CASE REPORT

Cyclosporine therapy during pregnancy in a patient with β-thalassemia major and autoimmune haemolytic anemia: a case report and review of the literature

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Abstract
Recent advances in the management of hemoglobinopathies offer an improved potential for safe pregnancy with favourable outcome in patients with β-thalassemia major. Autoimmune diseases that are common in women at reproductive age might be fulminant and hardly manageable in pregnant women with thalassemia. Thus immunosuppressant drugs like cyclosporine A could be necessary in order to maintain good maternal and foetal health. We present a case report of a 35-year-old woman with β-thalassemia major, splenectomy, autoimmune hemolytic anemia and insulin treated diabetes mellitus who was treated with cyclosporine A during her pregnancy, and delivered a healthy male infant. First line therapy with steroids was ineffective, due to deregulation of diabetes mellitus.

Keywords: Autoimmune hemolytic anemia, cyclosporine A, immunosuppressant, pregnancy, thalassemia major

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Introduction

Recently, life expectancy of patients with β-thalassemia major (β-TM) has greatly improved, as a consequence of better transfusion regimens and regular chelation programs. It has recently been reported that 91% of the women with thalassemia that achieve pregnancy spontaneously or following gonadotropin induced ovulation has delivered successfully healthy infants[1]. However, pregnancy in thalassemic women is considered of high risk- monitoring by a group of specialists is mandatory[2].

Increased survival contributed to the emergence of new problems among the thalassemic patients such as autoimmune conditions, nephritis, diabetes, arthritis, fibromyalgia and asthma[3-5]. Autoimmune diseases are common in women of reproductive age and are either fulminant or hardly manageable during pregnancy[6]. Since several immunosuppressive drugs are found to be harmful for the babies, new drugs that could secure both mother's and foetal life like cyclosporine A become valuable.

Autoimmune hemolytic anemia (AIHA) is an immune disorder caused by antibodies directed against unmodified autologous red cells. The disorder may be a primary (idiopathic) or a secondary disease. Autoimmunization to erythrocyte antigens is a frequent complication in patients with β-thalassaemia major. Several factors might contribute to the high autoimmunization rate, including non- phenotypic blood exposure and alloantibody formation prior to positive Coombs test. The diagnosis is based on the presence of anemia along with several signs of haemolysis such as reticulocytosis, low haptoglobin, increased lactate dehydrogenase, elevated indirect bilirubin, and positive direct antiglobulin test (Coombs test). Corticosteroids and/or immunoglobulin are considered as first line therapy, while cyclosporine A, vincristine, cyclophosphamide, rituximab, and other immunosuppressive drugs can be used in unresponsive patients [3,7,8]. Autoimmune hemolytic anemia is rarely reported in pregnancy and may influence the newborn causing fetal erythroblastosis and anemia. When the hemolytic process is well controlled with treatment, prognosis seems to be quite good for the fetus[8].

Cyclosporine A (CsA) is an immunosuppressive agent that attenuates T -cell mediated responses by inhibiting the formation of interleukine-2 (IL-2). It was first used to prevent successfully kidney and liver transplant rejection. Cyclosporine A is also used in a number of autoimmune diseases such as dermatological-psoriasis, severe atopic dermatitis, pyoderma gangrenosum, rheumatologic-rheumatoid arthritis, ulcerative colitis and Crohn's disease[6].

Herein, we describe a case of a pregnant woman with β-thalassemia major, AIHA and insulin treated diabetes mellitus (DM) II, who delivered a healthy child while treated with cyclosporine A. The patient gave consent to the publication of this report. We also present a brief review of the literature.

Case Report

A 35-year-old thalassemic woman with normal menstrual cycle was following a regular transfusion schedule since 6 months of age in order to maintain haemoglobin (Hb) concentration of 9-10 gr/dl. Cholecystectomy and splenectomy were performed at ages of 13 and 14, respectively. Serum ferritin levels varied between 700-1500 ng/ml (normal range: 10-291 ng/ml). When deferiprone became available, it replaced desferioxamine, which was her first chelation

