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ORIGINAL ARTICLE

Pregnancy in patients with thalassemia major: a cohort study and conclusions for an adequate care management approach

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Abstract An improvement in quality of life and survival occurred among thalassemia major (TM) patients: pregnancy in such patients has become a reality. Safe pregnancy and delivery require efforts to ensure the best outcomes. Between 2007 and 2016, 30 TM patients had 37 pregnancies. We analyzed the hematological parameters before, during, and after pregnancies and in 19 patients a cardiovascular magnetic resonance (CMR) T2* was performed. The mean age at first pregnancy was 30 ± 4 years; the current mean age is 35 ± 5 years. Twenty-four patients (80%) had a single pregnancy, five patients (17%) had two pregnancies, and one patient (3%) became pregnant three times. Seventeen pregnancies (46%) were spontaneous, 20 (64%) needed gonadotrophin-induced ovulation and/or reproductive technologies. All pregnancies resulted in live births. Seven were twin pregnancies (19%). The mean gestational hemoglobin was 9.2 ± 0.5 g/dl, lower than pre- and postpregnancy (9.8 ± 1 g/dl, p = ns and 9.6 ± 1 g/dl, p = 0.02, respectively). Median ferritin levels increased progressively (1071, range 409–5724 ng/ml, before pregnancy vs 2231, range 836–6918 ng/ml, after pregnancy, $p < 0.0001$). CMR before pregnancy showed a normal cardiac T2* (mean 35.34 ± 8.90 ms) and a mean liver iron concentration (LIC) of 3.37 ± 2.11 mg/g dry weight (dw). After pregnancy, the mean cardiac T2* was 31.06 ± 13.26 ms and the mean LIC was significantly increased (9.06 ± 5.75 mg/g dw, p = 0.0001). Pregnancy is possible and safe in thalassemia major. During pregnancy, iron accumulates, especially in the liver; a prompt resumption of chelation after delivery is mandatory.

Keywords Thalassemia major · Pregnancy · Delivery · Hypogonadism · Magnetic resonance T2*

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Introduction

Thanks to the developments in blood transfusion support, major strides have been achieved in prolonging the life expectancy in thalassemia major (TM) patients and improving their quality of life [1–4]. Blood transfusions, however, were associated with iron deposition in the pituitary gland and subsequent hypogonadotropic hypogonadism. Despite regular transfusions, patients used to suffer from delayed or absent onset of puberty and infertility. Advances in iron chelation allowed a maximum benefit of blood transfusion all with prevention of excess iron in tissues [5–8]. These benefits haven translated in higher standards of life over the last decades [3]. Family planning and pregnancy consideration for female patients have become a reality that physicians taking care of thalassemia patients have to address. Nowadays, spontaneous pregnancies or requests to have children are quite common in TM patients [9–11]. Since pregnancy in TM patients takes many dimensions, different specialists are invited to get on board to ensure the best outcomes for patients.

The aim of this paper is to review our experience, describing the approach, the follow up, and the outcomes of pregnancies in patients with TM followed in two centers and proposing cases of clinical practice advice for the management of this condition.

Methods

Study population

From 2007 to 2016, we evaluated 34 TM women who desired to become pregnant at the Rare Disease Centre at Fondazione IRCCS Ca' Granda in Milan and at Division of Hematology and Oncology at the American University of Beirut Medical Centre: 30 patients had pregnancies in this period of time (37 pregnancies); two patients were not considered eligible for pregnancy for very high thrombotic risk and two patients underwent inductions and embryo transfers without success.

We considered their conditions and complications of TM present at the time of their request. We analyzed the hematological parameters before, during, and after pregnancies (hemoglobin and ferritin levels, iron intake). We recorded complications during pregnancies, delivery, and babies' outcomes and, in a subgroup of 19 patients, cardiac and liver iron overload changes before and after pregnancies. We registered chelation treatment before and after delivery, as all patients stopped chelation treatment after the positivity of pregnancy test.

Hematological parameters

We analyzed mean hemoglobin (Hb) and ferritin levels at least 6 months before and after pregnancy and during pregnancy. Iron intake (mg Fe/kg/day) was calculated with the formula: (volume of blood red cells transfused × hematocrit × 1.08)/weight of patients (kg)/days.

