ORIGINAL ARTICLE

Pregnancy in Patients with Renal Transplants in Malaysia

L S Hooi, FRCPE*, G Rozina, FRCPE, M Y Wan Shaariah, FRCPE ***, S M Teo, MRCP****, C H H Tan, MRCP*****, S Bavanandan, MRCP******, Y Rosnawati, MRCP******

*Haemodialysis Unit, Hospital Sultanah Aminah, Johor Baru, **Haemodialysis Unit, Hospital Pulau Pinang, ***Haemodialysis Unit, Hospital Seremban, ****Haemodialysis Unit, Hospital Ipoh, ***** Haemodialysis Unit, Hospital Kuching, ******Department of Nephrology, Hospital Kuala Lumpur

Summary

There were 72 pregnancies in 46 renal transplants (RTs) between 1984 and 2001, 89% from living donors, 11% cadaveric. Mean age at RT was 26.9 ± 4.3 years and at pregnancy 30.7 ± 4.7 years. Mean time to pregnancy after RT was 4.5 ± 3.1 years. 54% were unplanned. 45 (63%) resulted in surviving infants, 37% delivered by Caesarean section. 35% were premature. Mean birth weight was 2.38 ± 0.57 kg. 64% were on cyclosporine. No patient had an acute rejection during pregnancy; 38% had pre-existing hypertension. Complications include urinary infection (13%), proteinuria (15%) and preeclampsia (15%). Mean serum creatinine before pregnancy was 112.7 ± 32.6 umol/l, 1 year post-pregnancy it was 119.4 ± 38.7. The mean time of follow up of mothers is 4.9 ± 3.5 years. 10 year graft survival was 83% and patient survival 94%.

Key Words: Pregnancy, Renal transplant

Introduction

Pregnancy after renal transplantation (RTs) is uncommon and has not been studied in Malaysian patients. Successful pregnancies in RTs are reported with increasing frequency. In counselling female patients with RTs it would be useful to describe pregnancy outcomes locally so that they may make an informed decision on future pregnancies.

The main problems reported in pregnancies in patients with RTs include prematurity, low birth weight, graft dysfunction and acute rejection. Pregnancy in RTs is safer if the mother is in good health for 2 years, has a stature that is associated with good obstetric outcome, has minimal or no proteinuria, has no hypertension (HT) or mild and well controlled HT. Other favourable factors are absence of graft rejection and hydronephrosis. The patient should have stable creatinine < 180 umol /l and on low dose immunosuppression - prednisolone < 15 mg/day, azathioprine < 2 mg/kg/day, cyclosporine < 5 mg/kg/day [1, 2, 3, 4].

This article was accepted: 4 September 2002
Corresponding Author: Hooi Lai Seong, Haemodialysis Unit, Hospital Sultanah Aminah, Johor Baru

The objective of this study is to determine maternal and foetal outcome of pregnancies in RTs.

Materials and Methods

This is a multicentre retrospective analysis of all pregnancies in patients with a functioning RT in Malaysia. The outcome of the patient, foetus or baby is recorded. The study started in 1975 and ended in December 2001.

Total number of RTs, total number of female RTs and total number of female RTs between 18 and 45 years of age at RT was extracted from the National Renal Registry (NRR) database [5].

Ascertainment: In 1999 all RTs done between 1990 and 1998 were reviewed by the NRR and this included information on pregnancies. A case file of all pregnant RTs between 1979 - 1991 which was kept in Hospital Kuala Lumpur (the main RT centre in the country) was also used. In 2000, 92% of all RTs were followed up in government centres. The reporting to NRR from these centres is 100% [5].

Any pregnancy that occurred before 1990 and after 1998 had to be further ascertained. Self reporting by nephrologists who had looked after such patients and reports from transplant clinic nurses were utilised. Letters were sent to private nephrologists, paediatricians, obstetricians for further case finding.

For each pregnancy an in depth survey was done by the authors. Data was collected from patient interview, case notes, obstetric notes and perinatal notes.

Statistics: The data was presented as mean $\pm$ standard deviation. The statistical tests applied were the Chi-square (χ^2) test and student t test. $p < 0.05$ is taken as statistically significant. Kaplan Meier survival function was used to estimate patient and graft survival. Statistical analyses were done using Medcal® (r) for Windows. Cox proportional hazards model was used to determine the effect of pregnancy on graft and patient outcome compared to females with transplants from the same age group (using SPSS for Windows version 10).

Results

There were 1916 renal transplants registered in Malaysia from 1975 to 2000 and 1171 RTs were alive at the end of 2000.

