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ORIGINAL ARTICLE

Outcome of Pregnancy and Impact on Kidney Function Among Renal Transplant Recipients; a Retrospective Study

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ABSTRACT

Background: Pregnancy after kidney transplantation may be associated with maternal, fetal complications. In our study, we evaluated the outcome of pregnancy after kidney transplantation.

Methods: Retrospective cohort study conducted on 236 patients out of 3000 kidney transplant recipients who underwent kidney transplantation at Mansoura Urology and Nephrology Centre between March 1976 and December 2019, divided into two groups, group I; 118 kidney transplant recipients experienced pregnancy after kidney transplantation and Group II; 118 kidney transplant recipients who didn't experience pregnancy after kidney transplantation.

Results: Frequency of pregnancy in our center is 191 pregnancies in 118 women after kidney transplantation between 1976 and 2019. We found the mean pregnancy age between (26.27- 29.89), the mean gestational age between (33.69-33) weeks. The live birth rate is 126 (66%). Preterm delivery rate is 85 (44.5%), neonatal death 8 (4.1%), miscarriage 59 (30.9%), intrauterine fetal death 6 (3.1%) and birth defect 4 (2%). The frequency rates of gestational hypertension is 87 (45.5%), pre-eclampsia 48 (25.1%), gestational diabetes 19 (9.9%), and urinary tract infection 36 (18.8%). Cesarean section is the most common method of delivery in our study 133 (69.6%).

Conclusions: The risks of maternal and fetal complications are high among pregnant kidney transplant recipients, including pregnancy-induced hypertension, increased pre-eclampsia rates, gestational diabetes, and cesarean section rates. Serum creatinine and 24-hour urinary protein tend to increase during and after pregnancy which may impair the graft outcome. Pregnancy counseling is necessary to avoid high-risk or unwanted pregnancies.

Keywords: Kidney transplantation, Pregnancy, Hemodialysis..

INTRODUCTION

Renal transplantation improves the fertility of women of child-bearing age [1]. Studies have been published examining the obstetric and renal outcomes of the resultant pregnancies [2]. The possibility of a term pregnancy is one of the benefits of solid organ transplantation for women. The gonadal dysfunction, caused by the kidney or another organ's failure, is reverted within a few months after normal graft function. However, unplanned pregnancies in transplant recipients may compromise graft function and survival and may also risk unnecessary fetal exposure to immunosuppressive medications. Thus, pregnancy planning is essential in these patients, who wish to know the contraindications and complications and issues concerning the baby's health and their future kidney function [3].

All the used drugs for immunosuppression can cross the circulation of the mother and fetus in varying degrees. Due to their risk of teratogenicity and toxicity, it is vital to control immunosuppressive medication during pregnancy [4]. Prednisone and methylprednisolone are the most popular corticosteroids used in renal transplant recipients; prednisone is considered (category B) while methylprednisolone is considered (category C). The likelihood of premature membrane rupture and gestational hypertension is often raised by large doses of corticosteroids above 20 g a day that is seldom associated with fetal adrenal hypofunction and congenital anomalies [5].

Azathioprine is considered safe during pregnancy, although azathioprine has been classified as a class D by FDA. Teratogenicity is linked with azathioprine in animal studies used at high doses of 6 mg/kg and no reported congenital disabilities in doses below 2 mg/kg [6].