Assessment of myocardial T2* and cardiac function by CMR

A cardiovascular magnetic resonance (CMR) T2* was performed before and after pregnancies to register cardiac and hepatic iron load in 19 patients. One patient had no CMR T2* pre-pregnancy; three patients had no CMR T2* after pregnancy. CMR T2* was performed at the CMR Unit Department of Cardiology "A. De Gasperis" at Niguarda Ca' Granda Hospital in Milan, using a 1.5 T MR scanner (Avanto Siemens, Erlangen). All T2* images were analyzed using postprocessing software (CMR Tools, Imperial College, London). CMR evaluation was performed blinded to patients' clinical data and the calculation was performed by a single operator. Normal cardiac T2* was defined >20 ms; T2* <10 ms indicated severe cardiac siderosis and T2* between 10 and 20 ms moderate-to-mild cardiac siderosis. MIC was calculated from T2* value with the formula described by Carpenter et al.: Fe (mg/g dry weight (dw) = $45 \times (T2^*)^{-1.22}$ [12].

Assessment of liver iron concentration

Liver iron concentration (LIC) was calculated from liver T2* applying the formula $[1/(T2^*/1000)] \times 0.0254 + 0.202$ [13].

Induction of pregnancy

Spontaneous and induced pregnancies were registered. In induced pregnancies, controlled ovarian stimulation was initiated on days 2–3 of a withdrawal bleeding, after discontinuation of hormonal replacement therapy. Highly purified hMG (75 FSH/75 LH, Meropur, Ferring Pharmaceuticals) or recombinant FSH/LH (150 rFSH/75 rLH, Pergoveris, Merck-Serono) was administered daily. The initial dose was chosen according to clinical history, ovarian appearance, and the expected number of mature follicles needed. Serum concentration of antimullerian hormone was considered a feasible criterion for the choice of the starting dose, since it does not give reliable information on ovarian reserve and response because of chronic hypogonadotrophic hypogonadism and effects of previous hormonal replacement therapy. From day 6 onward, the daily gonadotrophin dose was estimated according to serum estradiol levels and a transvaginal US. In order to reduce the risk of multiple pregnancy, controlled ovarian stimulation for temporized sexual intercourses or intrauterine insemination was canceled or turned into an in vitro fertilization cycle when more than three leading follicles are growing. Final oocyte maturation was triggered with the use of 5000–10,000 IU highly purified hCG (u-hCG, Gonasi, IBSA Pharmaceuticals) or 250 μg recombinant hCG (r-hCG, Ovitrelle, Merck-Serono) when the mean diameters of the leading follicle/s were >18 mm. Couples were instructed for having sexual intercourses within 48 h from triggering, while intrauterine insemination or oocyte retrieval was scheduled 36 h after hCG injection. Luteal phase supplementation with vaginal progesterone (Progeffik 200 mg, Effik Pharmaceuticals—Crinone 8%, Merck-Serono) was given until pregnancy test and, in case of pregnancy, continued until the 12th week.

Statistical analysis

For continuous variables, we reported mean and standard deviation (SD). For ferritin level, which had a right-skewed distribution, we presented the median (with range minimum-maximum). Crude comparisons of continuous variables between the period before, during, and after pregnancy were performed with Student's paired *t* test [14].

Results

Patients' characteristics

Patients' characteristics before pregnancies are shown in Table 1. Thirty-four patients have been evaluated for the desire of pregnancy but only 30 women were enrolled and they had overall 37 pregnancies between 2007 and 2016. Out of 34, two patients were not considered eligible for pregnancy for very high thrombotic risk and two patients underwent induction and embryo transfer without success. The current mean age is 35 ± 5 years, while the mean age at the first pregnancy was 30 ± 4 years. At baseline, in all patient's first pregnancy, the mean Hb level was 9.8 ± 1 g/dl, the mean iron intake was 0.33 ± 0.08 mg iron/kg/day, the median ferritin levels were 1071 ng/ml (range 409–5724 ng/ml). CMR T2*, available for 18 patients before pregnancy, showed a normal cardiac T2* (mean 35.34 ± 8.90 ms) and a mean LIC of 3.37 ± 2.11 mg/g dw; only four out of 18 patients (22%) presented a mild/moderate liver iron overload (mean LIC of 6.27 ± 2.66 mg/g dw). In the total group of patients, six Italian patients were HCV-RNA positive before pregnancy; none of the patients was positive for chronic hepatitis B.

