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Review

Renal Transplantation and Pregnancy

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Abstract

Introduction: Although pregnancy after kidney transplantation is feasible, complications are relatively common and this needs to be considered in patient counseling and clinical decision making.

Review: Fertility generally returns after renal transplantation. Approximately 74% of pregnancies in kidney transplant recipients end successfully in life births. Published reports suggest that pregnancy has no adverse affects on graft survival although patients with higher pre-pregnancy serum creatinine have a trend toward increased post-pregnancy serum creatinine. There is, however, a significantly increased risk of preeclampsia, gestational diabetes, cesarean section and preterm delivery compared to the general population. Almost half life births are preterm, and low birth weight is very common. Immunosuppressive medications are required to be continued during pregnancy in transplant recipients to prevent graft rejection, except for sirolimus and mycophenolate mofetil (MMF) which are contraindicated during pregnancy. The incidence of birth defects in the live born is similar to the general population, except for pregnancies exposed to MMF which have a high incidence of birth defects. Every female in the reproductive age group should be counseled regarding pregnancy including the potential risks to the graft, to the mother and to the child. Timing pregnancy should be based upon whether graft function is optimal, but the general recommendation is to wait one year post transplantation before conception.

Conclusion: Pregnancy in renal transplant patients should be planned with combined care from surgeons, nephrologists, obstetricians, pediatricians and dietitians which offers the best chance of a favorable outcome in the mother and the fetus.

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Introduction

Pregnancy in kidney transplant patients was considered hazardous in the past. This concept has been revisited over the past years. The first reported successful pregnancy in a kidney transplant recipient occurred in a kidney recipient from an identical twin sister in 1958 [1]. The number of patients receiving an organ transplant and the incidence of pregnancy in the kidney transplant patient population has increased over the past decade. Advances in surgical techniques and immunosuppressive therapy have improved the survival and quality of life in organ transplant patients. Thus, the number of women within the reproductive age group with organ transplants has also increased. This development demands a heightened awareness of the factors relevant to organ transplantation and pregnancy.

Pregnant patients, who are either on dialysis or are recipients of renal transplants, may have high blood pressure and are at risk of infections, especially the transplant recipients [2]. If a transplanted kidney is functioning well, the patient's chances of having a healthy baby are about as good as for a woman without kidney disease. Moreover, pregnancy while having optimal graft function is unlikely to have adverse effects on kidney function.

Fertility, Conception and Pregnancy Issues

Pregnancy is relatively uncommon in patients with end stage renal disease [ESRD] since they suffer from ovarian dysfunction, anovulatory vaginal bleeding, amenorrhea, high prolactin levels, and loss of libido. As renal function improves following kidney transplantation, endocrine functions generally improve which leads to normal menses and ovulatory cycles; resuming fertility in most women [3]. However, irregular bleeding is still a major

concern among women with transplanted kidneys. In a study of menstrual problems after kidney transplantation, Ghazizadeh *et al* reported normal menstruation in 49%; oligomenorrhea, hypomenorrhea, or amenorrhea in 31.2%; and hypermenorrhea in 19.8% of 114 patients [4].

About 1 in 50 women of child-bearing age with functioning grafts become pregnant [5]. Pregnancies in transplanted women are often unproblematic. Nonetheless, such patients should always be considered to be at high risk. A major concern for kidney transplant recipients is whether pregnancy will worsen renal function and lead to graft loss. Overall, in the majority of recipients studied, pregnancy does not appear to cause irreversible problems with graft function if the function of transplanted organ is stable prior to pregnancy [6, 7]. In early reports, the overall risk of graft loss was reported to be 10-20 percent [8]. More recently, The UK renal transplant registry reported the outcome of 188 pregnancies among kidney transplant recipients from 1994 to 2001 [9]. There were live births in 79% of pregnancies. Two-year post-pregnancy graft survival was 94% for patients in that cohort, compared to 93% among matched controls. A univariate survival analysis, however, suggested an association between drug-treated hypertension during pregnancy and poorer post-pregnancy graft survival. In patients with pre-pregnancy serum creatinine > 1.7 mg/dl, a trend toward increased post-pregnancy serum creatinine was identified [9].

Although pregnancy can cause an increase in the glomerular filtration rate, which could theoretically lead to hyperfiltration and resultant glomerulosclerosis, the hyperfiltration of pregnancy is flow related which does not cause concomitant increase in the intraglomerular pressure [10]. As in women with renal insufficiency who have not received kidney transplantation, the serum creatinine level at the time of conception is an important determinant of successful pregnancy in women with kidney transplants. The outcomes of pregnancy depend on pre-pregnancy renal function. If a woman has a pre-pregnancy serum creatinine level of less than 1.4 mg/dl, the chances of having a successful pregnancy are 96 percent. However, if a pre-pregnancy creatinine is more than 1.4 mg/dl, the outlook for a successful pregnancy drops to 70-75 percent and one third of these pregnancies end in therapeutic or spontaneous abortions [11]. Potential causes of worsening renal function in a pregnant transplant patient include pre-eclampsia, acute or chronic rejection, recurrent kidney disease, dehydration, obstruction of the transplant ureter by the pregnant uterus, infection and medication toxicity.

The long term effects of pregnancy on renal graft is less clear but one of the few studies done on this suggests that pregnancy does not adversely affect the long term survival of the renal graft as well as the patient [12].

