

Pregnancy after Renal Transplantation: Experience in Singapore General Hospital

P K Tan,*^{MBBS (S'pore), MRCOG (Lond)}, A S A Tan,**^{FAMS, MRCOG (Lond), M Med (O&G)}, H K Tan,***^{FAMS, MRCOG (Lond), MRACOG (Aust)},
A Vathsala,****^{FAMS, MD (USA), FRCP (Edin)}, S K Tay,^{†FAMS, MD (Lond), FRCOG (Lond)}

Abstract

Introduction: Renal transplantation offers the best hope for those women with end-stage renal disease who wish to have children. However, pregnancy after renal transplantation is associated with increased maternal and fetal morbidity. The aim of this retrospective study was to review the outcome of pregnancy in renal transplant patients in Singapore General Hospital. **Materials and Methods:** Forty-two pregnancies, occurring between December 1986 and December 2000, in 25 out of 141 renal transplant women in their reproductive age group (18 to 45 years old) were identified from our high-risk pregnancy record and retrospectively analysed. **Results:** Thirteen (31%) pregnancies were unsuccessful; 10 abortions, 2 ectopic pregnancies and 1 stillbirth. The remaining 29(69%) successful pregnancies were complicated by maternal anaemia (65.5%), superimposed hypertension (44.8%), premature rupture of membranes (27.6%), urinary (17.2%) and lower genital tract (13.8%) infections, abnormal glucose tolerance test (13.8%), premature delivery (44.8%), low-birth-weight babies (44.8%), small-for-gestational-age babies (20.7%) and intrauterine growth restriction (20.7%). There were no documented cases of multiple pregnancies, congenital anomalies or deterioration of renal function. The outcome of pregnancy was not statistically influenced by preconception renal function and transplant-conception interval. **Conclusions:** Successful pregnancy is possible in women after renal transplantation. Such pregnancy is often associated with increased maternal and fetal complications and should be managed by a multidisciplinary approach in a tertiary centre. The function and survival of renal allograft was not adversely affected by pregnancy.

Ann Acad Med Singapore 2002; 31:285-9

Key words: Conception, High-risk pregnancy, Kidney transplant, Pregnancy outcome, Renal allograft

Introduction

Successful renal transplantation significantly improves the sexual and reproductive functions of women with end-stage renal disease and offers the best hope for those who wish to have children. Conception rate has been reported to improve dramatically from 1 in 200 dialysis patients to 1 in 50 women with a functioning renal transplant.¹

Pregnancy after renal transplantation, however, is associated with increased maternal and fetal morbidity. It is, therefore, important for renal transplant women who wish to embark on a pregnancy to understand the implications of its high-risk nature. The aims of this retrospective study were to review our experience in management of pregnancy after renal transplantation and to correlate obstetric outcome with selected preconception criteria.

Materials and Methods

All pregnancies in renal transplant women were identified from the database of high-risk pregnancy records. Forty-two pregnancies in 25 female transplant patients were jointly managed by the Departments of Obstetrics and Gynaecology and Renal Medicine, Singapore General Hospital between December 1986 and December 2000.

Data on the cause of renal failure, date and type of renal transplant, immunosuppressive therapy, anti-hypertensive treatment and renal function of each patient were collected and retrospectively analysed. Demographic data and obstetric outcome of each pregnancy of the transplant patients were retrieved from their antenatal records in our Medical Record Office. The outcome of pregnancy and antenatal complications were correlated to the pre-pregnancy renal function and transplant-to-conception

* Registrar

** Senior Consultant and Chief, Section of Fetal Maternal Medicine

*** Consultant

Department of Obstetrics and Gynaecology

† Senior Consultant, Department of Obstetrics and Gynaecology

Director, Division of Research

**** Senior Consultant

Department of Renal Medicine

Singapore General Hospital

Address for Reprints: Dr Tan Poh Kok, Department of Obstetrics and Gynaecology, Singapore General Hospital, Outram Road, Singapore 169608.

interval. Data related to the neonatal outcome for each newborn including the gestational age, birth weight, Apgar scores at 1 and 5 minutes and any neonatal complications were collected.

