At term pregnancies in transfusion-dependent beta-thalassemic women

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Summary

The health background management and outcome of five pregnancies in women affected by Cooley Disease are described and the preconceptual guidance and care are considered. The patients were selected from a group of 103 thalassemic women divided into three subgroups according to their first and successive menstruation characteristics. Only one woman needed induction of ovulation. A precise and detailed pre-pregnancy assessment was done before each conception. All the women were in labour at 38 weeks' gestation, and five healthy babies were born at term, weighing between 2,600 and 3,200g. The improvement in current treatments will result in a continuous increase in pregnancies in thalassemic women, making pregnancy a real eventuality for them. Furthermore, we are studying the possibility of collecting foetus umbilical cord blood after delivery, with the aim of obtaining complete marrow reconstitution in an attempt at heterologous transplantation to the mother.

Key words: Beta-thalassemia major; Fertility; Pregnancy; Umbilical cord blood; Transplantation; Marrow reconstitution.

Introduction

Beta Thalassemia major, also called Cooley disease, is a severe transfusion-dependent kind of anaemia which often causes infertility. It is due to iron deposits in the endocrine organs following the multiple blood transfusions needed for this illness. Gonadal function is impaired in most patients affected by the homozygous kind of this disease. It is especially prevalent in females and is expressed either by a delay in the onset of puberty and menstruation or by secondary amenorrhoea [1]. The commonest abnormality is hypogonadotropic hypogonadism, but the relatively high prevalence of other endocrine impairments, causing multiple endocrinopathies, is also well recognised. These kinds of endocrine complications are related to serum ferritin levels and to cumulative hemosiderosis [2]. The aetiology of the above-mentioned reproductive disorders is linked to the anatomical and functional disarray affecting the components of the central nervous system-gonadal axis (the functionality is often impaired at all three levels, i.e. gonads, anterior pituitary and hypothalamus) but it is almost always primarily caused by pituitary dysfunction [3-5]. Up to the end of 1980 there were not many reports of pregnancy in patients with beta-thalassemia major and, only a few of them were carried out successfully [6-8]. Nowadays, thanks to improved paediatric and haematological care, patients affected by Cooley disease may live to be 40 or 50, and can enjoy a quite normal standard of life. Thus, maintaining a strict therapeutic regimen, women regularly transfused and well-chelated can attempt pregnancy [9-12]. In this report we describe the evolution and the successful outcome of five at term pregnancies carried out by four women affected by transfusion-dependent beta-thalassemia. After reviewing the care and the complications during and after their pregnancies, the issue concerning the appropriate preconception counselling of such patients is discussed.

Materials and Methods

For several years we have been following 103 women from an endocrine and reproductive perspective. They were affected by transfusion-dependent beta-thalassemia major which had been diagnosed when they were between 6 and 8 months old. All patients attended the Paediatric Institute of Catania University and were aged between 18 and 30. They received a blood transfusion every 15-20 days in order to maintain a haemoglobin concentration above 10 g/dl, and were under strict desferrioxamine chelating therapy to avoid excessive iron overloads. The patients were divided into three groups according to their first and successive menstruation characteristics: 1) patients with primary amenorrhoea, 2) patients with secondary amenorrhoea and, 3) patients with normal menstruation. In detail, of these 21 women who desired children: five were affected by primary amenorrhoea, six with secondary amenorrhoea and the remaining ten women had normal menstruation. Finally five pregnancies occurred among these 21 women: two among the patients who were affected respectively by primary and secondary amenorrhoea, and three were carried out by women with spontaneous menstruation. It is remarkable that two of the last three pregnancies were carried out successfully by the same woman; thus a total of four women were followed (Table 1). Average values of ferritin fluctuated between 500 and 1,000 ng/ml, and AST and ALT transaminases were between 25 and 100 U/l. All patients were vaccinated against hepatitis B virus (HBV), and two were splenectomized, particularly the woman affected by primary amenorrhoea and one woman with normal periods. Only the woman affected by primary amenorrhoea needed induction of ovulation to stimulate her pregnancy. The evaluation of eligibility depends on the results of a series of examinations regarding the heart, kidneys, thyroid, pancreas and peripheral arteries. Haemosiderotic parenchymal deterioration, particularly of the myocardium, makes these patients

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potentially fragile, while the induction of ovulation may be stressful even for a healthy woman. All the other women had spontaneous and physiological pregnancies. Finally it is important to emphasize that all the partners of these women were negative for the thalassemic trait.

According to the guidelines previously established by Tuck *et al.* [13], a precise and detailed pre-pregnancy assessment was done before each conception. It consisted of a series of clinical and laboratory assays, including checks for diabetes and hypothyroidism, hepatitis B and C and for blood group antibodies. Cardiac function was assessed symptomatically and by echocardiography and exercise electrocardiography. Rubella immunity was checked and immunisation was given when a woman was found to be susceptible. During pregnancy the monitoring of all these factors continued, including frequent checks for aminotransferase (AST and ALT transaminases).

