Pregnancy after Cardiac Transplantation. Report of one Case and Review

Solange Bordignon, Anna Marcela Aramayo, Daniel Nunes e Silva, Cíntia Gründler, Ivo Nesralla

Porto Alegre - Brazil

A 14-year-old female patient became pregnant 6 years after heart transplantation. The pregnancy evolved uneventfully, and the newborn infant was healthy. Five months after delivery, the mother was in good condition with preserved ventricular function, and the baby had normal neuro-psychomotor development. Even though the case reported here was a success, pregnancy following cardiac transplantation is considered a high-risk condition and remains contraindicated.

Cardiac transplantation is a widely accepted technique, constituting a treatment for patients with end-stage cardiac disease. The number of recipients surviving transplantation keeps growing with improvement in quality of life, including sexuality and delivery, and obtainment of significant results. Many female patients with damage in target organs such as the heart, lungs, kidneys, liver, bone marrow, and pancreas are infertile. Restoration of the normal function of any of these organs through transplantation has lead to conception and pregnancy. On the basis of data available since the first pregnancy in a renal transplant recipient in 1958 [1], it has become evident that reproduction after organ transplantation is possible. The desire to become pregnant is common and normal in women of childbearing age, including recipients of cardiac transplants.

In the United States, a mean of 2,500 transplantations is performed per year, with an expected survival rate of 80% in one year and 65% in 5 years [2,3]. The female cardiac transplant recipient population accounts for 21% to 38% of the cases, a great percentage of which is of childbearing age. Since 1958, more than 2,400 pregnancies have occurred in transplant recipients. Successive pregnancies have been reported in kidney, liver, and bone marrow transplant recipients.

Pregnancy after cardiac transplantation involves a delicate circumstance and should not be encouraged. The denervated heart may respond to hemodynamic changes associated with pregnancy, and a rejection-free graft requires freeserial endomyocardial biopsies and invasive hemodynamic monitoring.

The objective of this study is to report the case of a 14-year-old female patient became pregnant 6 years after heart transplantation.

Case report

The patient is a 14-year-old single white female student from Porto Alegre. She had been healthy until April of 1990 when she developed edema, dry cough, and dyspnea. She was admitted to the Instituto de Cardiologia/IC-FUC for diagnostic investigation. She underwent electrocardiography, echocardiography, coronary angiography, and myocardial biopsy, being diagnosed with dilated cardiomyopathy and severe mitral and tricuspid regurgitation. The echocardiogram showed diffuse hypocontractility with a shortening fraction (ΔD) of 16% and signs of incipient pulmonary hypertension. The hemodynamic study revealed biventricular failure. In May of '90, she was referred to the cardiac transplant program of the institution, and surgery was performed in December of '91. In the early postoperative period, she underwent 2 surgical interventions due to bleeding. She was discharged from the hospital in February of '92 and was clinically asymptomatic. A myocardial biopsy revealed degree 1A (focal acute rejection), and treatment with 500mg/day of cyclosporine, 75mg/day of azathioprine, and 20mg/day of prednisone was indicated. The dose of cyclosporine was gradually reduced to 200mg/day associated with 50mg/day of azathioprine. The patient remained asymptomatic until June of '96, when she was hospitalized with jaundice and itching due to drug-induced hepatitis. Azathioprine was then suspended and the symptoms resolved. The patient was informed about the risk of a possible pregnancy and contraception with condoms or a vaginal diaphragm was indicated. Nevertheless, in December '97, 6 years after transplantation, she was diagnosed with a 5-week pregnancy. The pregnancy, which evolved unevent-fully, was followed up with weekly prenatal visits and regular medical visits to the ambulatory cardiac disease and pregnancy clinics of the IC-FUC. Serum levels of cyclosporine were monitored with radioimmunoassay with monoclonal antibody (RIA), and its doses were adjusted to obtain therapeutic levels (200-800mg/mL). A progressive

Instituto de Cardiologia/Fundação Universitária de Cardiologia - Porto Alegre
Mailing address: Solange Bordignon - Rua Gal. Ibá Mesquita Ilha Moreira, 40/602 - 91340-180 - Porto Alegre, RS, Brazil

increase in the cyclosporine dose was required during pregnancy. Blood pressure levels assessed on medical visits were never higher than 140/90mmHg; the ejection fraction evidenced by serial echocardiograms remained stable (fig. 1). Pregnancy was followed up with monthly fetal echography, and no abnormalities were observed. Cardiac function was regularly monitored two-dimensional echocardiography with color Doppler, and all parameters were normal. Renal function did not significantly change during the gestational period. In July of '98, at the 36th week of pregnancy, a cesarean section under general anesthesia was performed as indicated by the obstetrician. The female newborn infant weighed 2,300g and measured 46 cm. Her Apgar score was 8 at the first minute and 8 at the 5th minute. Mother and daughter evolved satisfactorily. Five months after birth, the child had no abnormalities, and her neuropsychomotor development was adequate for her age. The mother was in good condition, her blood pressure was 130/80mmHg, her heart rate was 86bpm, her ejection fraction was 74.7%, and she was in NYHA functional class I, with no rejection episode. Currently the patient is taking 200mg/day of cyclosporine.