691 (36%) were in women of which 532 were in 522 women between the ages of 18 to 45 years at the time of transplant. There were 72 pregnancies in 46 mothers. 25 patients had 1 pregnancy, 16 patients had 2 pregnancies, 5 patients had 3 pregnancies. There was I set of triplets. Demography is described in Table I.

There is a disproportionate number of pregnancies in females with living related donor RTs (LRRT) 74% compared to 32% of all female RTs and 35% of all RTs in Malaysia. The earliest pregnancy was in a LRRT transplanted on 30/4/79 and the latest was in a LRRT transplanted on 28/8/98. Of the 34 LRRTs the donor was the mother in 18, father in 8, sister in 4 and brother in 4.

Fourteen had been pregnant pre-RT. The two therapeutic abortions (TOP) were for social reasons in one and severe renal failure at 5 months in the other case. Of the 21 pregnancies pre-RT which resulted in live births one child weighed 2.5 kg (low birth weight), 1 was premature requiring Caesarean section (LSCS), 1 had congenital adrenal hyperplasia and in one delivery was normal but the mother went into end stage renal failure (ESRF) two months later. 1 baby was premature and died after 4 days.

There was one maternal mortality due to eclampsia in 1991. One patient died with functioning graft (arrythmia, 9 years after pregnancy) and 4 grafts have failed as of December 2001 (4 years in two patients, 6 years and 10 years after pregnancy). One patient had a failed graft 1 year post-pregnancy due to non-compliance to immunosuppressive drugs, died 14 months later of subdural haematoma. None were lost to follow-up. The 10 year graft survival (patient alive with functioning graft) was 83% and patient survival 94% censored at 31/12/2001 (Figure 1). The Cox proportional hazards model showed that patients who have had a pregnancy had significantly better graft and patient survival ($p = 0.000$ and $p = 0.016$ respectively) after correcting for type of renal transplant, diabetic status and age at RT compared to female patients in the same age group who had not.

The characteristics of the pregnancies are on Table II. The standard maintenance immunosuppression regime was prednisolone (pred) 10 mg/day with azathioprine ± cyclosporine (CyA). Cyclosporine was added universally for transplants done after 1990.

In 57 pregnancies azathioprine (aza) was given throughout. The dose was unknown in 4. In the rest the mean dose at the beginning was 1.6 ± 0.4 (range 0.8 - 2.5) mg/kg/day and the mean at the end of pregnancy was 1.5 ± 0.5 (range 0.8 - 2.5) mg/kg/day. All doses of azathioprine > 2 mg/kg/day were in patients on prednisolone and azathioprine alone and lower doses were used when patients were on triple regime. Cyclosporine was used in 46 pregnancies, mean dose 3.4 ± 0.9 (range 1.8 - 3.6) mg/kg/day at the beginning compared to mean dose of 3.8 ± 0.8 (range 1.9 - 5.9) mg/kg/day at the end of pregnancy.

Maternal outcomes are described in Table III. Indications for lower segment caesarean section (LSCS) were hypertension in 9, raised creatinine in 3, full term in 3, foetal distress in 2, intra-uterine growth retardation (IUGR) in 1 and unknown in 1. The reasons for therapeutic abortion include age 40 years in 2, recent acute rejection in 1, raised creatinine during last pregnancy in 1, too soon after RT in 1 and social reasons in 4. All the TOPs were from unplanned pregnancies.

No mother had acute rejection during pregnancy. 5 (11%) had AR in the past. In one the AR episode was 1 month before conception and pregnancy was terminated. Graft function was maintained hereafter.

The serum creatinine was recorded 9, 6, 3 and 0 months before conception and the average was calculated. It was also recorded one year after the end of the pregnancy. Creatinine data was lost for 7 pregnancies occurring before 1992. These involved 4 mothers. One was the maternal mortality; in one the graft was lost 6 years after the third pregnancy and in the other 2 the grafts are still functioning! One patient became pregnant after 6 months RT and one patient after 4 months RT (creatinine 90 and 115 umol/l respectively). Of the 6 mothers who are not yet 1 year post-pregnancy all have stable serum creatinine.

In the 15 with increasing creatinine during pregnancy there was 1 maternal mortality with stillbirth, 1 spontaneous abortion, 1 therapeutic abortion, 6 LSCS and 6 normal deliveries.