Mycophenolic acid (MPA) (category D) is viewed by FDA as commonly linked to limbs and facial anomalies, lip and palate cleft, diaphragm, congenital hernia, and congenital heart defects [4]. Genetic defects and abortion have risen by 23% and 49% in MPA treatment [7]. During pregnancy, MPA is contraindicated and should be avoided six months before conception. What should be done for unplanned pregnancy during treatment of pregnant women with MPA remains uncertain, but the decision must be made for each case after careful counseling [8]. Throughout pregnancy, CNIs are considered safe. The incidence of CNIs therapy identified congenital abnormalities (4-5%) is close to those of the general population (3-4%) [4]. Cyclosporine is associated with the elevated incidence of pre-eclampsia. Also, a high risk of IUGR, reduced birth weight, and lowered gestational age neonates. Sirolimus is categorized C according to the FDA. It has to be stopped six months before conception and during pregnancy [5].Fetal mortality and delayed skeletal ossification are observed in animal studies. Human studies on sirolimus use during pregnancy are limited [5]. However, pregnancy after kidney transplantation is associated with more maternal complications than pregnancy in the normal population, with a higher rate of pre-eclampsia, delivery by cesarean section, and more adverse fetal outcomes, including intrauterine growth restriction, pre-term delivery, and low birth weight resulting in increased neonatal morbidity and mortality [9].

Besides, the infants' prognosis is affected regardless of prematurity because they experience a higher risk of severe infections in the first year of life due to intrauterine exposure to immunosuppressant drugs [10]. While most studies have not found an overall negative effect of pregnancy on graft function and survival, they have found an association between graft function at the time of conception and subsequent deterioration of function and graft loss. The parameters that were found to be related to decreased graft function and loss after pregnancy were the time between transplantation and pregnancy, estimated glomerular filtration rate (GFR) and level of urinary protein pre-pregnancy, and hypertension [11].

Studies have also shown an increase in graft loss during and after pregnancy among sensitized patients [12] and a higher risk of graft failure due to rejection in pregnancies occurring in the first and second-year post-transplantation [13]. Most of these observations were found in studies using non-pregnant recipients' controls. Still, most did not match the study group in several critical clinical parameters, such as the creatinine level pre-pregnancy or the cause of native kidney failure [14]. Studies on pregnancy outcomes after kidney transplantation in the Arab world demonstrated that Pregnancies in kidney transplant recipients are most successful in those with adequate kidney function and controlled comorbidities. Like other regions, the risk of pre-eclampsia (26%) and gestational diabetes (7 %) in pregnant kidney transplant people in the Middle East was higher than in the general population. The frequency of cesarean delivery was 61%, and pre-term babies' incidence reached 46 [15]. Our study aimed to evaluate pregnancy outcomes after kidney transplantation and the effect on graft function in female renal transplant recipients at Mansoura Urology and Nephrology Center.

METHODS

A case-control(retrospective) study was conducted at Urology and Nephrology Center, Mansoura University.

Ethical consideration: Our study is a retrospective study. Written informed consent was obtained from all participants. The study was approved by the research ethics committee of the Faculty of Medicine, Mansoura University. According to The Code of Ethics of the World Medical Association (Declaration of Helsinki), the study was done for studies involving humans. The data was retrieved from our patient information system at Urology and Nephrology Center after an agreement from the head of the center's department and director. We confirm that we do not use patients' names, initials, or hospital numbers. The medical research and ethics committee of Zagazig University approved the study. The work was carried out following The Code of Ethics of the World Medical Association.

Subjects: The data of all kidney transplant recipients who underwent renal transplantation in the Urology & Nephrology Center, Mansoura University, Egypt, from March 1976 to December 2019, were retrospectively analyzed. We found a total number of 704 female renal transplant recipients out of 3000 kidney transplant recipients. Four hundred forty-seven kidney transplant ladies are in the child-bearing period; 118 out of them got married and got pregnant. The study included 236 patients, 118 kidney transplant recipients who got married and pregnant, included in group1, matched with 118 kidney transplant recipients, included in group 2, according to age, duration of renal transplantation, and fitting in primary immunosuppressant drugs.

Immunosuppression Protocols: all patients received calcineurin inhibitors (CNI)-based immunosuppressive therapy, consisting mainly of cyclosporine or tacrolimus, CNI trough levels were followed every month. Mycophenolate mofetil (MMF) was stopped before conception by six weeks, mTOR (Rapamune) was ceased four months before conception, and they were replaced by azathioprine (AZA) in a dose of 1.5-2 mg/kg/day. Mycophenolate mofetil (MMF) was resumed at the end of 1st week post-partum. Pregnancy allowed after one year of Rituximab(16).