therapy. Echocardiography was within normal limits with ejection fraction between 62-78%. She was sero-negative for Hepatitis C, Hepatitis B, and Human Immunodeficiency Virus (HIV). She was diagnosed with DM II at the age of 19 (1995) and was treated with oral drugs. At the age of 21 (1997), she was diagnosed with AIHA and has started oral steroids as therapy. When diagnosis was established, her laboratory blood results were the following: Direct Coombs was positive IgG(++) C3d (+), indirect Coombs was also positive (+), lactate dehydrogenase (LDH) 700 UI/L (normal range: 0-246 UI/L), total bilirubin levels 7 mg/dl (normal range: 0.3-1.2 mg/dl) and unconjugated bilirubin 5.8 mg/dl (normal range: 0-0.2 mg/dl). The patient was initially treated with prednisolone 1 mgr/kgr/day for three months, without any improvement. Although the patient transfused with compatible blood units, her haemoglobin was quickly reduced due to shorter lifetime of red blood cells. As prednisolone therapy was ineffective, the combination of low dose steroid with intravenous immunoglobulin (400 mg/kgr for 4 days/monthly, for six month) was used as second line therapy. Due to partial response she remained on maintenance therapy with prednisolone 10mg per day. At November 2001 she was started on cyclosporine A (3 mg/kgr/day), since steroids had to be discontinued due to aseptic hip necrosis and direct Coombs was still positive, IgG (+), C3d (+), while indirect Coombs was negative. Then, we attempted twice to interrupt cyclosporine A but we noticed relapse of AIHA since blood transfusion was incompatible, she returned to strongly positive IgG (+++) C3d (+), indirect (+), and we noticed a decrease of haemoglobin.

In 2009 she discussed for the first time the possibility of a future pregnancy and for that reason she stopped receiving cyclosporine A and was started again on steroids along with insulin therapy. Due to poor regulation of diabetes she returned to cyclosporine A. The ferritin levels were 671 ng/ml and her routine evaluation for heart and liver hemosiderosis with T2* weighed magnetic resonance imaging (MRI) was normal. At the age of 34 (2010), she conceived with in vitro fertilization and ceased chelation therapy. At that time her creatinine levels was 0.85 mg/dl, (normal range: 0.66-1.10 mg/dl), urea 49 mg/dl (normal range: 17-43mg/dl), SGOT 32 IU/l, SGPT 40 IU/l (normal range:10-37 IU/l and 10-45 IU/l respectively) with positive direct Coombs IgG (+), C3d (+), LDH 264 UI/L (normal range: 0-246 UI/L) total bilirubin 1.4 mg/dl (normal range: 0.3-1.2 mgr/dl). During pregnancy, she remained hemo-dynamically stable with normal renal function (creatinine 0.75 mg/dl, urea 32 mg/dl) and liver function (SGOT 35 IU/l, SGPT 42 IU/l), normal blood glucose levels under insulin (105mg/dl) and a relative stable condition regarding hemolysis parameters (positive direct Coombs IgG (++), C3d (+,)negative indirect Coombs, LDH 226 UI/L, total bilirubin 1.6mg/dl. The dose of cyclosporine A was adjusted to reach plasma levels of 150-250 ng/ml with monthly monitoring. In the 34th week of gestation, she noticed bleeding and felt labor pains. The pregnancy was considered as high risk and caesarean section was successfully performed. The patient gave birth to a healthy male infant weighting 2410 gr, with normal somatic and psychomotor development without any clinical or laboratory evidence of newborn hemolysis. The last follow up was one month after delivery and during this time she remained stable under cyclosporine A (3 mgr/kgr/day) and with a normally growing child. After a period of 40 days post partum she started chelation therapy with a combination of deferiprone (75 mgr/kgr per day) and desferioxamine (40 mg/kgr subcutaneosly twice a week) as her ferritin level was 2800 ng/ml.

Discussion

During pregnancy, the most suitable way to treat autoimmune disorders and specifically AIHA are corticosteroids, as they are considered to have the least harmful effects to both mother and foetus[8]. However, in our case steroids use had limitations due to co-existing DM. The deregulation of blood glucose levels could easily put in risk the health of mother and foetus.