Hypertension was defined by World Health Organisation criteria for hypertensive disease in pregnancy as a diastolic blood pressure of 90 mm Hg or more.² Anaemia was defined as a haemoglobin level of less than 11 g/dL. Premature delivery was defined as live birth before 37 completed weeks of pregnancy and low birth weight as birth weight of less than 2500 g. Intrauterine growth restriction (IUGR) was clinically defined as the slowing of fetal growth velocity during 2 or more consecutive ultrasonographic measurements done 3 weeks or longer apart. Small-for-gestational-age babies were defined as those with birth weight below the 10th centile for the corresponding gestational age.

The Fisher's exact test and Student's *t*-test were used, when appropriate, for statistical analysis with *P* less than 0.05 considered as a significant value.

Results

Between December 1986 and December 2000, a total of 141 female patients in the reproductive age group (18 to 45 years) underwent renal transplantation in Singapore General Hospital and 25 of these patients had a total of 42 pregnancies after transplantation. Eleven patients received a living-donor transplant while 14 had a cadaveric transplant. All patients had primary renal disease before their renal transplantation. The median age of the patients at the time of conception was 33.1 years (range, 26.3 to 42.4 years) and the median transplantation-to-conception interval was 48 months (range, 8 to 190 months). At the time of conception, all patients received conventional immunosuppressive therapy (azathioprine and/or prednisolone) and, in addition, 12 patients also received cyclosporin-A. All patients except 2 had pre-existing hypertension before pregnancy which were controlled with either a beta-blocker (propranolol), calcium channel-blocker (nifedipine) or methyldopa. All patients continued to receive their immunosuppressive treatment during pregnancy. Anti-hypertensive agents were changed to methyldopa during pregnancy in all except 4 patients.

The outcomes of the 42 pregnancies are summarised in Table I. All the 29 successful pregnancies resulted in singleton live births. Multiple pregnancy was not observed in any of the women. Nine patients experienced 13 unsuccessful pregnancies which included 7 spontaneous abortions (6 missed abortions and 1 inevitable abortion), 3 therapeutic abortions, 2 ectopic pregnancies and 1 stillbirth. Four unsuccessful pregnancies came from 1 patient who had 6 pregnancies after her renal transplantation in 1985.

At age 35, she had an inevitable abortion at 8 weeks of gestation, 17 months after an ectopic pregnancy in 1989. She subsequently had a successful pregnancy in 1992 followed by 2 missed abortions in 1995 and another successful pregnancy in 1997. Maternal complications in patients with successful pregnancies are shown in Table I. The pregnancy outcomes and selected antenatal complications were studied according to preconception renal allograft function and the transplant-to-conception interval. The results are presented in Table II.

Superimposed hypertension complicated 13 (44.8%) of the 29 successful pregnancies. Severe proteinuric hypertension developed in 5 patients whose pregnancies were terminated by caesarean section. Four patients developed impaired glucose tolerance during the course of their pregnancy. Lower genital tract infection with candidiasis was detected on microscopy in 5 patients. Three of the 4 patients who developed urinary tract infection (UTI) during pregnancy had mixed bacterial growth detected on urine culture. One patient developed recurrent UTI in the third trimester of her pregnancy and was treated with long-term antibiotics based on the drug-sensitivity result of her urine culture which grew *Escherichia coli*.

Premature birth (delivery before 37 weeks of gestation) occurred in 13 (44.8%) of the 29 pregnancies between 30 and 36 weeks of gestation. Of the 13 premature births, 2 occurred before 32 weeks and 11 between 32 and 36 weeks of gestation. Preterm premature rupture of membranes (PPROM) was documented in 8 pregnancies between 30 and 36 weeks of gestation. There was poor correlation between lower genital tract infection and premature rupture of membranes (PROM). Only 2 of the 5 patients with lower

TABLE I: OVERALL PREGNANCY OUTCOME AND MATERNAL COMPLICATIONS

Outcome	No.*	(%)
Successful pregnancy	29	(69)
Unsuccessful pregnancy	13	(31)
Early spontaneous abortion	7	
Therapeutic abortion	3	
Ectopic pregnancy	2	
Stillbirth	1	
Total number of pregnancies	42	(100)
Complication	No.*	
Anaemia (Hb <11g/dL)	19	
Superimposed hypertension	13	
Premature rupture of membranes	8	
Maternal infection		
Lower genital tract infection	5	
Urinary tract infection	4	
Abnormal glucose tolerance	4	