Pregnancies and their development

All pregnancies characteristics are reported in Table 2. Twenty-four patients (80%) had a single pregnancy, five patients (17%) had two pregnancies, and one patient (3%) became pregnant spontaneously three times. All 37 pregnancies, but 17 (46%) which were spontaneous, were conceived after gonadotrophin-induced ovulation and/or reproductive technologies. Seven were twin pregnancies (19%). In all patients' first pregnancy, the mean gestational pre-transfusion Hb level was 9.2 ± 0.5 g/dl, slightly lower than their pre- and postpregnancy values (9.8 ± 1 g/dl, p = ns and 9.6 ± 1 g/dl, $p = 0.02$, respectively). The iron intake did not change significantly during pregnancy; chelation was stopped and transfusion intervals were shorter. It has been shown an increase in iron overload, considering ferritin levels and CMR T2* data. Median ferritin levels increased progressively (1071, range 409–5724 ng/ml, before pregnancy vs 2231, range 836–6918 ng/ml, after pregnancy, $p < 0.0001$). After pregnancy the CMR T2* was available in 16 patients (one patient refused, two patients have not yet done): the mean cardiac T2* was stable (31.06 ± 13.26 ms) and the mean LIC was significantly increased from pre-pregnancy value (9.06 ± 5.75 mg/g dw, $p = 0.0001$). Three out of 16 patients (19%) had cardiac iron overload and 12 out of 16 (75%) liver iron overload after pregnancy. Two out of three patients (67%) showing cardiac iron overload after pregnancy had a moderate liver iron overload before pregnancy. In two patients with multiple pregnancies, hepatic iron overload was persisting during the subsequent pregnancies. All pregnancies proceeded without cardiac, endocrinologic (e.g., hypothyroidism or diabetes), or thrombotic complications. No transfusion reactions occurred and no immunization developed during pregnancies.

Delivery and puerperium outcome

All 37 pregnancies resulted in live births. All patients but two underwent caesarean section. One patient had three natural deliveries and another had a single spontaneous delivery. The mean of the weeks before delivery was 37 ± 2: three patients (10%) delivered before week 35. All patients were

Table 1 Patients' characteristics before pregnancy (overall population for all pregnancies)

	All patients (n = 30)	Lebanese patients (n = 11)	Italian patients (n = 19)
Actual mean age ± SD, years	35 ± 5	33 ± 5	37 ± 4
Mean age at pregnancy ± SD, years	30 ± 4	28 ± 3	32 ± 4
Race (Caucasian/oriental/other), n	30:0:0	0:0:11	19:0:0
Mean pre-transfusional ± SD, g/dl	9.8 ± 1	10.0 ± 4.8	9.6 ± 0.6
Mean iron intake (mg Fe/kg/day)	0.33 ± 0.08	0.27 ± 0.06	0.37 ± 0.07
Median serum ferritin, ng/ml	1071 (409–5724)	1279 (586–5724)	841 (409–2970)
Mean LIC ± SD, mg/g dw[a]	3.37 ± 2.11	/	3.37 ± 2.11
Mean cardiac T2* ± SD, ms[a]	35.34 ± 8.90	/	35.34 ± 8.90
MIC, mg Fe/g dw[a]	0.64 ± 0.23	/	0.64 ± 0.23

SD standard deviation, *LIC* liver iron concentration, *MIC* myocardial iron concentration

[a] Data available for a subgroup of Italian patients (see text)