Discussion

From the pioneering days of heterotopic cardiac transplantations in animals at the beginning of the century to the first experiences with human beings in the '60s, several obstacles have been overcome. Currently, survival for 5 years is estimated to be between 60% and 82% [1-3]. Approximately 30% of cardiac transplantations are performed in women, many of whom are of childbearing age[4]. The first pregnancy after cardiac transplantation was reported by Löwenstein et al [5] in 1988. In July '98, Branch et al [6] reported the existence of reports in the international literature of 47 pregnancies after cardiac transplantation in 35 women, as 12 of them had had more than one pregnancy. From the 35 first pregnancies, 26 live births, a twin delivery, 4 spontaneous abortions, and 6 therapeutic abortions resulted. From a second pregnancy after cardiac transplantation, 11 births and 2 spontaneous abortions resulted. In Brazil, the first report published on pregnancy after cardiac transplantation was by Almeida et al [7] in 1995.

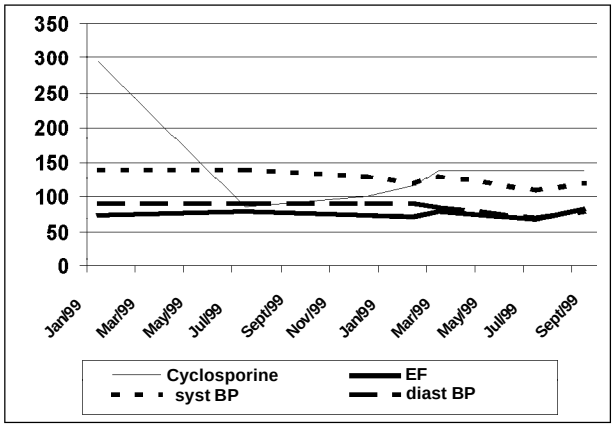

Fig. 1- Evolution of the laboratory tests and blood pressure. Cyclosporine – serum levels of cyclosporine in ng/mL; EF – ejection fraction in %, assessed on echocardiogram; syst BP – systolic blood pressure in mm Hg; diast BP – diastolic blood pressure in mm Hg

Pregnancy after cardiac transplantation has been contraindicated because of the risks to the mother and conceptus [8]. In the pregnant woman, the risks relate mainly to hemodynamic alterations and immunosuppressive therapy, determining an elevation in maternal morbidity but not in mortality [8]. During pregnancy, blood volume increases significantly, an average of 50%. This increase begins in the 6th week of pregnancy and reaches a peak in the 32nd week of pregnancy. Cardiac output increases from 30% to 50% and heart rate from 10 to 20bpm. Systemic blood pressure decreases in the first and second trimesters, reaching pregestational levels at the end of pregnancy. The most evident change is elevation in end-diastolic volume [9-11]. In the transplanted patient, cardiac output is usually reduced, ventricular compliance is smaller than that in the normal ventricle, and this is maintained by the high central venous pressure [10,11]. Intracardiac pressures are normal at rest, but during exertion, ventricular diastolic pressure drastically increases [11]. In cardiac transplantation, the heart is denervated and loses the vagal stimulus, determining an elevation in heart rate at rest, which is usually between 95 and 115bpm. Hypersensitivity to circulating catecholamines also occurs [10]. If these changes occur in a transplanted pregnant woman, they can adversely affect the heart, with an increase in cardiac contractility, in central venous pressure, in blood volume, and in cardiac output [7,10]. Therefore, cardiac overload occurs, which in its natural evolution results in an increase in the diameter of the right ventricle with tricuspid regurgitation [7]. These hemodynamic changes are usually well tolerated by transplanted patients during pregnancy. However, hypertension and preeclampsia are more prevalent in these women [13,14]. The major risks in regard to immunosuppressive therapy in pregnant women are high indices of gestational diabetes, premature rupture of the membranes, hypertension, adrenal insufficiency, and infection [3,4,15]. Other alterations include a higher incidence of postpartum depression, anemia, and cholestatic jaundice [8,14,16].

In regard to the conceptus, the major complication is intrauterine growth retardation, accompanied by spontaneous abortion, prematurity, adrenal insufficiency, low-birth-weight, and teratogenicity [6,11,16]. Prematurity is frequent because of the premature rupture of membranes[4]. Abortion is more frequent because of the increased risk of infections caused mainly by *Listeria*, cytomegalovirus, herpesvirus, and rubella virus [17]. Factors related to hypertension cause a higher prevalence both of low-birth-weight infants and intrauterine growth retardation [18-20]. The drugs used in immunosuppressive therapy cross the placental barrier and may have a teratogenic effect [4,7]. Lymphopenia, hypogammaglobulinemia, thrombocytopenia, and thymus hypoplasia are reported in children of women who used azathioprine associated with prednisone; these alterations, however, were reversed[4]. Cyclosporine is found in fetal circulation in concentrations similar to that found in the mo-

ther [21], exerting a possible immunosuppressive effect on the fetus [7]. In experiments with animals, the immunosuppressive therapy had a teratogenic and fetotoxic effect [7]; however, no appropriate and well-controlled studies on pregnant women are available. Scott et al [16], reviewing 30 cases, found no congenital anomalies, or fetal and neonatal death.