Follow-Up Data: The transplant registry at Mansoura urology and nephrology center was reviewed for both groups to assess the transplant outcome using univariate and multivariate analysis. All pregnancies were allowed after one year of renal transplantation if stable allograft function for six months (normal renal function, creatinine clearance >40ml/min), in the absence of hypertension (<140/90 mm Hg) and proteinuria (<300 mg/day).

We define patients with gestational hypertension as systolic BP is 140 mmHg or more and diastolic BP 90 mmHg or more after 20 weeks of gestation without suggestive pre-eclampsia symptoms of proteinuria(17). Currently, according to the American Association of Obstetricians and Gynaecologists (ACOG) diagnostic criteria of pre-eclampsia, proteinuria is not a must in the diagnosis of pre-eclampsia and defined as new-onset hypertension after week 20 of gestation in a normotensive patient with any features of end-organ dysfunction such as elevated serum creatinine more than 1.1 mg/dl or double the baseline serum creatinine in the absence of other renal diseases, elevated liver enzymes double the normal or more, thrombocytopenia <100,000/microliter, pulmonary edema, cerebral symptoms, or visual symptoms(18). Gestational diabetes (GDM) has been defined as a state of glucose intolerance first recognized during pregnancy around 22-24 weeks(19).

Anemia was defined as hemoglobin levels below 11 g/dl. Pre-term birth was defined as birth before 37 WG, and low birth weight was<2500 g.

In scheduled pregnancy, ACEIs and ARBS should be stopped and replaced by other antihypertensive drugs such as CCB, Alfa methyldopa, and B. blockers. Aspirin (75 mg/day) was initiated from 12 WG until one week before delivery. Calcium supplement also was taken by a dose of 1.5-2 gm/day starting from 20 WG until the end of pregnancy. Both of them may decrease the risk of pre-eclampsia. 400 ug /day of folic acid was taken one month before conception until the first three months of pregnancy, then start an iron supplement. Erythropoietin was introduced according to Hb level. Low molecular weight heparin (enoxaparin) 1mg/kg/day/12 h SC was initiated if there was a history of thrombosis, vasculitis, antiphospholipid syndrome. And all the patients were not allowed for regular breasting feeding. During pregnancy, we evaluate the patients monthly for clinical data as (blood pressure, urine output, LL edema, pre-eclampsia clinical picture) and lab. Data such as serum creatinine, blood urea, urine analysis, urine culture, liver enzymes, serum uric acid, CBC, 24 h urinary protein, fasting & postprandial venous plasma sugar (each visit in people with diabetes and every three months in non-diabetics), and Close follow up of cyclosporine, and FK level occurred /2-3 weeks from the beginning of pregnancy. Radiological doctors assess the graft function by abdominal ultrasound (when indicated). Graft greyscale ultrasound and Doppler ultrasound if there is clinical suspicion of acute rejection, acute tubular necrosis, or renal artery thrombosis. Obstetric doctors evaluate the pregnancy by abdominal ultrasound and Doppler monthly tell 34weeks then weekly until time of delivery.

STATISTICAL ANALYSIS

Results were recorded with SPSS version 21 for windows, tabled, and analyzed (SPSS Inc. Chicago). The T-test has been used to compare the continuous data between the two groups. The categorical data were compared using the Chi-Square Test. The One-way ANOVA was used to compare both groups as regard serum creatinine and the 24-hour urinary protein. During each pregnancy, the descriptive analysis was applied to estimate the results of pregnancy and complications. The graft and the patient survival were assessed using the Kaplan-Meier technique. Statistically significant P-value <0.05 has been considered.

