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Pregnancy after Renal Transplantation

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Abstract: ***Background: Pregnancies in renal transplant recipients continue to remain challenging due to the risks to graft, fetus and mother. This is a retrospective case-note review aiming to identify graft, fetal and maternal outcomes in such pregnancies. Aim: Identification of maternal, fetal and graft outcomes of pregnancies in renal transplant recipients. Methods: This is a retrospective study of pregnancies in renal transplant recipients over ten years in a tertiary care hospital. Medical records were reviewed for maternal outcomes (hypertension, gestational diabetes, anemia, infections, Caesarean section), fetal outcomes (therapeutic abortions, miscarriages, prematurity, low birth weight), and effect of pregnancy on allograft function. During the study period there were twelve pregnancies in women with renal transplant. Results: There were eight live births with healthy babies. Median age at conception was 28 years. 58.3% of women had preexisting hypertension and the overall incidence of hypertension was 83.3%. One woman developed gestational diabetes. 50% of pregnancies were complicated by antenatal infections and anaemia was found in 50% of patients. 65.5% needed a Caesarean section. The incidence of preterm delivery was 55.5%. 33% of babies were small for gestational age. There were two first-trimester miscarriages, one second-trimester miscarriage and an iatrogenic preterm delivery at 26 weeks. All women had a stable renal function at conception. A decline in graft function was observed in 33.3% of patients and there were no cases of acute rejection. Conclusion: Most pregnancies after kidney transplantation are successful but rates of maternal and neonatal complications remain high. Significant causes of morbidity in this study were hypertension, prematurity and fetal growth restriction. Our study reaffirms the need for multidisciplinary care in patients living with renal transplant because of the increased risk of maternal and fetal complications.***

Keywords: Pregnancy, high-risk, renal, transplantation, maternal, fetal, outcome

1. Background

Renal transplantation dramatically improves sexual function in both men and women with end-stage kidney disease who commonly experience sexual dysfunction and infertility (1, 2). In women this dysfunction is a result of altered hypothalamic function associated with hormonal imbalance including high Follicle-Stimulating Hormone (FSH), Luteinizing Hormone (LH), and prolactin levels (3). Other factors like vasomotor dysfunction, prescribed medications, and psychological factors also contribute to infertility (3, 4). Pregnancy is thus rare in women with end stage renal disease, including those requiring dialysis (5). Renal transplant reverses many of the aforementioned hormone aberrations, resulting in normal ovulatory cycles and regular menstruation (3,6).

In 1956, 23-year-old Edith Helm, the world's longest surviving transplant recipient, received a kidney from her identical twin sister. Two years later, she delivered a healthy full term boy by Caesarean section (7). Since then, many successful pregnancies have been reported in renal transplant recipients and considerable change has come across immunosuppression protocols and thus, graft function (8,9).

Pregnanciesin renal transplant recipients pose multiple problems to the mother and the baby due to an increased risk of adverse maternal complications like preeclampsia and hypertension, risk of adverse fetal outcomes like premature birth, low birth weight, and the risk of decline in graft function (5). In this study, we aim to report the outcomes of 12 pregnancies in renal transplant recipients spanning the period from 2008 to 2018.

Aim

To identify maternal, fetal and graft outcomes in twelve pregnancies in renal transplant recipients.

Design

Retrospective case-note review.

2. Methods

We performed a retrospective study of twelve pregnancies in ten renal transplant recipients over a period of 10 years at Fernandez Foundation, Hyderabad.

Electronic medical records were reviewed for the following details: age at the time of conception; time interval between pregnancy and transplantation; parity; presence of hypertension or other co-morbid conditions; drugs of immunosuppression; other medications. The details of the course of each pregnancy, maternal, fetal and graft adverse outcomes were also reviewed.

- Maternal adverse outcome measures: hypertension during pregnancy, gestational diabetes, anemia, infections, Caesarean section, and any other complications.
- Fetal adverse outcome measures: therapeutic abortions, miscarriages, preterm deliveries, low birth weight, and congenital abnormalities.
- Effect of the pregnancy on allograft function: We compared serum creatinine as an index of graft function before and after pregnancy. Decline in graft function was defined by an increase in serum creatinine of more than 0.3 mg/dL.

