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CASE REPORT

Pregnancy under everolimus-based immunosuppression

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Summary

The ability to give birth to a live child is one of the best success of kidney transplantation. While there are an increasing number of pregnancies reported in kidney transplant recipients treated with cyclosporine or tacrolimus, there is little evidence of pregnancy among kidney transplant recipients exposed to sirolimus or everolimus. We present the first successful delivery in an organ transplant recipient exposed to everolimus during the whole gestation. The absence of congenital anomalies in the child as well as the recipient's successful renal outcome are promising, although pregnancy in renal transplant recipients exposed to everolimus should be considered at higher risk.

Introduction

End-stage renal disease is often accompanied by impaired reproductive function, that may be partially restored after a kidney transplantation. The ability to give birth to a live child is one of the best success of kidney transplantation. However, although more than 14 000 pregnancies have been reported worldwide in organ transplant recipients [1], pregnancy is still considered high risk for both the mother and the fetus [2,3]. The occurrence of recipient's hypertension and some degree of renal dysfunction are independently related to a high risk of complications during pregnancy, and the change in extracellular volume may indirectly induce graft deterioration because the blood levels of the immunosuppressive drugs become more difficult to manage [3].

With the widespread use of sirolimus and everolimus as primary immunosuppressant in organ transplant recipients, a question has recently raised if these drugs may be intrinsically teratogenic, and may be therefore contraindicated for pregnancy in organ transplant recipients [4]. While previous studies have reported that the rate of congenital anomalies in the offspring of transplant recipients treated with cyclosporine or tacrolimus is similar to that of general population [1], there are little experiences with newer drugs, such as sirolimus and everolimus. Although sirolimus association with prematurity, fetal mortality and reduced fetal weight has been reported in rats, no teratogenic or carcinogenic risk was reported in any animal study.

There are no specific studies investigating the role of everolimus during pregnancy: however, a recent study demonstrated that everolimus may increase the level of the Human leukocyte antigen-G (HLA-G), a protein primarily expressed during pregnancy, that helps to maintain maternal-fetal immune tolerance [5].

We describe the first case of a successful pregnancy in a female kidney transplant recipient, in which everolimus was continued throughout the whole gestation.

Case report

A 30-year-old woman with end-stage renal disease of unknown etiology, received on November 3, 2007 a kidney transplantation from a 42-year-old deceased donor. She was initially immunosuppressed with a triple therapy including everolimus, cyclosporine and steroids. She was discharged on the seventh postoperative day with a serum creatinine of 1.6 mg/dl.

On December 2008, she presented with a serum creatinine of 2.1 mg/dl and a kidney biopsy confirmed the presence of an acute rejection, which completely resolved after steroid therapy(serum creatinine 1.4 mg/dl, proteinuria 430 mg/d) The patient was discouraged to have pregnancy, and all risks of proceedings with moderate renal dysfunction and our absolute lack of knowledge about the risk of pregnancy during everolimus therapy were clearly explained to the patient. In August 2009, she presented with amenorrhea and with a positive pregnancy test. An ultrasound showed a normal fetus of approximately 12 weeks of gestation. It was decided to continue with the same immunosuppression, giving that the risk of abnormal fetal development was likely to be low at this stage of the pregnancy. Kidney function remained stable during the pregnancy (SCr 2.1 mg/dl) and the patient received everolimus 0.75 mg bid, blood level 4.5 ng/ml, cyclosporine 100 mg bid, blood level 170 ng/ml, and steroids 5 mg. Protocol screening imaging of the fetus showed no morphologic alterations. In December 2009, during week 30, the patient presented with a sudden worsening of renal function (SCr 3.86 mg/dl, proteinuria 1230 mg/d) and with severe hypertension (blood pressure 160/90 mmHg), with no clinical signs of peripheral edema. The patient underwent a caesarean section, giving live birth to a 1280-g healthy female baby, with an Apgar Score of 10 and no congenital malformations, who was immediately transferred to neonatal intensive care unit.

The mother's renal function worsened during the early follow up (SCr 4.5 mg/dl), and a kidney biopsy showed the presence of an interstitial nephritis with no signs of acute rejection. Graft function gradually improved after antibiotic therapy (piperacillin/tazobactam 4,5 g/d), and at 6-month post-delivery follow up the recipient's serum creatinine was 2.4 mg/dl, and she received everolimus 0.75 mg bid, blood level 5.3 ng/ml, cyclosporine 125 mg bid, blood level 175 ng/ml, and steroids 5 mg.

At 12 months, the newborn showed normal growth without detectable significant disorders.

Discussion

Common practice guidelines of pregnancy after kidney transplantation, suggest that mycophenolate mofetil (MMF) or sirolimus based immunosuppression are not recommended. Further, renal transplant recipients with a moderate graft failure at the time of conception have a higher risk of graft failure and complications with the newborn [2]. There are 10 transplant recipients reporting 11 pregnancies with exposure to sirolimus (nine livebirths, two spontaneous abortions) in the National Transplantation Pregnancy Registry [1]. Birth defects were reported in two of the nine liveborn and included: cleft lip, cleft palate and microtia (initial mycophenolate mofetil exposure with late pregnancy exposure to sirolimus) and in the second case Tetralogy of Fallot (no concomitant MMF). There was one recipient of a combined kidney and pancreas transplantation, who reported a spontaneous abortion [1]. There are only a limited number of case reports with exposure to sirolimus during pregnancy as well [6–9]. While most recent reports [6–9] showed successful delivery with sirolimus used during first and second trimester of gestation, or even with exposure throughout the whole gestation in conjunction with poor graft function [9], to date there have been no reports to the National Transplantation Pregnancy Registry of recipients exposed to everolimus during pregnancy. We report the first successful delivery in an organ transplant recipient with everolimus exposure throughout the whole gestation. It should be questioned that everolimus immunosuppression would have to be switched to conventional immunosuppression before pregnancy: however, MMF therapy is contraindicated in pregnant kidney recipients and a change in immunosuppressive therapy in a patient with unstable renal function would probably result in a worsening of graft function. Although a single success would not be strong enough evidence to suggest that everolimus may be safe or appropriate during pregnancy, the absence of congenital anomalies in the child as well as the recipient's successful renal outcome suggest that everolimus therapy might not be an absolute contraindication for pregnancy. However, there is still much to learn regarding the safety of everolimus and poor graft function during pregnancy, but the good results reported in patients exposed to sirolimus during pregnancy are encouraging [9].

Conclusion

Everolimus should not be considered an absolute contraindication to pregnancy in kidney transplant recipients. Giving the rapidly growing use of everolimus in immunosuppressive protocols after kidney transplantation, it seems mandatory to encourage promptly reporting any additional cases of pregnancy during everolimus exposure, to give a better understanding of the safety profile of this immunosuppressant during pregnancy.

Authorship

MV: wrote the paper. DC: collected the data. PV: gave the final approval to the manuscript.

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