From the mothers on CyA there were 26/46 pregnancies (57%) with hypertension (21 pre-existing, 3 transient and 2 new but persistent). In those not on CyA there was hypertension in 7/26 pregnancies (27%), 6 pre-existing and 1 new. The association between cyclosporine and hypertension is statistically significant ($p = 0.03$). In 5 there was preexisting and persistent proteinuria and in

6 it was transient. Pre-eclampsia (oedema, proteinuria and hypertension) occurred in 10 pregnancies. One patient had pre-existing diabetes mellitus with 2 pregnancies.

There were 6 perinatal deaths all from mothers transplanted before 1990 who were on prednisolone and azathioprine alone (Table IV). There were 49 live births (19 LSCS and 30 spontaneous vaginal deliveries [SVD]), 17 premature. Of the latter gestation ranged from 27 - 36 weeks, average 33 weeks.

In 27 pregnancies with hypertension, mean birth weight of baby was 2.21 $\pm$ 0.64 kg and in 22 pregnancies without hypertension, mean weight was 2.59 $\pm$ 0.40 kg (significantly different, p = 0.02).

In 16 deliveries where the APGAR score could be found, average was 8.1 at 1 minute and 8.9 at 5 minutes. Two babies had respiratory distress syndrome born at 31 and 27 weeks respectively, 0.8 kg and 1.2 kg at birth. There were no babies with fits, mental retardation, congenital abnormalities or developmental delays.

Of the 16 pregnancies which occurred less than 2 years post-RT 12 (75%) were unplanned. Serum creatinine pre- and post-pregnancy remained stable and normal. There were 4 miscarriages, 4 therapeutic abortions, 1 LSCS and 7 normal deliveries (SVDs). One full term baby needing LSCS had foetal distress with low APGAR scores at delivery and died soon after. One baby born by SVD died at 28 weeks gestation. The result is 6/16 (38%) live infants compared to 39/56 (70%) live infants in those who conceived more than 2 years post-RT (p = 0.04).

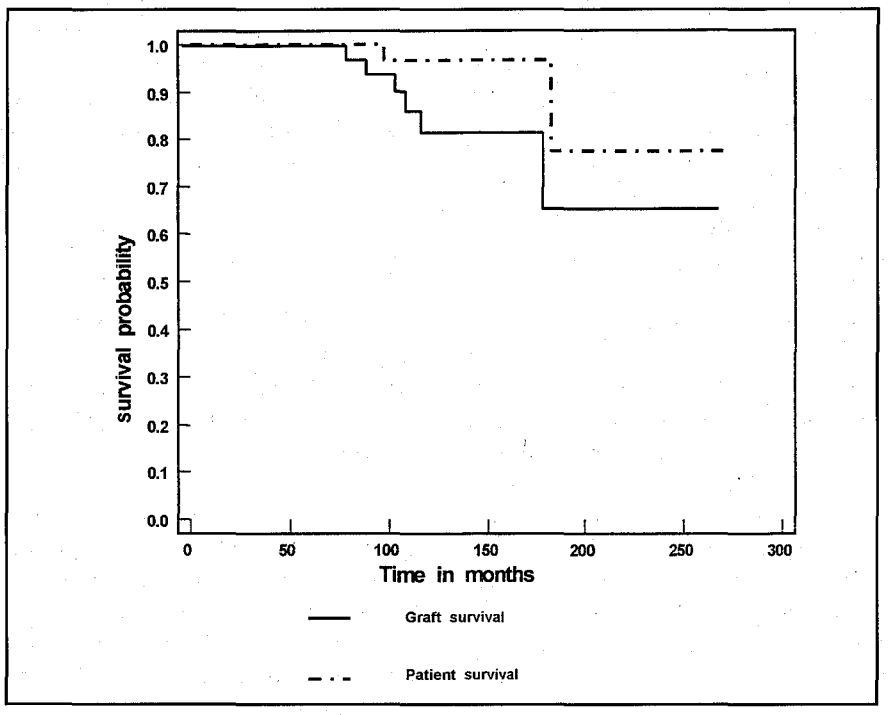

Fig. 1: Patient and graft survival (N = 46)

Table I: Demography of renal transplants with pregnancies (N = 46)