All women received multidisciplinary care including regular antenatal checkups with obstetrician, simultaneous follow-up with nephrologist, nutritionist and anaesthesiologist as necessary. Thorough clinical assessment and pertinent laboratory investigations were performed at each visit. Close fetal monitoring by clinical evaluation; ultrasound to rule out structural anomalies and fetal growth surveillance from 28 weeks were conducted. Mode of delivery was decided based on obstetric indications.

Chronic hypertension was defined as systolic Blood Pressure (BP) ≥140 mm Hg or diastolic BP ≥90 mm Hg that predates the onset of pregnancy. Preeclampsia was defined as new-onset hypertension after 20weeks of gestation with new-onset proteinuria. Chronic hypertension with superimposed preeclampsia was defined as chronic hypertension with new-onset proteinuria or other signs/symptoms of preeclampsia or HELLP syndrome after 20 weeks of gestation. Proteinuria was defined as the excretion of 300 mg or more of protein in a 24-hour urine collection or a protein to creatinine ratio of at least 0.3 (each measured as mg/dL) (10). Anemia was defined as hemoglobin levels below 11 g/dL. Preterm birth was defined as birth before 37 weeks of gestation, and Small for Gestational Age (SGA) was defined as birth weight less than 10th centile for gestational age.

3. Results

There were twelve pregnancies identified in ten recipients. The median age at conception was 28 years and 8 out of 12 women were primipara (75%). One pregnancy was conceived using ovulation induction and the remaining were spontaneous conceptions. All women in this study conceived at least 2 years after transplantation, mean interval between transplant and pregnancy being 5.6 years. Eight women received a transplant from their mother and four from their brother. All were live donor transplantations. The initial nephropathy was unknown in two patients. The maternal characteristics are depicted in table 1.

Table 1: Maternal Characteristic (n=12)	
Mean maternal age	28 years (Range 24-33 years)
Mean duration since transplant	5.6 years (Range 1-10 years)
Primigravidae (%)	75
Spontaneous conception (%)	91.6
Renal parameters at conception	All were normal

The following immunosuppression regimens were used: prednisolone, azathioprine and cyclosporine - 33.3%, prednisolone, azathioprine and tacrolimus - 41.6%, prednisolone and azathioprine – 16.6%, azathioprine, tacrolimus and deflazacort - 8.3%.

Table 2: Pregnancy Outcomes (n=12)	Number (%)
Live births	8 (66.6)
Stillbirth	1 (8.3)
Miscarriages	3 (25)

The pregnancy outcomes are recorded in Table 2. There were eight live births with healthy babies. There were two first trimester miscarriages (both of these women went on to have successful second pregnancies) and one second trimester miscarriage at 16 weeks. An iatrogenic preterm delivery at 26 weeks gestation performed due to rapid deterioration in renal function and uncontrolled blood pressures resulted in a stillborn baby.

Maternal complications

The overall incidence of hypertension complicating pregnancy in this study was 83.3%.Seven pregnancies (58.3%) were complicated bychronic hypertension out of which three (42.8%)developed superimposed preeclampsia. Three of the previously normotensive women developed preeclampsia during pregnancy (60%).

No patient was diabetic pre-pregnancy. One woman developed gestational diabetes, which was controlled with dietary modifications. 50% of pregnancies were complicated by antenatal infections, the commonest of which were urinary tract infections (3 cases), respiratory tract infections (2 cases), gastroenteritis (2 cases) and vaginitides (2 cases), all of which were treated successfully. Anaemia was found in 50% of patients and 16% were complicated by preexisting avascular necrosis of hip secondary to corticosteroid therapy.

Mode of delivery was decided based on obstetric indications alone. 65.5% needed a Caesarean section and the most common indication was presumed fetal compromise. All surgeries were done under regional anaesthesia and there were no intra-operative complications.

Fetal outcomes:

There were eight live births and one stillbirth.

Table 4: Fetal outcomes	Number (%)
Small for gestational age	3 (33)
Prematurity	5 (55.5)
Neonatal jaundice	2 (22.2)

Three babies (33%) were small for gestational age at birth. Mean birth weight was 2.2 kg. The weight distribution is shown in Chart 1.