RESULTS

Our study showed 118 kidney transplant recipients got pregnant 191 times, 64 kidney transplant recipients got pregnant for the second time, while 9 of them got pregnant for the third time. We have found that the mean age of pregnancy between (26.27- 29.89), the mean gestational age between (33.69- 33) weeks, the live birth rate is 126 (66%). Preterm delivery rate is 85 (44.5%), neonatal death 8 (4.1%), miscarriage 59 (30.9%), intrauterine fetal death 6 (3.1%) and birth defect 4 (2%). The frequency rates of gestational hypertension are 87 (45.5%), pre-eclampsia 48 (25.1%), gestational diabetes 19 (9.9%), urinary tract infection 36 (18.8%), and graft rejection 8 (4.1%) during pregnancy. cesarean section is the most common method of delivery in our study 133 (69.6%). At last follow-up, most patients were

alive with functioning graft with no statistically significant difference between the two groups. Also, no significant difference as regard graft failure incidence was observed.

Table (1) showed no statistically significant difference among both groups regarding the recipient and donor's demographic data and their relationship. Table (2) showed that Most of our patients suffered from hypertension and maintained on hemodialysis. The difference was statistically insignificant. Table (3) showed that the mean age at first pregnancy was 26.2 years. Gestational ages at 1st, 2nd, and 3rd pregnancy were 33.69, 35, 33 years, respectively. Mean serum creatinine before pregnancy was 1.1 mg/dl, and 24-hour urinary protein was 0.5 g/day.

Table (4) showed that Gestational related hypertension was the most frequent pregnancy-related side effect, 87 out of 191 pregnancies complicated with gestational-related hypertension. Preeclampsia developed in 48 out of 191 pregnancies. Cesarean section was the most frequent method used for delivery. Most pregnancy cases have live-birth. There were 65 non-live-birth cases. Eight patients experienced rejection episodes during pregnancy. Table (5) showed that most patients were alive with functioning grafts at the last follow-up, with no statistically significant difference between the two groups.

Table (6) showed that serum creatinine was higher during and after 1st pregnancy with a statistically significant difference compared to before pregnancy data ***(p-value: 0.0001).*** Also, the 24-hour urinary protein was higher during and after 1st pregnancy with a statistically significant difference compared to before pregnancy data ***(p-value: 0.0003)*** There is no statistically significant difference in serum creatinine during and after 2nd pregnancy compared to before pregnancy data ***(p-value: 0.34).*** 24-hour urinary protein was higher during and after 2nd pregnancy with a statistically significant difference compared to before pregnancy data ***(p-value: 0.0001).*** There was no statistically significant difference in serum creatinine and proteinuria during and after 3rd pregnancy compared to before pregnancy data ***(p-value: 0.76, p-value: 0.669).***

Figure (1) showed no statistically significant difference between both groups regarding 5,10-, and 15-year's graft survival (p-value: 0.08). Figure (2) showed no statistically significant difference between both groups regarding 5,10-, and 15-year's patient survival (p-value: 0.14).

Table 1: Demographic data of the recipients and donors among both groups:

	Pregnant Group 118 KTRs*	**Non- Pregnant Group 118 KTRs***	**p Value**
Recipient age (years) mean±SD	21.8±4.9	23.1±5.7	0.063**
Donor age (years) mean±SD	38.27±10.62	37.75±11.74	0.723**
Donor gender. Male No. (%)	56 (47.5%)	54 (45.8%)	
.female No. (%)	62 (52.5%)	64 (54.2%)	0.794***
Consanguinity. Related No. (%)	104 (88.1%)	103 (87.3%)	
.unrelated No.(%)	14 (11.9%)	15 (12.7%)	0.563***

*Kidney transplant recipients, **Student t-test, ***Chi-square test

Table 2: Pre-transplant medical condition among both groups

	Pregnancy Group 118 KTRs* No. (%)	**No- Pregnancy Group 118 KTRs* No. (%)**	**p Value**
Pre-transplant hypertension	57 (48.3%)	55 (46.6%)	0.794**
Pre-transplant diabetes mellitus	1 (0.8%)	3 (2.5%)	0.313**
Pre-transplant Dialysis	113 (95.8%)	111 (94.1%)	0.553**
Pre-emptive transplant	5 (4.2%)	7 (5.9%)	0.5**

