Outcome of Pregnancies in Renal Allograft Recipients

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Abstract
Despite documented success and long term safety of thousands of pregnancies in female renal allograft recipients in Western countries, pregnancy is still a rare event, and considered risky in India in these patients. Four initial cases with their adverse outcome in the Indian context are presented.

INTRODUCTION
After renal transplantation there is marked improvement in reproductive, endocrinal and sexual function, with return of ovulatory cycle in women, fertility is usually restored within 1-12 months.1 If proper contraceptive methods are not used, all the female renal allograft recipient of child bearing age are at risk of getting pregnant, infact 1 in 50 women of reproductive age group will get pregnant after renal transplantation.2

First successful pregnancy after renal transplantation was reported in 1958,3 since then more than thousands of pregnancies had already been reported.4 More than hundred reports have been published from Western countries concerning both short as well as long term safety of pregnancy in renal allograft recipients.5 Beside this safety and successful outcome of repeated pregnancies, twin, triplets, and pregnancy in combined kidney and pancreas,6 combined kidney and liver transplant recipient7 had also been reported in patients on conventional (prednisolone and azathioprine) as well as patients on triple drug immunosuppressive (cyclosporine, azathioprine prednisolone) regimen.

In India, pregnancy in a renal allograft recipient is still a rare event and considered risky. There are only a few anecdotal case reports from India and developing countries. Our Case 1 was probably one of the first cases of pregnancy is renal allograft recipient in India.9 We report our experience of pregnancies in four female renal allograft recipients at a tertiary care referral renal transplantation centre in South India.

CASE REPORTS

Case 1
A 26 years female received renal allograft from her mother (one haplotype match) for her end stage renal failure due to reflux nephropathy in 1990.

Two years prior to transplantation she was detected to be hypertensive and developed severe, pre-eclampsia and renal failure during third trimester of her first pregnancy.

Pregnancy was terminated prematurely at 22 weeks to control the hypertension and renal failure. Her hypertension remained uncontrolled. She presented to us with end-stage renal failure, accelerated hypertension and urinary tract infection. She underwent renal transplantation after two months of maintenance haemodialysis. The graft functioned immediately, and her serum creatinine level declined to 0.8 mg/dl on day 5.

She had normal menstruation one month after renal transplantation. The couple was advised for barrier contraception to avoid pregnancy for at least one to two years, but it was ignored.

Four months after transplantation she reported with amenorrhea of two months. Pregnancy test was found positive. Ultrasound also confirmed the presence of embryo in uterus. At this time she was taking cyclosporine 6 mg/kg/day, azathioprine 2 mg/kg/day, prednisolone 20 mg/day. Her serum creatinine was 0.8 mg/dl, her creatinine clearance was 61.7 ml/minute, and 24-hour proteinuria was 267 mg/day. Her blood pressure was 160/100 mm of Hg on two antihypertensive drugs.

She was advised against continuation of the pregnancy, but due to personal and social reasons she decided to continue the pregnancy against the medical advice. She was kept under strict medical supervision with nephrologist and obstetrician with frequent monitoring of graft function, fetal growth and maturity. Immunosuppressive drugs were continued in the usual dosages.

At 34 weeks of gestation when she developed severe preeclampsia and premature rupture of membrane without progression of labor, she underwent lower segment caesarian section. A healthy (2.6 kg) male baby was born; surgery and post-operative period remained uneventful.
During puerperium and later follow up, mother and baby did not have any complication. Breast feeding was not encouraged and baby was kept on top feeds. She was electively withdrawn from cyclosporine six years after transplantation due to financial reasons.

Presently 12 years after delivery her graft functions are excellent with a serum creatinine of 0.9 mg/dl and creatinine clearance of 59 ml/min, 24-hour proteinuria was 222 mg/day. Her son is healthy, has normal physical and mental development without any medical problem.

**Case 1**
A 23 years female received renal allograft from her father HLA identical for her ESRD due to chronic interstitial nephritis of undetermined etiology in January 1997. She was on triple immunosuppressive drugs for initial one year, when cyclosporine was withdrawn due to financial reasons. Her baseline serum creatinine was 0.8 mg/dl, with GFR of 98 ml/min. Her blood pressure remain uncontrolled despite three antihypertensive drugs. She was lost to follow up two years after transplantation.

Four year after transplantation she presented to us with amenorrhoea of three months with edema feet, uncontrolled hypertension and proteinuria. She was found to be having 12 weeks pregnancy and moderate renal failure (serum creatinine 2.8 mg/dl). She was advised medical termination of pregnancy, which she refused due to social and family reasons. She continued her pregnancy against the medical advice for two weeks further, when she agreed for medical termination of pregnancy.

After uneventful medical termination of pregnancy her graft function continued to deteriorate despite satisfactory control of hypertension. She was advised graft biopsy which she refused. Her graft function continued to deteriorate; she also developed heavy proteinuria and accelerated hypertension when she agreed for graft biopsy, which showed advanced chronic allograft nephropathy with marked fibrosis and glomerulosclerosis. Her graft failed within one year of pregnancy and she was put on maintenance haemodialysis, which she continued for three months and then lost to follow up.

**Case 2**
A 32 years female received renal allograft from her brother HLA identical for her ESRD due to chronic interstitial nephritis of undetermined etiology. She was on triple immunosuppressive drugs for initial one year, when cyclosporine was withdrawn due to financial reasons. Her baseline serum creatinine was 0.8 mg/dl, with GFR of 98 ml/min. Her blood pressure remain uncontrolled despite three antihypertensive drugs. She was lost to follow up two years after transplantation.