*denotes the absolute number of patients

TABLE II: PREGNANCY OUTCOME AND ANTENATAL COMPLICATIONS ACCORDING TO PRECONCEPTION RENAL FUNCTION AND TRANSPLANT-TO-CONCEPTION INTERVAL

Pre-pregnancy serum creatinine	Therapeutic abortion (n = 3)	Spontaneous abortion (n = 7)	Term delivery (n = 17)	Preterm delivery (n = 13)	IUGR (n = 6)	Low birth weight (n = 13)
<125 $\mu\text{mol/L}$	2	0	2	1	0	2
>125 $\mu\text{mol/L}$	1	7	15	11	6	11
<i>P</i>	ns	ns	ns	ns	ns	ns
Transplant-conception interval	Therapeutic abortion (n = 3)	Spontaneous abortion (n = 7)	Term delivery (n = 17)	Preterm delivery (n = 13)	IUGR (n = 6)	Low birth weight (n = 13)
<2 years	1	6	12	8	4	7
>2 years	2	1	5	4	2	6
<i>P</i>	ns	ns	ns	ns	ns	ns

IUGR: intrauterine growth restriction; ns: not significant

genital infection had PROM. IUGR was identified clinically in 6 (20.7%) of the successful pregnancies. The growth restriction was detected between 26 and 30 weeks of gestation in 2 patients and between 30 and 36 weeks in another 4 patients.

Renal function remained stable throughout pregnancy in all women with successful pregnancies. The serum creatinine levels of these patients are illustrated in Figure 1. The mean serum creatinine level in patients who achieved successful pregnancies was 112.7 $\mu\text{mol/L}$ (95% CI, 33.1–192.3) at the time of conception and 106.4 $\mu\text{mol/L}$ (95% CI, 29.7–183.0), 102.2 $\mu\text{mol/L}$ (95% CI, 33.9–170.5) and 106.0 $\mu\text{mol/L}$ (95% CI, 40.4–171.5) during the first, second and third trimesters, respectively. There was no statistical difference between the mean creatinine levels at the time of conception and each trimester of pregnancy (Fig. 2). Acute rejection episode was not observed in any of the women during pregnancy. Comparing the mean serum creatinine values at conception and after delivery at 1 year and 7.5

years (Fig. 3) using the *t*-test, there was no statistically significant evidence of deterioration in renal graft function in all the women when they were followed up for a median period of 91.5 months (range, 9 to 150 months) after delivery.

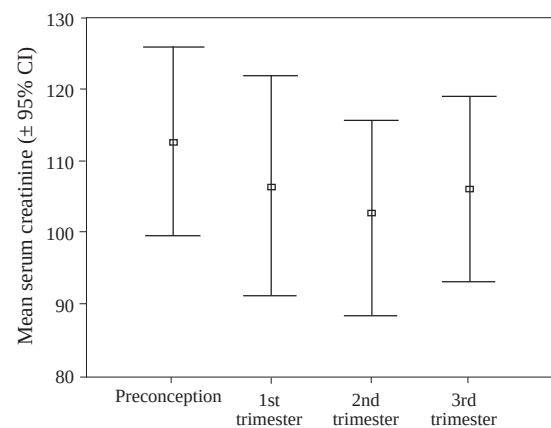


Fig. 2. Mean serum creatinine levels at preconception and during pregnancy.*
* The difference in mean creatinine values between preconception and each trimester of pregnancy are not statistically significant using *t*-test ($P > 0.05$).