*****Kidney transplant recipients,**Chi-square test

Table 3: Baseline characteristics of the pregnant group

	Pregnancy Group 118 KTRs* No. (%)
Age at 1st pregnancy (years) mean±SD	26.27±4.37
Age at 2nd pregnancy (years) mean±SD	28.02±4.01
Age at 3rd pregnancy (years) mean±SD	29.89±4.6
Gestational age of 1st pregnancy (weeks) (years) mean±SD	33.69±6.4
Gestational age of 2nd pregnancy (weeks) (years) mean±SD	35±5.6
Gestational age of 3rd pregnancy (weeks) (years) mean±SD	33±7.5
S.creatinine before pregnancy (mg/dl) mean±SD	0.9±0.2
24-hour urinary protein (g/day) mean±SD	0.4±0.2

***Kidney transplant recipients

Table 4: Overall Pregnancy outcome

	Number of pregnancies 191 No. (%)
Gestational hypertension	87 (45.5%)
Pre-eclampsia	48 (25.1%)
Gestational diabetes	19 (9.9%)
Urinary tract infection during pregnancy	36 (18.8%)
Graft rejection during pregnancy	8 (4.1%)
Delivery Method:	
Vaginal	31 (16.2%)
cesarean	133 (69.6%)
Pregnancy outcome:	
Live birth	126 (66%)
Miscarriage	59 (30.9%)
Intra-uterine fetal death	6 (3.1%)
Pre-term	85 (44.5%)
Neonatal death	8 (4.1%)
Birth defect	4 (2%)
Graft rejection after pregnancy	10 (5.2%)
Hypertension at last follow-up	61 (31.9%)
Diabetes at last follow-up	13 (10.9%)

Table (5): Condition at last follow up years among both groups

	Pregnancy Group 118 KTRs* No. (%)	**No- Pregnancy Group 118 KTRs* No. (%)**	**p Value**
Living with functioning graft	84 (71.1%)	71 (60.1%)	0.07 x2
Living on dialysis	24 (20.3%)	29 (24.5%)	0.52 x2
Died with functioning graft	5 (4.2%)	6 (5.1%)	0.75 x2
Died with failed graft	5 (4.2%)	12 (10.2%)	0.078 x2

***Kidney transplant recipients, x2Chi-square test

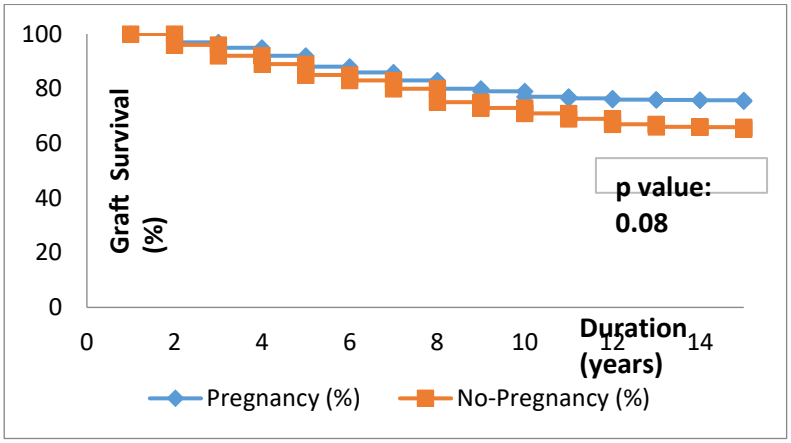

Figure 1: Kaplan-Meyer curve illustrating graft survival analysis between both groups.