Immunosuppressive treatment during pregnancy is related to teratogenesis, so drugs such as methotrexate and azathioprine are usually avoided. However, there is conflicting data concerning cyclosporine A. Cyclosporine A is a calcineurine inhibitor routinely used as graft versus host disease (GVHD) prophylaxis after stem cell transplantation. It is classified as having a C category risk by the Food and Drug Administration (FDA), which means that, although the risk to the foetus has not been ruled out in human and /or animal studies, benefits of its use may exceed risk[6]. The most common side effects of cyclosporine A for the mother are renal dysfunction**,** hypertension, cramps, hirsutism, tremor, convulsions, headache, gum hyperplasia, diarrhoea, nausea/vomiting, hepatotoxicity, abdominal discomfort, paresthesia, flushing leucopenia, and lymphoma sinusitis . Babies born from mothers receiving cyclosporine A may be premature or small for gestational age or present congenital malformations (skeletal retardation) that could contribute to increased rate of neonatal morbidity and mortality[6,8,9]. In the present case, the 2410 gr of body weight of the newborn at the 34th week is considered normal.

To our knowledge there is no systemic overview of the use of cyclosporine A in pregnancy, and in fact there are only a few controlled studies of immunosuppressive drugs in pregnancy[9]. All information regarding the use of cyclosporine A during pregnancy is coming from case reports of women who underwent transplantation[6]. Today, some of the women who receive organ transplants are in reproductive age, and they may consider pregnancy after transplantation despite the immunosuppressive medication.

The first post-transplant pregnancy with successful delivery in humans was reported more than 50 years ago, and today, three major registries (European Dialysis and Transplantation Association Registry, UK Transplant Pregnancy Registry and National Transplantation Pregnancy Registry in USA) collect data about post-transplant pregnancies. These registries have together accumulated data from more than 14 000 births among female solid organ transplant recipients[10-12]. In a meta-analysis, concerning pregnancy outcome after cyclosporine A therapy during pregnancy,

the overall prevalence rate for malformations was slightly increased than the range of 2-3% reported for the general population. However, this analysis has limitations[6]. Bearing in mind that the data refer to transplantations, the involved patients usually receive additional drugs with possible teratogenic effect and bias the outcome.

There is very limited data concerning the use of cyclosporine A during pregnancy in β-thalassemic major patients. These patients may be at increased risk of side effects due to impaired liver function secondary to iron overload or blood borne infections[2]. Our patient had not liver impairment, neither functional nor parenchymal, and no side effects were reported during cyclosporin A treatment.

Even though post-transplant pregnancies under cyclosporine A therapy usually have positive outcome, they are associated with an increased risk of hypertension, preeclampsia, miscarriage and pre-term delivery of babies that are small for gestational age. Moreover, there are several concerns regarding specific effects of cyclosporine A on foetal and post-natal development[13,14]. Animal studies have shown that intrauterine exposure (IUE) to cyclosporine A at different developmental stages can induce permanent renal nephron deficiency in the offspring[15].

In the present case the offspring had normal renal function and no renal malformation was reported. The severity of these effects seems to differ between species and no study so far has identified similar effects in humans[16].

A recent study found that direct cyclosporine A exposure during pregnancy correlated to reduced implantation frequency and increased number of foetal deaths in a dose-dependent manner. This observation is in line with previous findings in rats[17]. The observed reduced implantation rate suggests that cyclosporine A, somehow, affects the endometrium or decidua in a way not identified so far. Even though there is a concern regarding implantation, in our patient, fertilization was successful at first attempt.

Taking under consideration the fact that a 35 years old woman with β- thalassemia major, AIHA, and DM could not receive steroids first line treatment, due to deregulation of glucose levels, a second line therapy such as cyclosporine A had to be chosen, in order to achieve a normal course and a successful outcome of pregnancy. Cyclosporine A has to be cautiously used during pregnancy, when the potential benefit outweighs the theoretical risk. In the present case both the mother and foetus were in good clinical condition while being in continuous and close monitoring by a group of experts during and after pregnancy.

In conclusion, cyclosporine A is an immunosuppressive agent used to prevent graft rejection and treat autoimmune disorders. Pregnancies under cyclosporine A treatment are associated with slightly elevated risks for obstetric and post-natal complications. Although limited bibliography is favourable towards reproductive performance and pregnancy outcome in women using cyclosporine A, further studies are needed to confirm these findings.

Disclosure

All authors have nothing to declare.

Conflict of Interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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