Race	
Chinese	25 (54%)
Malay	14 (30%)
Indian	4 (9%)
Iban	3 (7%)
Primary renal disease	
Unknown	35 (76%)
Systemic lupus erythematosus	5 (11%)
Glomerulonephritis	4 (9%)
Others	2 (4%)
Duration starting renal replacement therapy to transplant	
Mean 1.2 ± 2.2 years	Range 0 - 15.5 years
Date of transplant	
< 1980	2 (all on prednisolone and azathioprine) (4%)
1981 - 1990	16 (3 on cyclosporine) (35%)
1991 - 1998	28 (all on cyclosporine) (61%)
Age at RT	
Mean 26.9 ± 4. 3 years	Range 17 - 35 years
Type of RT	
Living related donor RT	34 (74%)
Living unrelated donor RT from India	7 (15%)
Cadaveric RT from China	4 (9%)
Local cadaveric RT	1 (2%)
Pregnancy history of mothers before RT	
No previous pregnancies	32 (69.6%)
1 spontaneous abortion	1 (2.2%)
1 therapeutic abortion (TOP)	2 (4.3%)
2 spontaneous abortions	1 (2.2%)
1 child	2 (one neonatal death) (4.3%)
2 children	6 (13.1%)
> 2 children	2 (4.3%)
Acute rejection before pregnancy	5 (11%)

Table II: Characteristics of the pregnancies (N = 72)

Year of conception	
< 1980	0 (0%)
1981 - 1985	2 (3%)
1986 - 1990	6 (8%)
1991 - 1995	23 (32%)
1996 - 2000	40 (56%)
2001	1 (1%)
(range 1984 - May 2001)	
Age at pregnancy (years)	
21 - 25	10 (14%)
26 - 30	25 (35%)
31 - 35	23 (32%)
36 - 40	13 (18%)
41 - 45	1 (1%)
Mean 30.7 $\pm$ 4.7 years (range 23 - 41 years)	
Time after RT	
0 - 2 years	16 (22%)
2 - 5 years	29 (40%)
6 - 10 years	23 (32%)
> 11 years	4 (6%)
Mean 4.5 $\pm$ 3.1 years (range 4 months - 14.3 years)	
Type of immunosuppressives during pregnancy	
Pred and aza	26 (36%)
Pred and CyA	13 (18%)
Pred, aza and CyA	33 (46%) (in 2 azathioprine stopped before end of pregnancy, one because of fatty liver and the other because liver enzymes elevated in Hepatitis B positive patient)

Table III: Maternal outcomes of pregnancies (N = 72)

SVD	32 (including 2 stillbirths) (44.4%)
LSCS	19 (26.4%)
Spontaneous abortion (A)	11 (including 1 triplet pregnancy) (15.2%)
TOP	9 (13%)
Molar pregnancy (M)	1 (1%)
Serum creatinine before pregnancy (average of 4 readings) (umol/l)	
Unknown	9 (12%)
Mean 112.7 ± 32.6 umol/l (range 72 - 282 umol/l)	
Serum creatinine one year after end of pregnancy (umol/l)	
Not reached 1 year	6 (8%)
Unknown	6 (8%)
Died	1 (1%)
Already in ESRF	1 (1%)
Mean 119.4 ± 38.7 umol/l (range 59 - 250 umol/l)	
Maternal mortality	1/72 (1%) [eclampsia]
Rising creatinine during pregnancy (> 20% from baseline)	15 (21%)
Hypertension	33 (46%)
Pre-existing	27 (38%)
Transient	3 (4%)
New and persistent	3 (4%)
Proteinuria	11 (15%)
Pre-eclampsia	10/72 (14%)
Urinary tract infection	9/72 (13%)
Graft survival	
5 years	97.8% (93.5 - 100, 95% CI)
10 years	83 % (68.1 - 97.9, 95% CI)
Patient survival	
5 years	97.8% (93.5 - 100, 95% CI)
10 years	94.5% (86.7 - 100, 95% CI)
Bilateral tubal ligation after pregnancy	16/46 (35%)
Years of follow-up of mother after her last delivery	
Mean 4.9 ± 3.5 years	Range 0 - 14.8 years

Table IV: Foetal Outcomes

Pregnancy planned	23 (32%) (10 SVD, 8 LSCS, 5 A)		
Unplanned	39 (54%) (17 SVD, 8 LSCS, 4 A, 1 M, 9 TOP)		
Unknown	10 (14%) (5 SVD, 3 LSCS, 2 A)		
Perinatal deaths	6/51 (4 neonatal deaths and 2 stillbirths) (12%)		
Live births	49/72 (68%)		
Premature	17/49 (35%)		
IUGR	7/49 (14%)		
Weight of live births	Full term	Premature < 37 weeks	Total
> 2.5 kg	21 (66%)	5 (29%)	26 (53%)
1.5 - 2.5 kg (LBW)	9 (28%)	5 (29%)	14 (29%)
1 - 1.5 kg (Very LBW)	0 (0%)	4 (24%)	4 (8%)
< 1kg (Extremely LBW)	0 (0%)	1 (6%)	1 (2%)
Unknown	2 (6%)	2 (12%)	4 (8%)
Mean weight of live births		2.38 ± 0.57 kg (range 0.8 - 3.45 kg)	
Age of live children (N = 45)		4.9 ± 4.1 years (range 5 months to 17.3 years)	