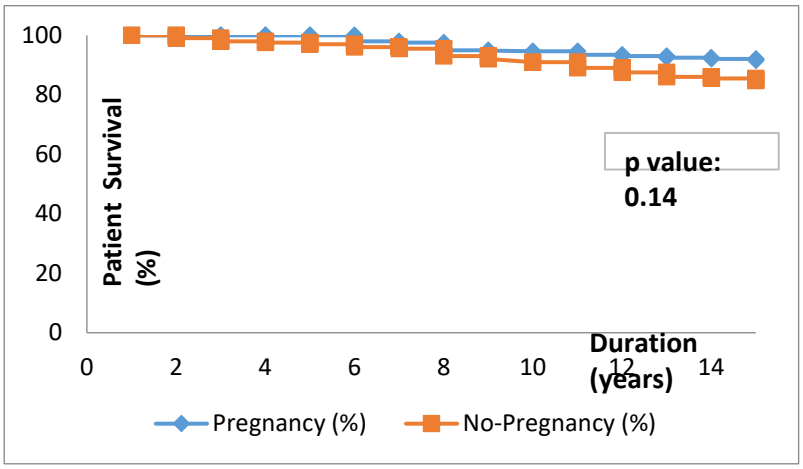

Figure 2: Kaplan-Meyer curve illustrating patient survival analysis between both groups.

DISCUSSION

For women with ESRD, pregnancy is a serious and challenging problem. Hypothalamic-pituitary suppression induces amenorrhea in women on dialysis. Consequently, they have trouble conceiving and often suffer from infertility [20]. Kidney transplantation has been shown to significantly boost fertility and increase the probability of pregnancies as an ESRD treatment choice [21]. However, maternal comorbidities and gestational complications are frequent among women with RT that affect the birth outcome compared to controls [22].

Our study included 118 KTRs who experienced pregnancy 191 times, 64 KTRs got pregnant for the second time, while nine got pregnant for the third time. Pregnancy has become a common consequence of kidney transplants due to improvements in recipient management. With or without proteinuria, pregnancy-induced hypertension was observed in 87 pregnancy cases out of 191 (45.5%). Our results are comparable to Shah et al.'s(18)results that reported incidence of gestational hypertension after kidney transplantation by about 52% to 69%.

Preeclampsia developed in 48 pregnancy cases out of 191 (25.1%). These rates were much higher than the general population (3.8%) (23).Vannevel et al. (24)reported a higher pre-eclampsia rate (38%) among 52 kidney transplant women.

Urinary tract infections diagnosed by a positive urine culture occurred in 36 pregnancy cases out of 191(18.8%) in our study, and it is less than reported in Shah and Verma's(3)study results (40%).

Allograft rejection was observed in 8 cases during pregnancy (4.1%), and tenpatients (5.2%) developed chronic rejection after pregnancy, lower than the 9% to 14% reported in other series as Sarween et al.(25). Gestational diabetes developed in 19 (9.9%) RT recipients, 13 of them (10.9%) developed diabetes after pregnancy and continue on hypoglycaemic drugs.

This improvement in the maternal outcome and decreased rate of RT pregnancy complication in our results may be due to a good selection of healthy transplant women that advised to get

pregnant and subsequently received better medical care from multiple specialties

As regard fetal outcome in our study, 85 out of 191 pregnancy cases were born pre-term, the pre-term birth rate was (44.5%) slightly less than that reported in other study results such as Ponticelli et al.(4),who said, small birth weight pre-term deliveries have often occurred intransplantation recipients. Also, the Pre-term birth rate in Sarween et al.(25)study was (64%) and comparable to Beroukhim et al.,(26)study results (44.4%).

There were 4 cases (2%) of reported malformations (birth defect) in the newborns in our study results that contributed to immunosuppressant medications used in unplanned pregnancies. Still, Cruz Lemini et al.,(27)study results showed no reported malformations in the newborns, which is consistent with reports that the immunosuppressant medications used were not teratogenic.

Our study results showed that the live birth rate was (66%), 126 pregnancy cases out of 191, and this comes lower than the rate of live-birth (75-80%), which have been recorded from the united states by the national transplant pregnancy registry Sarween et al.,(25). The higher live-birth rates may be encouraging, but there may be bias in selecting healthy individuals that advised to get pregnant and subsequently received better medical care from multiple specialties.