The frequency of blood transfusions had to be increased with the aim of maintaining the pre-transfusion haemoglobin concentration. Desferrioxamine therapy was stopped as soon as pregnancy was diagnosed (even if in the literature several cases have been reported in which no direct toxicity had been observed [14]) because the average values of ferritin were just a little higher than the normal range. Probably during gestation the foetus keeps the values almost normal due to a particular chelating activity. Therapy was quickly resumed after delivery which was justified because even if toxic levels of iron are associated with severe complications and can be fatal, the effective iron chelator, deferoxamine, has possible teratogenic risks [15].

Other pregnancy monitoring for blood pressure, proteinuria, fetal growth and care during labour and delivery were carried out according to usual obstetric practice and criteria.

Results

Only one out of the five pregnancies we followed required the induction of ovulation. Moreover, the same woman carried out two of the pregnancies. All the women were in labour at 38 weeks' gestation, and five healthy babies were born at term weighing between 2,600 and 3,200 g. Caesarean delivery was preferred because of the frequent "infertility/sterility" that occurs in the natural history of patients with this impairment. None of these women was either HIV positive or suffered from diabetes, however they were controlled with a diet. All of them had increased transaminases, but in only one case was it necessary to practice a therapy based on "silimarina". Moreover all women had transfusion-transmitted hepatitis C prior to pregnancy, but only the one affected by secondary amenorrhoea received interferon two years before embarking on pregnancy because she tested positive for HCV-RNA. Four of the newborns were HCV negative: only one was HCV positive but HCV-RNA negative, so it was unnecessary to prescribe therapy.

Finally, no cardiac dysfunctions, kidney diseases, or other important problems were reported.

Discussion

We believe that several ethical and theoretical questions should be evaluated before considering technical problems. We should never forget that beta-thalassemic patients are fragile and are knowingly exposed to a lot of risks. The responsibility to decide which patients should have ovulation induction when needed, pregnancy and labour with an acceptable amount of risk, and to fix safety limits rests with physicians. The possibility of inducing pregnancy in women affected by such a disease was judged to be "perfectly moral from the Catholic point of view" by the Center for Bioethics of the Catholic University of the Sacred Heart, Rome, as has been explained in previous studies regarding this matter [16].

Finally, the improvements in current conventional treatments, especially in the management of iron deposits, the longer survival rates, and the new approaches to assisted conception, when needed, will result in a continuous increase in pregnancies in women affected by beta-thalassemia. Due to continued advances in treatment since the 1980s, and to periconceptional counselling – which limits pregnancy only to women in good general condition – intrauterine growth retardation, foetal loss and preterm labour are remarkably reducing.

To sum up we have reason to believe that pregnancy is now a real possibility for women affected by Cooley disease who are regularly transfused and well-chelated. Pregnancy does not have devastating effects on the course of the disease nor on the foetus's general well being As a matter of fact, it seems that the evaluation of cardiac function, combined with a low iron load and satisfactory endocrine and hepatic controls can ensure a full term pregnancy with minimal adverse effects, and no severe obstetric complications except for the high incidence of caesarean section [17].

Thus we can think of it as a normal pregnancy without foetal loss, foetal intrauterine growth retardation and preterm labour. Furthermore we are studying the possibility of collecting a good quantity of umbilical cord blood after foetus delivery and before placental detachment, in an attempt at heterologous transplantation to the mother [18] (Figure. 1). This is a possibility, especially if the mother is totally HLA-matched or also partially matched

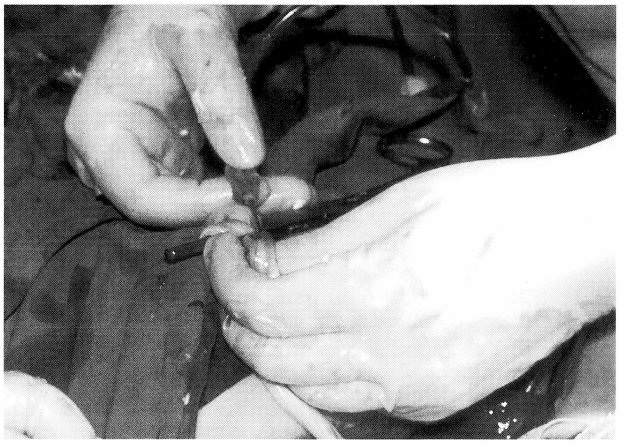

Figure 1. — Photograph showing the collection of umbilical cord blood during a caesarean section performed on a thalassemic woman.

with her newborn because umbilical cord blood has been shown to possess a significant quantity of CD34+ stem cells. These particular haematological stem cells have a great capacity to repopulate bone marrow and are now used to try alternative approaches to several malignant and non-malignant haematological diseases. Following this procedure, after several laboratory passages of CD34+ recovering, metabolism monitoring, enrichment and clonogenic cultures, the aim is for complete marrow reconstitution to a thalassemic mother, thanks to the help offered by her donor-newborn.

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