Discussion

This series is a comprehensive survey of known pregnancies in renal transplants in Malaysia. There is a likelihood that some first trimester spontaneous abortions and TOPs went unreported but births are unlikely to have been missed. Reporting to the NRR have made the data accessible. The first RT was done in Malaysia in 1975 and the first pregnancy occurred in 1984. Only a small number of females with RTs become pregnant and this may be due to counselling of women against pregnancy especially in those with renal failure, previous acute rejection or severe hypertension.

The rate of pregnancy is 8.8% of all RTs in females between 18 - 45 years of age which concurs with other reports of 2 - 14% [2, 6, 7, 8]. 63% resulted in live infants which is acceptable compared to other reports of 50 - 75% [9, 10, 11].

This group of mothers have unusually good graft and patient survival compared to the prevailing rate [5]. They may have the least morbidity and are a self selected group. Only 11% had acute rejection (AR) before pregnancy compared to about 30% in general series [11]. None had AR during pregnancy although this is reported to occur in 9 - 15% [12, 13].

Pregnancy did not seem to affect long term graft function. There were similar serum creatinine readings before and one year after delivery. This is in agreement with other long term series [2, 14, 15]. This may be because problems were detected early and indications for early TOP and delivery include raised serum creatinine.

Only 2 pregnancies started with creatinine >200 umol/l and post-partum graft loss was not encountered. In some series the incident serum creatinine is related to post-partum graft loss [11].

Pre-existing hypertension (38%) and preeclampsia (15%) is a problem. Hypertension occurs in 24 - 30% in other series [1, 16]. Cyclosporine is implicated in hypertension in the mother [17]

and this is associated with low birth weight (LBW) [10].

Half of all pregnancies were unplanned and this may be due to lack of counselling. This has consequences for foetal outcome especially in those less than 2 years post-RT. Patients on dialysis who were previously infertile have to be advised about their fertility returning almost immediately [12, 18]. All the 9 (13%) TOPs were in the unplanned group. They were done for social reasons and concern either by the patient or physician for the possible detrimental effect on the transplant rather than ongoing graft dysfunction. This is supported by the fact that 35% were sterilised after the pregnancies. The TOP rate in other series was 17 - 26% [12].

The spontaneous abortion rate was 15%; it is 16 - 42% in other series [9, 19]; this is not increased over the general population. Caesarean section rate of 37% is moderate as other series report rates of 0 - 100% depending on local practice [1, 8, 9, 12, 13, 16, 17, 20, 21, 22, 23]. 35% of babies were premature compared to 20 - 60% in other reports [1, 2, 7, 10, 16, 19, 21, 22]. This compares with 5 - 15% in the general population.

Perinatal mortality was 12% which is similar to other series [7, 24] and about 10 times that of the general population. All the perinatal deaths were contributed by mothers on prednisolone and azathioprine alone, transplanted before 1990. No perinatal deaths have occurred in mothers transplanted later on the triple regime of cyclosporine, prednisolone and azathioprine. Pregnancy outcome may have improved in the last decade with better immunosuppression, obstetric and perinatal care.

The incidence of LBW is 39% (up to 64% in other series) [1, 8, 25]. Intra-uterine growth retardation (IUGR) is reported in 8 - 40% [7, 19, 22, 24]. It is 14% in this series.

Conclusion

Females of childbearing age with functioning RTs should be given pre-pregnancy counselling and contraceptive advice and pregnancies planned for a better outcome. The patients who have had a pregnancy are a young and long-lived cohort with few bad prognostic features. Transplant and patient outcome is good. 63% resulted in a live infant, complicated by hypertension in half, prematurity in one third with an average birth weight of 2.4 kg.

Successful pregnancy is possible after RT. Hypertension and functional status are the major determinants of outcome. All pregnancies however favourable should be treated as high risk because of the propensity for preeclampsia, infection, IUGR and perinatal mortality and should be closely followed up in a tertiary care institution.

Acknowledgements

We would like to thank the Director-General of Health, Malaysia for permission to publish this paper. We thank Dato' Dr. Zaki Morad for furnishing records of the first dozen pregnancies. We thank S/N Lee Day Guat for helping to extract the data from the National Renal Registry. We thank all doctors and paramedics who helped to collect the data.