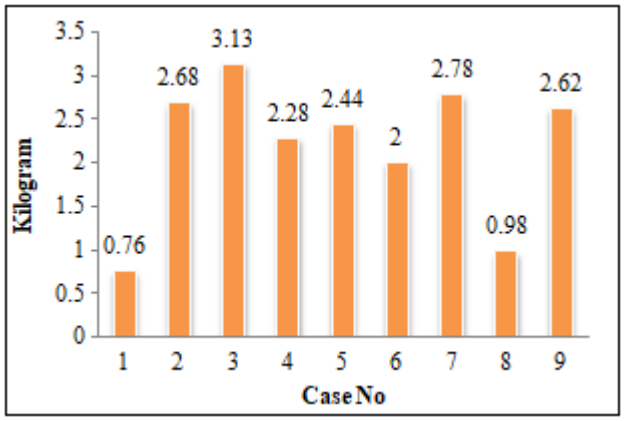

Chart 1: Birth weight distribution

Table 3: Maternal complication (n=12)	Percentage (number)
Chronic hypertension (%)	58.3 (7)
New onset hypertension (%)	25 (3)
Infections (%)	50 (6)
Anaemia (%)	50 (6)
Decline in renal function (%)	33.3 (4)

The incidence of preterm delivery was 55.5%. 60% of all preterm births were iatrogenic and 40% were spontaneous preterm births. Mean gestational age at delivery was 34.6 weeks and the mean gestational age at delivery in the preterm group was 32.4 weeks.

There were no congenital abnormalities noted. Neonatal jaundice occurred in 22% of all babies.

Graft function

All women had a stable renal function at conception. Mean creatinine was 0.97 mg/dL during early pregnancy and 1.22 mg/dL at the time of delivery. There were no cases of acute rejection, but graft function declined during pregnancy in four patients. One mother died two months after delivery due to complications related to progressive renal impairment and dialysis. The remaining three patients regained normal renal function by six months postpartum.

4. Discussion

Although a majority of pregnancies after renal transplant result in a live birth, both maternal and fetal adverse events are common. Most of the current knowledge regarding pregnancies in renal transplant recipients comes from limited data from retrospective studies and meta-analysis of the United States National Transplant Registry (NTPR) and United Kingdom Transplant Registries (UKTPR) (11).

There is considerable debate regarding the optimal time of conception after renal transplant. According to American Society of Transplantation guidelines, the ideal time of conception is between one and two years after transplantation, whereas a delay of two years is recommended by European best practice guidelines (12,13). KDIGO guidelines allow for pregnancy after one year of transplantation provided there is stable renal function and cessation of teratogenic drugs. The transplant to conception intervals in this study ranged between two to ten years and all women had stable renal function at conception.

The incidence of chronic hypertension in our series was 58.3%, which is similar to 63% reported by NTPR (14), 69% by UKTPR (15) and 77% by Thompson et al. (16). However, the incidence of preeclampsia in pregnancies after renal transplant has been reported with a large variation in literature. Many factors including the type of immunosuppressive drugs, graft function, obesity, smoking, alcohol and the presence of native kidney contribute to the risk of development of hypertension in pregnancy (17). UKTPR reported an incidence of 5%, NTPR reported 32% (14), 29% was reported by Thompson et al. (16), 37% by Gutiérrez et al. (18) and as high as 47%by Yassaee F et al. (19). In this study, preeclampsia was found to complicate 50% of all pregnancies. In pregnancies with chronic hypertension, 43% developed superimposed preeclampsia. In this setting, superimposed preeclampsia was identified by new onset proteinuria in a previously non-proteinuric woman or by the development of HELLP syndrome.

Transplant recipients have an increased risk for infection as a result of the use of immunosuppressive medications (20), the commonest being urinary tract infection with reported incidence of up to 42% due to reflux and mild hydronephrosis after transplant (21, 22). Pregnancy itself predisposes to urinary tract infection, which is possibly related to dilatation of renal collecting ducts and ureters. In this study, urinary tract infections occurred in 25% of women. Other infections observed were upper respiratory tract infections, gastroenteritis and vaginitides.

Many studies have reported a high incidence of anaemia in renal transplant recipients ranging from 31% to 62%. This appears to be due to impaired renal function or use of drugs (19, 21, 23). In this study, anaemia was found in 50% of women and this is comparable to the aforementioned studies.

Post-renal transplant pregnancies are expected to have a higher incidence of diabetes mellitus, which can be explained by the use of immunosuppressive medications like steroids and calcineurin inhibitors and predisposition to diabetes due to ethnicity (24). Such an association was not found in this study. Screening for diabetes was performed for all women and only one developed gestational diabetes mellitus, which was controlled with medical nutrition therapy and exercise. Data from other studies, where there was no increase in incidence of diabetes compared to general population confirms our finding (5, 25).