Four year after transplantation she presented to us with amenorrhoea of three months with edema feet, uncontrolled hypertension and proteinuria. She was found to be having 12 weeks pregnancy and moderate renal failure (serum creatinine 2.8 mg/dl). She was advised medical termination of pregnancy, which she refused. Her graft function continued to deteriorate despite satisfactory control of hypertension. She was advised graft biopsy which she refused. Her graft function continued to deteriorate; she also developed heavy proteinuria and accelerated hypertension when she agreed for graft biopsy, which showed advanced chronic allograft nephropathy with marked fibrosis and glomerulosclerosis. Her graft failed within one year of pregnancy and she was put on maintenance haemodialysis, which she continued for three months and then lost to follow up.

As kidney function deteriorated, she was encouraged and baby was kept on top feeds. She was then advised medical termination of pregnancy, which she refused due to social, personal and family reasons. She continued her pregnancy against medical advice.

At 20 weeks of gestation she presented with spontaneous abortion, when she was found to have advanced graft dysfunction (serum creatinine 7.0 mg/dl), heavy proteinuria (4.2 gm/day) anaemia (hemoglobin 6.4 gm/dl) and uncontrolled hypertension. She was dialyzed and once she was stabilized a graft biopsy was done which showed advanced chronic allograft nephropathy, there was no improvement in renal function with conservative management, within few months of abortion her graft failed. She was put on maintenance hemodialysis, which she continued for three months, when the dialysis was discontinued due to financial reasons and she died with uremia.

**Case 3**
A 31 years female received renal allograft from her mother one haploid match, for her ESRD due to IgA nephropathy in 1994. She was on triple immunosuppressive drugs. Her baseline serum creatinine was 0.7 mg/dl. She had her first planned pregnancy in 1997 when her blood pressure was controlled on amlodipin 5 mg/day, and she was taking prednisolone 10 mg/day, azathioprine 1.5 mg/kg/day, cyclosporine 3 mg/kg/day. Her GFR was 70 ml/minute and 24 hour proteinuria of 120 mg/day. She was closely monitored by nephrologist and obstetrician. She had undergone normal vaginal delivery at full term. Her complete gestation period and delivery was uneventful. Five years after delivery, her graft function is excellent with serum creatinine of 0.8 mg/dl and GFR 68 ml/minute and 24 hour proteinuria 128 mg/day. Her daughter is five years and have normal physical and mental health and development.

**DISCUSSION**

For a woman with a functioning kidney graft, to undergo a successful pregnancy is the best possible proof of rehabilitation from ESRD. But pregnancy in a renal allograft women is not without risk, as there is high incidence of abortion, hypertension and pre-eclampsia, premature rupture of membrane, infections, prematurity and intrauterine growth retardation, beside this acute rejection is also more common during pregnancy. So all the pregnancies in renal allograft women should be considered high risk and should be managed at tertiary care centre by maternal fetal medicine specialist in conjunction with nephrologist and neonatologist and careful counseling and monitoring should be done to avoid unnecessary complication.

Antenatal care must incorporate serial assessment of renal function, control of blood pressure, early diagnosis and management of rejection, infection, anaemia and meticulous fetal surveillance. Immunosuppressive therapy is usually maintained at pre-pregnancy levels. Vaginal delivery is feasible, since the renal allograft is not an obstacle to delivery; caesarian section is required for obstetrical reason.
only. In agreement to previous reports\textsuperscript{2-4} our case reports shows that if pregnancy is planned in a patient with good general health, patient understands the importance and need of regular follow up, and stature compatible with good obstetric outcome and the time interval between transplantation and conception has exceeded more than 1-2 years, and patient has normal renal function (serum creatinine < 1.5 mg/dl), hypertension which is absent or satisfactorily controlled, no or minimal proteinuria, minimal immunosuppression (prednisolone < 15 mg/kg/day, azathioprin < 2 mg/kg/day, cyclosporine either absent or < 2-4 mg/kg/day), no evidence of active graft rejection, or pelvicalyceal distension then the outcome of the pregnancy is likely to be satisfactory. If these above criteria are fulfilled she can be reassured that pregnancy is unlikely to substantially alter the long term graft function.\textsuperscript{6} But if these criteria are ignored outcome of these pregnancies could be catastrophic, leading to morbidity, graft dysfunction and even mortality.

Aramenti VT et al\textsuperscript{7} had shown that transplant interval of shorter duration (< 1-2 years) has been associated with a greater risk of unsatisfactory outcome and longer duration of interval (> 5 years) after transplant is associated with lower incidence of prematurity and lower birth weight. So women should be advised to use optimal contraception in the first 1-2 years after renal transplant.

Willis FR et al\textsuperscript{8} had shown that despite a high incidence of preterm delivery, low birth weight and intrauterine growth retardation, the overall long term outcome for these children of renal transplant recipient mother is good. In agreement to this study our observation also showed that the long term outcome of these children of renal allograft mothers is satisfactory.

In India, regretfully many of these pregnancies are not planned, the allograft recipient being unaware that they could conceive and therefore they take prenatal care quite late in gestation.

This case report highlights that 1) Counseling for all the renal allograft recipient of child bearing age should be stressed; 2) Pregnancy and delivery of normal child is possible in renal allograft recipient, provided that, careful planning and monitoring of pregnancy is accomplished; 3) If pregnancy is planned and monitored appropriately, outcome is likely to be good, and these women can be reassured that pregnancy is unlikely to substantially alter their graft function, but unplanned and inappropriately monitored pregnancies can cause morbidity, graft dysfunction and even mortality; 4) In our renal transplant population social factors have a marked influence on patient’s decisions for pregnancy; 5) The long term outcome of these children of renal allograft mother is excellent.

This small report is likely to stimulate our colleagues in India, who are still uncertain about the pregnancies in renal allograft women, and help them to revise their views. It seems prudent on their part to discuss the possibility of having a baby with their patients in appropriate clinical circumstances.

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