References

1. Touraine J, Audra P, Lefrancios N et al. Pregnancy in renal transplant patients: 45 case reports. Transplant Proc 1997; 29: 2472-74.
2. First R, Andrew Combs C, Weiskittel P, Miodovni M. Lack of effect of pregnancy on renal allograft survival or function. Transplantation 1995; 59 (4): 472-76.
3. Lindheimer M, Katz A. Pregnancy in the renal transplant patient. Am J Kidney Dis 1992; 19(2): 173-76.
4. To W, Lam K, Chan Y. Pregnancy following renal transplantation: the experience in Hong Kong. J Obstet Gynaecol 1995; 21(3): 263-67.
5. Renal transplantation. In: Lim TO, Lim YN (eds.) Eighth report of theMalaysian dialysis and transplant registry, 2000. Malaysian Organ Sharing System / National Renal Registry, Malaysian Society of Nephrology.
6. Sturgiss S, Davison J. Perinatal outcome in renal allograft recipients: prognostic significance of hypertension and renal function before and during pregnancy. Obstet Gynecol 1991; 78 (4): 573-77.
7. Bar J, Fisch B, Wittenberg C et al. Prednisone dosage and pregnancy outcome in renal allograft recipients. Nephrol Dialysis Tranplant 1997; 12: 760-63.
8. Santamaria L, Duarte G, Costa J et al. Pregnancy and kidney transplantation: experience in a developing country. Am J Kidney Dis 1995; 25(3): 465-70.
9. Ha J, Kim S, Kim S. Pregnancy following renal transplantation. Transplant Proc 1994; 26(4): 2117-18.
10. Armenti V, Ahlswede K, Ahlswede B et al. National Transplantation Pregnancy Registry - outcomes of 154 pregnancies in cyclosporine-treated female kidney transplant patients. Transplantation 1994; 57(4): 502-6.
11. Armenti V, McGory C, Cater J et al. Pregnancy outcomes in female renal transplant recipients. Transplant Proc 1998; 30: 1732-34.
12. Gallery E. Pregnancy in women with renal transplants. Int J of Artif Organs 1989; 12 (3): 141-43.
13. Vennarecci G, Pisani F, Tisone O et al. Kidney transplantation and pregnancy. Tranplant Proc 1997; 29: 797-98.
14. Tanabe K, Kobayashi C, Takahashi K et al. Long-term renal function after pregnancy in renal transplant recipients. Transplant Proc 1997; 29: 1567-68.
15. Sturgiss S, Davison J. Effect of pregnancy on the long-term function of renal allografts: an update. Am J Kidney Dis 1995; 26 (1): 54-56.
16. Bakr M, Said M, Fouda M et al. Clinical course and outcome of pregnancies in recipients of renal allografts. Transplant Proc 1997; 29: 2787-89.
17. Bererhi L, Bedrossian J, Metiver F et al. Pregnancy in kidney transplantation: past and present experience. Transplant Proc 1997; 29: 2478.
18. O'Donnell D, Sevitz H, Seggie J et al. Pregnancy after renal transplantation. Aust NZ J Med 1985; 15: 320-25.
19. Framarino M, Poli L, Pierucci F et al. Pregnancy and kidney transplantation: clinical problems and experience. Transplant Proc 1993; 25 (3): 2188-89.
20. Pahl M, Vaziris N, Kaufman D, Martin D. Childbirth after renal transplantation. Transplant Proc 1993; 25 (4): 2727-31.
21. Moon J, Park S, Cheon K et al. Pregnancy in renal transplant patients. Transplant Proc 2000; 32: 1869-70.
22. Davison J. Pregnancy in renal allograft recipients: problems, prognosis and practicalities. Bailliere's Clin Obstet & Gynaecol 1994; 8 (2): 501-25.
23. Rahbar K, Forghani F. Pregnancy in renal transplant recipients: an Iranian experience with a report of triplet pregnancy. Transplant Proc 1997; 29: 2775.
24. Cararach V, Carmona F, Monleon F, Andreu J. Pregnancy after renal transplantation: 25 years experience in Spain. British J of Obstet & Gynaecol 1993; 100: 122-25.
25. Toma H, Tanabe K, Tokumoto T et al. Pregnancy in women receivin renal dialysis or transplantation in Japan: a nationwide survey. Nephrol Dialysis Transplant 1999; 14: 1511-16.