Rejection of the transplanted organ is an important complication of cardiac transplantation, even under immunosuppressive therapy, but this risk is not increased during pregnancy [6,16,22]. The most used immunosuppressive therapy in transplanted patients is the triple protocol comprising cyclosporin A, azathioprine, and corticotherapy with methylprednisolone or prednisone [1,15], which are also indicated in pregnant patients [7,13]. Cyclosporine is a lipophilic cyclic oligopeptide isolated from the fungus *Tolypocladium inflatum Gams*. It has a potent immunosuppressive effect, inhibiting the synthesis of interleukin-2 by the helper T lymphocyte and the proliferation of activated T cells, as well as other lymphokines [23], decreasing the immune response without a significant mielotoxicity [4]. The main side effects in transplanted patients are as follows: hypertension; renal, hepatic and neurologic damage; gingival hyperplasia; lymphoproliferative disorder; myocardial fibrosis; and hirsutism [24-26]. Hypertension is caused by afferent glomerular vasoconstriction that decreases glomerular filtration and withholds sodium, resulting in a nephrotoxic effect [14]. Cyclosporine may be used during pregnancy only if the benefits justify the potential damage to the fetus [4]. Breast-feeding must be contraindicated because cyclosporine is present in maternal milk [7]. During the third gestational trimester, due to hemodilution, the levels of serum cyclosporine are significantly reduced and an increase in the daily dose is required [23]. Azathioprine is a derivative of 6-mercaptopurine, whose action is mediated by inhibition of the synthesis of the purines, reaching DNA and RNA [15]. The adverse effects in transplanted patients include bone marrow suppression, with leukopenia, thrombocytopenia, and macrocytic anemia, increased susceptibility to neoplasias and infections, hepatotoxicity, pancreatitis, alopecia, and skin fragility [7]. Corticoids act upon macrophages and T lymphocytes, and also have a nonspecific immunosuppressive action. Prednisone is more used in the triple protocol and methylprednisolone is preferred in episodes of acute rejection [27].

The contraindication of pregnancy after cardiac transplantation is based on the already cited complications, and in some foreign centers therapeutic abortion is recommended [4,7,16]. No consensus exists about the ideal contraceptive method for female transplanted patients of childbearing age [28]. Contraceptive methods, such as condoms and vaginal diaphragms, have the smallest adverse effects, but due to their low effectiveness they are not widely recommended [4]. Intrauterine devices have low effectiveness in immunocompromised patients and have a higher risk of infection [4]. Combined oral contraceptives should only be considered for women without hypertension, and hepatic and thromboembolic diseases, because when associated with immunosuppressive agents they potentiate the occurrence of hypertension, hepatotoxicity, thromboembolism, cerebral stroke, cholestasis, edema, and gastrointestinal disorders [7,27,29]. Progestins are the current option because they can be used in the presence of hypertension and thromboembolism, are effective, and have low levels of adverse effects [28]. All hormone contraceptive methods require strict monitoring of the serum levels of the immunosuppressive agents because they may influence their metabolism [28]. Permanent contraceptive methods, such as tubal ligation and vasectomy, are a good option because they are safe and have no complications like the hormonal methods do; they, however, are difficult to reverse [4,7,16].

During pregnancy, the prenatal follow-up is fundamental and should be more strict and frequent when compared with that of normal gestations. The following examinations are indispensable during pregnancy: serum levels of cyclosporine, leukocyte and platelet counts, routine hemograms, echocardiography, and monitoring of renal function [14,22]. Radiographic examinations and myocardial biopsies are not routinely recommended [7].

The cardiac transplanted female usually tolerates vaginal delivery well, and a cesarean section should only be indicated for obstetric reasons [16]; however, the cesarean section rate in transplanted women is high [30]. During childbirth, the cardiac output is elevated in up to 25% by uterine contractions, which cause an increase in venous return; therefore, strict monitoring is required. In the early postpartum period, an increase in preload occurs due to blood drainage from the uterus to the peripheral circulation, which may require medical intervention [11]. In the puerperium, cyclosporine levels tend to increase, requiring a decrease in the daily doses of this drug [7].

Regardless the high successful indices obtained nowadays, pregnancy after cardiac transplantation continues to be considered a high risk procedure and requires special medical care. The major efforts should be directed towards strict contraception, and, in case of pregnancy, adequate control of the possible complications should be performed.

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