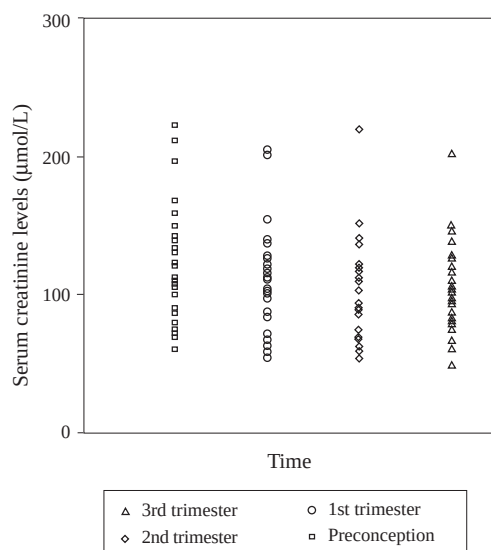


Fig. 1. Serum creatinine levels at preconception and during pregnancy.

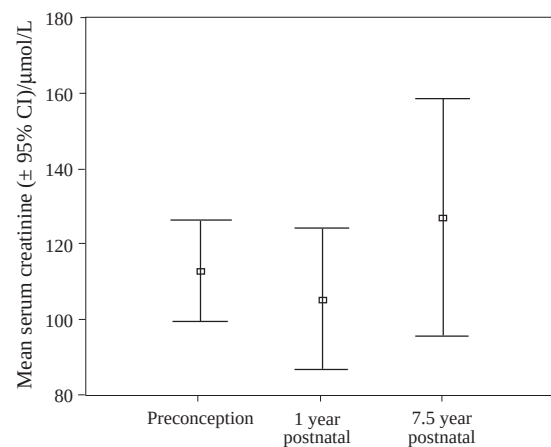


Fig. 3. Mean serum creatinine levels at preconception and after delivery.*
* The difference in mean creatinine values between preconception and after delivery at 1 and 7.5 years are not statistically significant using *t*-test ($P > 0.05$).

TABLE III: INDICATIONS FOR CAESAREAN SECTION

Indication	No.*
Emergency caesarean section	
Previous caesarean section	4
Fetal distress	4
Superimposed hypertension	3
Failed stimulation	2
Obstructed labour	1
Preterm breech	1
Abruptio placentae	1
Elective caesarean section	
Previous caesarean section	4
Superimposed hypertension	2
Obstructed labour	1
Previous renal transplant	1

*denotes the absolute number of patients

Twenty-four (82.8%) of the 29 successful pregnancies were delivered by caesarean section. There were only 5 (17.2%) vaginal deliveries, although 11 pregnancies were planned to be delivered vaginally. Emergency caesarean sections were performed in the other 6 pregnancies for fetal distress (2 cases), severe superimposed hypertension (2 cases), failed stimulation (1 case) and abruptio placentae (1 case). The commonest indication for surgical delivery was previous caesarean sections which accounted for 8 (33.3%) of the 24 operative deliveries. The other indications are summarised in Table III. Premature delivery (less than 37 weeks) occurred in 13 pregnancies (44.8%). The mean birth-weight ($\pm$ 2SD) of the babies was 2422 g ($\pm$ 1220 g) and 13 babies (44.8%) weighed less than 2500 g. Six babies (20.7%) were born small for gestational age. Congenital malformation was not seen in any of the newborns.

Discussion

Since the first reported case³ of pregnancy in a renal transplant patient in 1963, more than 7000 pregnancies after renal transplantation have occurred worldwide. Many studies have observed a higher rate of miscarriage, premature births, IUGR, low birth weight and perinatal mortality rate.³⁻⁷

Pregnancy in women of childbearing age after successful renal transplantation can be readily achieved and the incidence has been estimated at 2%.³ Our much better pregnancy rate of 17.7% (25 out of 141 patients), which has also been observed in a previous study,⁸ could be explained by our stringent transplant selection of younger patients with primary renal disease without other end-organ damages. Because of the improved chances of conception, renal transplant women should be given contraceptive counselling upon successful transplantation.

