thalassemic women. No fetal anomalies were reported in these successful pregnancies.

Furthermore, it has been reported that DFX treatment for 3 or more years reversed or stabilized liver fibrosis in 83 % of patients with iron-overloaded  $\beta$ -thalassemia [25]. This therapeutic effect was independent of reduced concentration of liver iron or previous exposure to hepatitis C virus [25]. We also confirm the aforementioned findings, because the degree of the liver fibrosis increased in the pregnant patients of our cohort who had to stop DFX, due to their pregnancies. Nevertheless, one patient of our study had enough time (at least 3 years) to receive DFX after her delivery, resulting to a decrease at the levels of liver fibrosis. Compliance to treatment is another vital factor, which affects the results and should be taken into account. We gave our maximum efforts to ensure high rates of compliance to treatment, when it was necessary, always counting in the psychological burden  $\beta$ -thalassemic patients carry and giving comfort and support to them.

In conclusion, the use of chelation before embarking upon a non-programmed pregnancy is conflicting. In our cases, inadvertent chelation treatment with DFX during the first trimester of pregnancy did not prevent delivery of healthy children. Nonetheless, it should be noted that the use of DFX is contraindicated in pregnant women and during breastfeeding, based on the approved product label. Further studies are needed to confirm these results.

## Learning points

- The life expectancy of thalassemic patients has recently increased approaching that of healthy individuals, mainly due to safer blood transfusions, the availability

of three iron chelators, new imaging techniques, treatment of hepatitis and closer follow-up. However, there are no adequate and well-controlled studies in pregnant thalassemic women regarding the role of chelation.

- Generally, iron chelation therapy is not recommended during pregnancy.
- In our study, inadvertent chelation treatment with deferasirox at early pregnancy did not prevent delivery of healthy children. Nonetheless, the use of deferasirox, deferoxamine and deferiprone is contraindicated in pregnant and/or breastfeeding women. These drugs should be used during pregnancy, only if the potential benefits outweigh the potential risk to the fetus.

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**Compliance with ethical standards**

**Conflict of interest** We declare we have no conflict of interest.

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