A majority of pregnancies in women after kidney transplant result in live births. Deshpande et al. observed a live birth rate of 73.5% in a meta-analysis of 4706 pregnancies, 71-76% were observed in the NTPR (26) and 79% in UKTPR (15). Our study found a comparable live birth rate of 66.6%.This can be attributed to a high rate of first trimester miscarriage of 16.6%. Excluding the above mentioned early pregnancy losses, a live birth rate of 80% was noted. Other large studies like Davison et al. noticed a similarly high first trimester loss rate, with a majority of pregnancies that go beyond first trimester resulting in a live birth (27).

There was one case of stillbirth due to iatrogenic preterm delivery at 26 weeks of gestation in a severely growth restricted fetus with Doppler compromise. Worsening maternal condition due to uncontrolled hypertension and deteriorating renal function necessitated the preterm delivery. Two pregnancies resulted in first trimester miscarriages. This confirms previous research data indicating rates ranging from 11-26% (26, 28) as compared to 8-9% in general population.

Data on pregnancies after renal transplant consistently shows a high incidence of preterm delivery and small for gestational age fetuses. Preterm delivery rates have been reported to be approximately 50% in the US, European and UK registries (15, 29) and as high as 64% in other center reports (30). A similar rate of 55.5% was observed in this study, of which 40% were due to spontaneous preterm labour and 60% were iatrogenicin view worsening maternal condition or presumed fetal compromise. This finding is in agreement with previous research data showing that most preterm deliveries in renal transplant recipients occur because of maternal and/or fetal compromise, rather than spontaneous preterm labour (24).

The incidence of SGA babies in this study was 33% and is comparable to reported rates between 30 and 50% in kidney transplant patients (24, 31). All cases of fetal growth restriction were associated with maternal hypertension and 66% of them had superimposed preeclampsia. The strong association between hypertension and risk of fetal growth restriction in the backdrop of renal disease has been advocated by many studies (24,31).

There is increasing concern regarding the effect of immunosuppressive drugs on the fetus as all of these drugs pass through maternal-fetal circulation to varying degrees (29). The commonly used medications in renal transplant recipients for maintenance immunosuppression are azathioprine, cyclosporine, tacrolimus, mycophenolate mofetil, sirolimus, rapamycin and prednisolone. Data from NTPR and many studies foundthe incidence of birth defects in pregnancies of renal transplant recipients to be similar to the general population, except for pregnancies with mycophenolate exposure which have a higher incidence of birth defects (32–34). In this study, the most common combinations of drugs used were prednisolone, azathioprine and tacrolimus (41.6%) and prednisolone, azathioprine and cyclosporine (33.3%). None of the mothers were exposed to mycophenolate and no birth defects were noted.

Renal transplant does not preclude a vaginal delivery as the renal allograft which is usually situated in the false pelvis does not obstruct the birth canal (22). However, a higher Caesarean section rate ranging from 43-64% has been reported by many studies, a majority being for fetal distress and 3% merely for the presence of an allograft (5,22,24–26). Our study has a comparable caesarean section rate of 65.5% and the most common indication was presumed fetal compromise. Mode of delivery was dictated by obstetric indications alone. All surgeries were done under regional anaesthesia, which is the preferred mode as documented in many other studies (35) and there were no anesthetic complications.

Considerable uncertainty exists regarding the effect of pregnancy on graft function and the mechanisms surrounding this (36). In this study, all women had a stable renal function at the time of conception and had conceived more than two years after transplantation. Decline in graft function, as defined by an increase in serum creatinine of more than 0.3 mg/dL, was observed in 4 patients. All four women had a component of hypertension complicating pregnancy. Three of them had normal serum creatinine levels 6 months postpartum. One woman died 2 months after delivery due to complications related to the deteriorating renal function. There were no cases of acute graft rejection. This confirms data from other studies which observed no increase in incidence of graft rejection compared to non-pregnant women, possibly owing to pregnancy being a state of reduced immunity (37, 38).

5. Conclusion

A majority of pregnancies after kidney transplantation are successful but rates of maternal and neonatal complications remain high. Significant causes of morbidity in this series were hypertension, prematurity and fetal growth restriction. Pre-pregnancy counseling about potential risks will enable pregnancy planning and help parents make an informed decision. Our study reaffirms the need for multidisciplinary care for pregnancies in patients living with renal transplant to minimize the potential complications and increase the chance of a successful outcome for the mother and the child.

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