Table 2 Pregnancies characteristics

	All patients (n = 30)	Lebanese patients (n = 11)	Italian patients (n = 19)
Total pregnancies, n	37	15	22
Type of pregnancy, n (spontaneous/induced)[a]	17:20	11:4	6:16
Twin pregnancies, n (%)	7 (26)	4 (27)	3 (14)
Mean weeks before delivery, n (%)	37 ± 2	38 ± 2	36 ± 2
Caesarean delivery, n (%)[a]	33 (89)	14 (93)	19 (86)
Pregnancies with live births, n (%)	37 (100)	15 (100)	22 (100)
Live births, n (total n = 44, M:F)	21:23	9:10	12:13
Mean birth weight (g)	2593 ± 640	3060 ± 746	2544 ± 713

[a] A single patient had three pregnancies with natural deliveries; another patient had natural delivery in a single pregnancy

treated after delivery with antibiotics and antithrombotic prophylaxis.

Complications of pregnancies and deliveries

Some complications were registered during pregnancy and after delivery. The pregnancies and delivery complications are shown in Table 3. The patient who had three pregnancies developed hypertension and proteinuria during all the pregnancies; two patients had rupture of their membranes, one patient developed "placenta accreta," one patient had placenta previa with postpartum prolonged bleeding, one patient had placental abruption, two patients presented postpartum subfascial hematoma, two patients developed postdelivery hypertension, and a patient developed polyhydramnios.

Outcomes in newborn

All pregnancies resulted in 44 live births (Table 2): 21 babies were males and 23 were females. None of the newborns had any complication at birth. The mean birth weight was 2593 ± 640 g. In Lebanese cohort, the mean weight at birth was slightly higher than that detected in Italian cohort (Table 2). Only two twins, with premature birth at 31 weeks, had a body weight under 1000 g and they needed to stay in the Intensive Care Unit for a period of 3 months.

After pregnancy and delivery, no babies showed HCV-RNA positivity during their clinical monitoring.

Table 3 Pregnancies complications (only in Italian population)

	All pregnancies (n = 37)
Total pregnancies with complications	13
Hypertension and proteinuria[a]	3
Postdelivery hypertension	2
Placenta accreta	1
Rupture of membranes	2
Postpartum subfascial hematoma	2
Postpartum prolonged bleeding in placenta previa	1
Placental abruption	1
Polyhydramnios	1

[a] A single patient had three pregnancies with hypertension and proteinuria

Iron chelation treatment

Chelation treatment was stopped in all patients after the positivity of pregnancy test. Before pregnancy, eight patients were on deferoxamine treatment, 16 on deferasirox, two on deferiprone, one on deferoxamine + deferasirox, and one on deferoxamine + deferiprone. For two patients, we had no data available regarding chelation treatment before pregnancy. All patients restarted iron chelation 2 or 3 weeks after delivery.

Discussion

For many years, pregnancy was impossible due to hypogonadic hypogonadism and considered as high risk for TM patients. In fact, pregnancy is associated with several perturbations in hormonal levels, cardiac function, and coagulation, all of which amplifying the baseline high risk among TM patients [15–18]. Thanks to the rigorous pre-pregnancy evaluation and strict follow-up throughout pregnancy and postdelivery, none of our patients developed diabetes, heart failure, or thrombosis. While pre-existing evidence supporting our strategy is lacking, our efforts were in fact inspired to a large extent by the guidelines and recommendations of the Thalassemia International Foundation [19]. Collaboration among different specialists including the hematologist, gynecologist, endocrinologist, geneticist, psychologist, cardiologist, hepatologist, anesthetist, and transfusion medicine specialist is key for planning and follow-up throughout pregnancy. In our cohort of patients, the team-based approach was instrumental for both counselling and management of acute complications (e.g., bleeding in placenta accreta, identification of a hematoma, treatment of hypertension, and management of complications).