Our overall successful pregnancy rate of 69% (29 out of 42 pregnancies) and success rate of 96.7% in those

pregnancies which continued beyond 28 weeks of gestation are comparable to those reported in the literature.⁹ Spontaneous abortions and therapeutic abortions in renal transplant recipients have been reported in about 14% and 20% of all pregnancies, respectively.⁹ In our series, the spontaneous abortion rate of 16.6% (7 out of 42 pregnancies) has been skewed unfavourably by the occurrence of 3 recurrent abortions (2 missed abortions and 1 inevitable abortion) in 1 patient, which could have been purely due to her advanced maternal age. Only 3 pregnancies (7.1%) resulted in therapeutic abortions which are due to sub-optimal preconception renal function. Such unplanned pregnancy could be reduced to a minimum with proper pre-pregnancy counselling and contraceptive advice. There were 2 cases of ectopic pregnancies in our study. One patient had a previous tubal ligation which was a predisposing factor for the ectopic pregnancy, while no obvious antecedent factor could be identified in the other patient. It is believed that ectopic pregnancy in renal transplant patient occurs as a result of pelvic adhesions secondary to previous urological surgery, peritoneal dialysis or pelvic inflammatory disease.¹⁰

Poorly-controlled hypertension during pregnancy has been reported to be associated with higher incidence of IUGR, stillbirths and neonatal deaths.^{11,12} In our series, IUGR was detected in 3 of the 13 pregnancies complicated by superimposed hypertension. In view of the poorer perinatal outcome, it is our practice to treat hypertension aggressively before renal transplant recipients with pre-existing hypertension are advised to contemplate pregnancy. The risk of infections, especially UTI, is increased during pregnancy due to immunosuppressive therapy. One series reported an incidence rate of 17% of UTI in pregnant renal transplant patients with 4% progressing to pyelonephritis despite treatment.⁵ Four pregnancies (14%) in our series were complicated by UTI but none of the patients developed pyelonephritis.

Our premature birth rate of 44.8% (13 of 29 pregnancies) is comparable to those documented in the literature^{6,9,13-15} and was largely due to PROM which was documented in 8 out of 29 (27.6%) pregnancies. It is postulated that long-term steroid therapy weakens the connective tissue of the fetal membranes and contributes to increased incidence of PROM. Premature delivery accounted for 12 (92%) of the 13 low-birth-weight (LBW) babies in our study. Low-birth-weight babies were also a common problem in other series (44.8%).^{13,16} This has also been attributed to the effects of renal impairment, vascular disease, or hypertension which may be present during or before pregnancy.¹⁷ The small-for-gestational-age babies in this series (20.7%) were mainly due to IUGR. Our study, limited by its small size and methodology, suggests that

the outcome of pregnancy and antenatal complications were not influenced by the transplant-to-conception interval and preconception renal function.

One of the main concerns of pregnancy in renal transplant patients is the potential adverse effect on the function and survival of the renal allograft. In our study, there was no evidence to suggest that renal graft function or survival was adversely affected by pregnancy. All patients with successful pregnancies had satisfactory renal function at the onset of conception and their renal function remained stable throughout the pregnancy and up to a median period of 91.5 months (range, 9 to 150 months) after delivery. Acute rejection of renal allograft was not observed in any of our successful pregnancies, although the incidence of serious rejection has been reported to be 9%.⁸ The risk of renal function deterioration during pregnancy is reported to be negligible when preconception renal function is adequate.^{3,18,19}

Our caesarean section rate of 82.8%, which is comparatively higher than those quoted in the literature,^{9,17,20} was probably due to our low threshold. Two caesarean sections were performed for obstruction of labour by the transplanted kidney although vaginal delivery should be possible in most cases as the renal allograft, which is placed extra-peritoneally in the false pelvis, does not usually obstruct the birth canal.⁹

Although birth anomalies^{5,21,22} have been reported in mothers using azathioprine and cyclosporine A, the absence of serious congenital malformations in our study supports the consistent observations in previous reports that there is no increase in the incidence of congenital anomalies in renal transplant recipients.^{23,24}

Conclusion

Our study has confirmed that pregnancy can occur readily and successfully in renal transplant patients. Women of childbearing age should be promptly advised to use adequate contraception after successful transplantation. Pregnancy in renal transplant women is associated with increased risk of fetomaternal complications and should be managed by a multidisciplinary approach in a tertiary centre. The prognosis of renal allograft is not adversely affected by pregnancy in women with a well-functioning transplant kidney. The risk of congenital malformations from *in utero* exposure to immunosuppressive therapy is minimal but further research is necessary to evaluate the long-term mutagenic effect on the offspring of renal transplant recipients.