There were 65 (34%) non-live-birth cases in our study, including miscarriage and intrauterine fetal deaths out of 191 pregnancy cases. Our results are higher than that of Sarween et al. (25)(14%),which may be attributed to the loss of follow-up and close monitoring during pregnancy.

Regarding labor and delivery, The cesarean delivery rate in our study was (81.4%), higher than that published by Deshpande et al., (25)study results (56.9%), and comparable to that in Cruz Lemini et al. (27)study results (71.23%). The high rate of cesarean delivery may be attributed to fetal complications, maternal complications, or lack of knowledge of the best delivery means.

As regard condition, at last, follow up among both groups, our study demonstrated that there is no statistically significant difference between both groups regarding 5, 10, and 15 year's graft survival, the majority of patients were alive with functioning graft with no statistically significant difference between the two groups, 84 kidney transplant recipients out of 118 in the pregnancy group (71.1%) and 71 (60.1%) kidney transplant recipients out of 118 in the no-pregnancy group. Rose et al.,(13)2016 results showed that the probability of allograft failure from any cause, including death at 1, 3, and 5 years after pregnancy was 9.6%, 25.9%, and 36.6%.

Also, there is no statistically significant difference between the 5, 10, and 15 years of patient survival.

Our study points of strength: our study demonstrated the effect of each pregnancy on graft function and the outcome of multiple pregnancies. Most kidney transplants in Egypt come from a living donor, not from a deceased donor, which carries advantages in transplantation. All patients in our center received their kidney grafts from living donors; therefore, our results might differ and could not be applied to the general transplant societies where cadaveric donors represent the primarykidney graft source. Also, our study showed that unplanned pregnancies had more maternal-fetal complications, including gestational hypertension, pre-eclampsia, pre-term birth, and congenital anomalies.

Study Limitations: Our study had some limitations as it was a retrospective study.

RECOMMENDATIONS

It is recommended that kidney transplant ladies of child-bearing age receive contraceptive counseling as a part of their routine care, and effective contraceptive methods should be started immediately after transplantation.

We also recommend good ante-natal evaluation of ladies who wish to get pregnant with strict and frequent follow up during pregnancy, aiming to decrease the rate of maternal and fetal morbidities and improve the graft outcome.

CONCLUSION

Although the outcome of live births is favorable, the risks of maternal and fetal complications are high in kidney transplant recipients, including pregnancy-induced hypertension, increased rates of pre-eclampsia, gestational diabetes, and cesarean section rates. The risk of miscarriage, prematurity, and the low birth rate is also high. Serum creatinine and 24-hour urinary protein tend to increase during and after pregnancy, impairing the graft outcome. Pregnancy counseling is necessary to avoid high-risk or unwanted pregnancies.

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SUPPLEMENTRY FILE

Table (S1): Graft function before, during and after pregnancy:

	Before pregnancy	During pregnancy	After pregnancy	p value
Serum creatinine (mg/dl) (1st pregnancy) mean±SD	0.9±0.2	1.1±0.3	1 ±0.3	***0.0001****
24-hour urinary protein (g/day) (1st pregnancy) mean±SD	0.4±0.2	0.5±0.3	0.4±0.1	***0.0003****
Serum creatinine (mg/dl) (2nd pregnancy) mean±SD	1 ±0.3	1.1±0.5	1.1±0.5	0.34*
24-hour urinary protein (g/day) (2nd pregnancy) mean±SD	0.4±0.1	0.6±0.2	0.7±0.2	***0.0001****
Serum creatinine (mg/dl) (3rd pregnancy) mean±SD	1.1±0.5	1.2±0.5	1.3±0.7	0.76*
24-hour urinary protein (g/day) mean±SD (3rd pregnancy)	0.7±0.2	0.6±0.3	0.7±0.3	0.669*

*Repeated measures ANNOVA test