In our study, the patients were evaluated for fertility in order to manage a spontaneous or induced conception (with induction of ovulation or spermatogenesis or with the use of reproductive technologies, as gynecological guidelines). In addition, partners were screened for thalassemia syndromes. Overall, we found that younger women had a higher rate of spontaneous conception and less complications at delivery. Pre-conception counselling is necessary to detect the presence of silent mutations in partners' carriers and issue recommendations accordingly. Patients had a complete physical examination (Fig. 1). In Fig. 1, we reported all the parameters and the different clinical aspects that we analyzed in our population and that we suppose to be evaluated before planning a pregnancy in TM patients. Tuck et al. in 2005 and recently Petrakos et al. suggested a pre-pregnancy assessment, and the criteria listed in the TIF guidelines were even more precise [20, 21]. Patients must be evaluated from a gynecological, cardiac, endocrine, hematologic, hepatologic (if necessary), and psychological points of view. The assessment of the cardiac function including electrocardiogram (ECG), Holter ECG, echocardiographic examination, and a clinic visit to the cardiologist. Patients who had any baseline cardiac dysfunction or arrhythmias were recommended to avoid pregnancy. In our cohort, none of the patients sustained any heart failure, alteration of cardiac parameters, or cardiac overload at CMR T2*: only one patient reported having prior surgery for closing an inter-atrial defect (ostium secundum) in her personal medical history, without episodes of heart failure or cerebral damage. In a report in 2005, Tuck et al. described their experience with TM mothers' previous cardiac dysfunction getting pregnancy. Two patients passed away 10 days and 9 months, respectively, after delivery [20]. A detailed endocrinology evaluation is needed to assess thyroid and adrenal function, bone health, and alterations in glucose metabolism. From the hematological/internist point of view, the ferritin levels and cardiac and liver CMR T2* need to be assessed before and after pregnancy. Up to now, papers describing pregnancies in TM patients [9, 10, 16] did not report data about iron overload during pregnancies. In 2014, Al-Riyami et al. described the increasing of LIC assessed by CMR T2* in three patients affected by TM after pregnancy: none of them developed cardiac iron overload. One of those patients was chelated in the third trimester [10]. In our population, at CMR T2* before pregnancy, all patients had a normal cardiac T2* and only four out of 18 (22%) presented a mild/moderate liver iron overload. After pregnancy, three out of 16 patients (19%) had cardiac iron overload and 12 out of 16 (75%) showed liver iron overload. Moreover, two out of three patients (67%) that showed cardiac iron overload after pregnancy had a moderate liver iron overload before pregnancy. These findings suggest that hepatic iron overload can precipitate cardiac iron overload. Therefore, we suggested to screen all patients for cardiac and liver iron overload and optimize iron chelation therapy prior to pregnancy. Our approach is to achieve a ferritin level of 1000 ng/ml or below, in the absence of evidence of cardiac or hepatic iron overload at CMR T2*. In literature, the estimated increase of serum ferritin is around 10% and is mainly related to the withdrawal of chelators and the increased need for blood transfusions [20, 22].

In addition, our serology panel included testing for hepatitis B surface antigen (HBs Ag), hepatitis C antibodies (HCV Abs), human immunodeficiency virus antibodies (HIV Abs), rubella, toxoplasma antibodies, and cytomegalovirus antibodies (CMV Abs). In the Italian cohort of patients, we had six