REFERENCES

1. Lindheimer M D, Katz A L. Pregnancy in the renal transplant patient. *Am J Kidney Dis* 1992; 19:173-6.
2. The hypertensive disorders of pregnancy. *World Health Organ Tech Rep Ser* 1987; 758:1-114.
3. Hou S. Pregnancy in transplant recipients. *Med Clin North Am* 1989; 73:667-83.
4. Penn I, Makowski E L, Harris P. Parenthood following renal transplantation. *Kidney Int* 1980; 8:221-33.
5. Registration Committee of the European Dialysis and Transplant Association. Successful pregnancies in women treated by dialysis and kidney transplantation. *Br J Obstet Gynaecol* 1980; 87:839-45.
6. Fine R N. Pregnancy in renal allograft recipients. *Am J Nephrol* 1982; 2:117-22.
7. David J M. Renal transplantation and pregnancy. *Am J Kidney Dis* 1987; 9:374-80.
8. Donnell D, Seritz H, Seggie J L. Pregnancy after renal transplantation. *Aust N Z J Med* 1985; 15:215-27.
9. Davison J M. Pregnancy in renal allograft recipients: problems, prognosis and practicalities. *Baillieres Clin Obstet Gynaecol* 1994; 8:501-25.
10. Scott J R, Cruikshank D P, Corry R I. Ectopic pregnancy in kidney transplant patients. *Obstet Gynaecol* 1978; 51:56S-8.
11. Jungers P, Forget D. Chronic kidney disease and pregnancy. *Adv Nephrol* 1986; 15:103-41.
12. Sturgiss S N, Davison J M. Perinatal outcome in renal allograft recipients: prognostic significance of hypertension and renal function before and during pregnancy. *Obstet Gynaecol* 1991; 78:573-7.
13. Armenti V T, Ahlswede K M, Ahlswede B A, Carter J R, Moritz M J, Burl J F. National Transplantation Pregnancy Registry: analysis of outcome/risks of 394 pregnancies in kidney transplant recipients. *Transplant Proc* 1994; 26:2535.
14. Muirhead N, Sabharmal A R, Reider M J, Lazarovits A I, Hollomby D J. The outcome of pregnancy following renal transplantation—the experience of a single centre. *Transplantation* 1992; 54:429-32.
15. O'Donnell D, Meyers A M, Botha J R, Sevit H, Seggie J L, Myburgh J A. Pregnancy after renal transplantation. *Aust N Z J Med* 1985; 15:320-5.
16. Cararach V, Carmona F, Monleon F J. Pregnancy after renal transplantation: 25 years experience in Spain. *Br J Obstet Gynaecol* 1993; 100:122-5.
17. Rudolph J E, Schweizer R T, Bartus S A. Pregnancy in renal transplant patients: a review. *Transplantation* 1979; 27:26-9.
18. Tanabe K, Kobayashi C, Takahashi K, Sonda K, Tokumoto T, Ishikawa N, et al. Long-term renal function after pregnancy in renal transplant recipients. *Transplant Proc* 1997; 29:1567-8.
19. Scott J R, Lau R J. Pregnancy following renal transplantation. *Clin Obstet Gynaecol* 1985; 28:339-49.
20. Picaud J C, Audra P, Putet G, Belle L, Salle B L. Infant born to kidney transplant recipients. *Arch Fr Pediatr* 1991; 48:323-7.
21. Pudals J M, Figueras G, Puig J M, Lloveras J, Aubia J, Masramon J. Osseous malformation in baby born to woman on cyclosporin. *Lancet* 1989; 1:667.
22. Armenti V T, McGrory C H, Cater J R, Radomski J S, Moritz M J. Pregnancy outcome in female renal transplant recipients. *Transplant Proc* 1998; 30:1732-4.
23. David J M. Towards long-term graft survival in renal transplantation: pregnancy. *Nephrol Dial Transplant* 1995; 10:85-9.
24. Ersay A, Oygur N, Coskun M, Suleymanlar G, Trak B, Yegin O. Immunologic evaluation of a neonate born to an immunosuppressed kidney transplant recipient. *Am J Perinatol* 1995; 12:413-5.