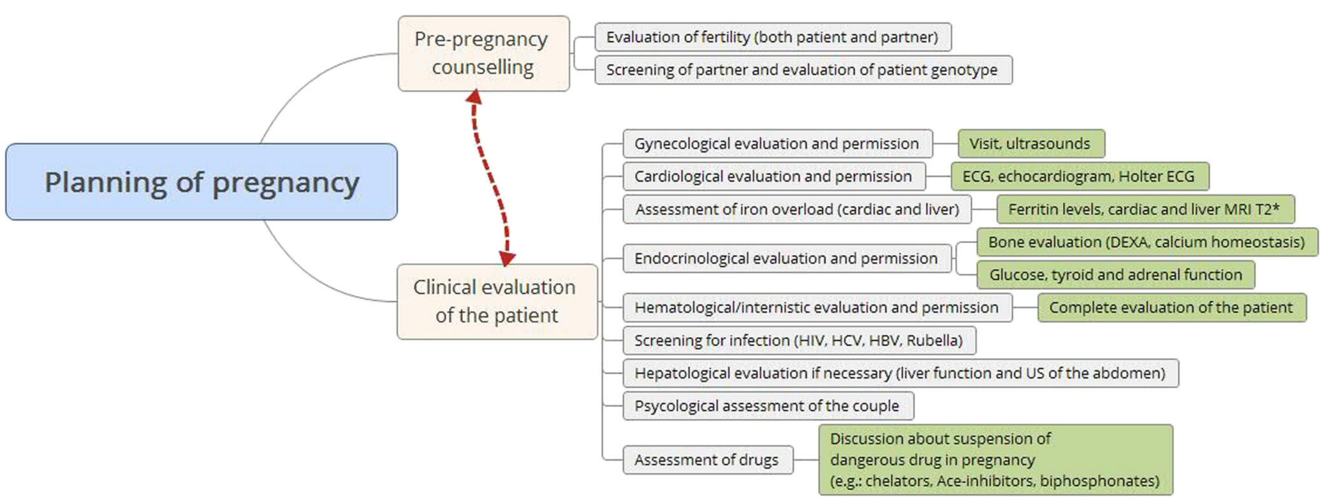

Fig. 1 Advices for evaluation of the desire of pregnancy in TM patients

HCV-RNA-positive patients without a vertical transmission to babies: nowadays, the different and diffuse treatments for hepatitis C will lead to a high reduction of cases of active hepatitis C in thalassemia patients, also in patients asking for a pregnancy in future.

We also referred the couples for psychological evaluation before pregnancy. Recent evidence showed a higher rate of anxiety and depression among pregnant TM patients, compared to controls [23]. This highlights the importance of effective psychological support all throughout pregnancy and even postpartum. A careful evaluation of polypharmacy is another critical aspect for successful pregnancy. Many medications such as bisphosphonates and hydroxyurea deemed not safe in pregnancy need to be stopped 6 months before pregnancy. Iron chelation treatment should also be interrupted at least for the first trimester given the potential harms associated with their use on fetal outcomes [24]. Antihypertensive drugs and other medications for the cardiovascular system were carefully evaluated as part of our pre-pregnancy evaluation. Once pregnancy started, regular checks of cardiac, liver, and thyroid functions were conducted aimed at detecting subtle changes that warrant monitoring or treatment (Fig. 2). During this period, preparation of packed red cells is strictly monitored, with a regular check for red cell antibodies. The transfusional support during pregnancy is increased [16, 20], with target transfusion threshold at hemoglobin of 10 g/dl. In our cohort, no significant differences were detected in iron intake before, during, and after pregnancies: we have to speculate about the accuracy of iron intake formula during pregnancy. Weight progressively increase throughout pregnancy, and in clinical practice, in our patients, we clearly observed an increase in the total volume of blood transfused due to the increased frequency of transfusional support: as those parameters are a component of the iron intake formula, those changes may impair the usefulness of the formula. Given the physiological increase in the pregnant woman's weight, the iron intake formula is not reliable in this setting.

A close cooperation between the hematologist/internist, gynecologist, transfusion medicine specialists, and anesthetists has to be established before and during delivery. The decision about delivery timing is taken at the team level, and a unanimous decision is relayed to the patient. In accordance with the TIF guidelines, and in line with our prior clinical experience, we recommended Caesarean section since it is safer than vaginal delivery in thalassemia patients, especially with the high prevalence of cephalopelvic disproportion among newborn [19, 20]. Caesarean delivery also prevents a prolonged delivery, with all the associated risks to the mother and the newborn [25]. Caesarean delivery is of particular importance for pregnant women with diabetes and cardiac problems. The preparation of packed red blood cells, especially in patient with alloimmune antibodies, prior to transfusional reactions is logistically more feasible ahead of time with caesarean delivery. Epidural anesthesia is highly desirable whenever feasible, due to the risk of difficult intubation in some patients with altered maxillo-facial configuration and to the risks associated with general anesthesia [19]. After delivery, antibiotic therapy and antithrombotic prophylaxis are rapidly instituted owing to the increased risk of infection and thrombosis (particularly in splenectomized patients) [17]. Psychological

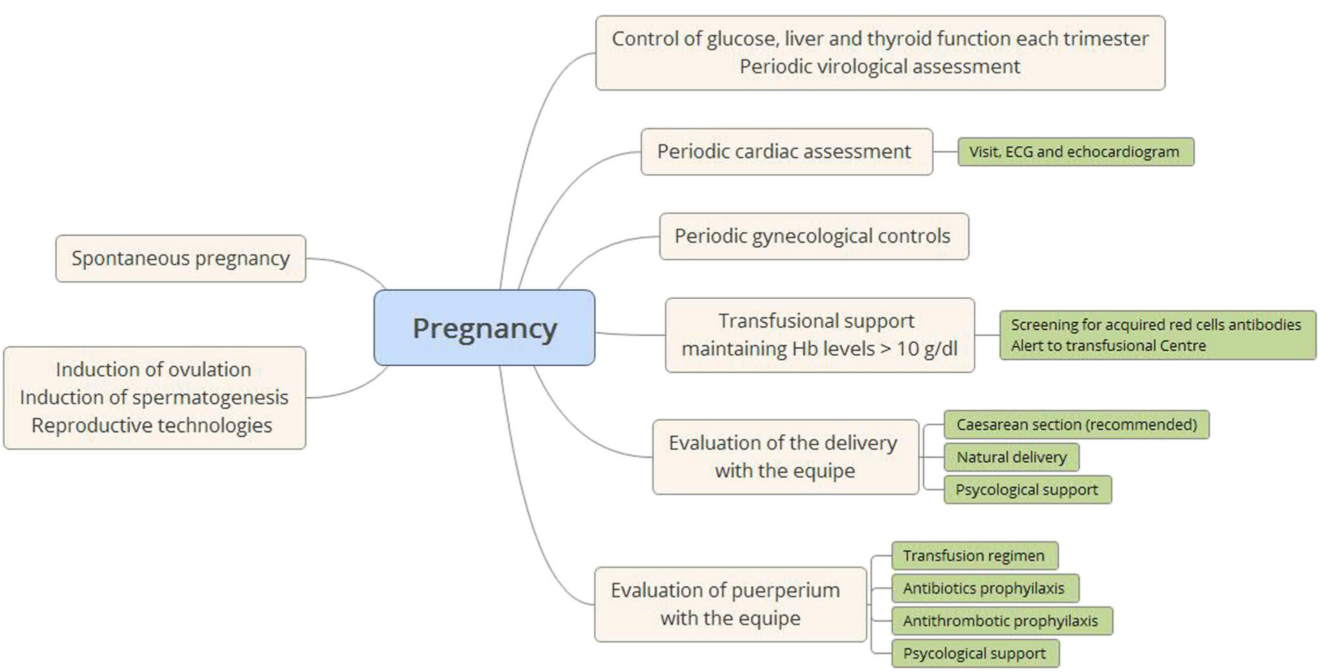

Fig. 2 Management of pregnancies in TM patients

support is advisable for the management of the babies and of the new familiar life: particular attention must be paid to early signs of anxiety and depression symptoms. In TIF guidelines, breastfeeding is encouraged in all cases except in the presence of HIV and/or hepatitis C RNA-positive and/or HBsAg positivity, because of the risk of vertical transmission [19]. Rapid restarting of chelation therapy should remain a priority after a prolonged interruption period. Emerging evidence supports use of deferoxamine during breastfeeding because of its low concentrations in the breast milk [19, 26]; nonetheless, clinical data about safety in humans is still lacking. Whether prolonged breast feeding with TM patients would exacerbate osteoporosis, not uncommon in this patient with low baseline mineral bone density, remains a question that needs further exploration in future trials [27]. In conclusion, proper counselling of the TM patient prior to pregnancy rests on a global assessment of the disease and individualization of each patient. The importance of collaboration among different specialists taking care of the pregnant patient cannot be overemphasized. Despite the improved outcomes in pregnant TM patients, there remain many unanswered questions regarding iron overload and best chelation therapy that need to be addressed in future clinical trials.

Compliance with ethical standards All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki declaration of 1975, as revised in 2008.

Informed consent was obtained from all patients for being included in the study.

Conflict of interest The authors declare that they have no conflict of interest.

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