Infant Risks and Outcomes

A recently published meta-analysis analyzed the outcome of 4706 pregnancies in 3570 kidney transplant recipients [13]. The overall post-transplant live birth rate was 73.5% and the overall post-transplant miscarriage rate was 14.0% compared to 66.7% and 17.1% respectively for the general US population. However, complications of preeclampsia (27.0%), gestational diabetes (8.0%), cesarean section (56.9%) and preterm delivery (45.6%) were higher than the general US population (3.8%, 3.9%, 31.9% and 12.5%, respectively). Pregnancy outcomes were more favorable in studies with lower mean maternal ages and obstetrical complications were higher in studies with shorter mean interval between transplant and pregnancy [13].

Prematurity is a frequent condition in post transplant conceptions. The severity of this risk depends on maternal renal function, the interval from transplantation to conception and blood pressure control. Higher pre-pregnancy creatinine, maternal anemia, and uncontrolled hypertension are associated with higher incidence of prematurity and its complications like intrauterine growth retardation (IUGR) and low birth weight (LBW).

The UK renal transplant registry report provided obstetric data for 121 live births after kidney transplantation [9]. Fifty percent of these were preterm. Termination of pregnancy by elective caesarean section or induction of labor was required for 64% and 24% of pregnancies, respectively. The main reasons were hypertension or preeclampsia 36%, deteriorating renal function 24%, intrauterine growth retardation 20%, and fetal distress 11%. Of infants, 52% had a low birth weight (LBW) and 22% had a very low birth weight (VLBW) [9].

Immunosuppressive Medications

Immunosuppressive drugs create a special concern in pregnant transplant recipients. Some of these medications have definite risks for the fetus, and are reviewed in Table-1.

Immunosuppressive medications are required to be continued during pregnancy in transplant recipients to prevent graft rejection. Most of the immunosuppressive drugs cross the placental barrier but due to extensive first pass metabolism of drugs in fetal liver, there is insignificant drug concentration in fetal circulation [11]. The American National Transplantation Pregnancy Registry (NTPR) has

Table-1: The US Food and Drug Administration (FDA) classification for commonly used immunosuppressive medications [14]

Drugs	FDA Safety Classification	Comments
Corticosteroids (prednisolone, methylprednisolone)	B – No evidence of risk in humans	Prednisolone does not appear to have teratogenic activity in humans at therapeutic doses. In utero exposure of human fetuses to a high prednisolone dose (>40 mg/day) increased the rate of spontaneous abortion, intrauterine fetal death, perinatal mortality, IUGR and LBW. Administration of glucocorticoid throughout pregnancy may cause adrenal suppression but this is rare with doses < 15 mg/day. Thymic hypoplasia without a significant immuno-deficiency, depressed hematopoiesis, lymphopenia, hyponatremia,and hyperkalemia have also been related to in utero exposure to prednisolone [11]
Cyclosporine	C – Risks cannot be ruled out	Cyclosporine treatment is associated with an increased incidence of abortions, stillbirths, prematurity, LBW and IUGR. Severe B cell depletion was described in newborns from renal transplant recipients receiving cyclosporine, azathioprine and prednisolone, and this depletion persisted at three months of life. Despite known nephrotoxicity, infants antenatally exposed to cyclosporine had normal renal functions. A few isolated cases of minor abnormalities have been described, including osseous hypoplasia (leg and foot) [11, 18]
Tacrolimus	C – Risks cannot be ruled out	Preterm birth is common. Transient hyperkalemia and transient renal impairment are common. Cases of congenital malformation have been reported without any consistent pattern of affected organs [11, 19]
Sirolimus	C – Risks cannot be ruled out	Few data are available on in-utero exposure to sirolimus. It is contraindicated in pregnancy [16, 17]
Azathioprine	D – Positive evidence of risk	The major reported side effects are spontaneous abortions, prematurity, IUGR and LBW. Infants from mothers administered azathioprine during pregnancy often presented neonatal leukopenia, thrombocytopenia, thymic hypoplasia, and decreased serum IgG, IgM, and/or IgA levels. These immunological abnormalities were transient and usually resolved at 1 year of age [11]
Mycophenolate Mofetil	D – Positive evidence of risk	Mycophenloate mofetil is contraindicated in pregnancy [17]. It is associated with high incidence of structural malformations, including hypoplastic nails and shortened fifth fingers, microtia and cleft lip and palate [20]

LBW: low birth weight; IUGR: intrauterine growth retardation

evaluated 2000 pregnancy outcomes in female transplant recipients. The incidence of birth defects in the live born was found to be similar to the general population, except for pregnancies with mycophenolic acid (MPA) exposure that had a 23% incidence of birth defects. Long-term follow-up of the offspring of transplant recipients has provided reassurance after 20 years of observation [15]. Immunosuppressive therapy based on cyclosporine or tacrolimus with or without steroids and azathioprine may be continued in renal transplant women during pregnancy. Other drugs, such as mycophenolate mofetil and sirolimus, are not recommended based on current information available [16, 17].

The benefit of treatment with corticosteroids during pregnancy outweighs the risk. There is no convincing evidence that systemic corticosteroids increase the incidence of congenital abnormalities. Any adrenal suppression in the neonate following prenatal exposure usually resolves spontaneously after birth and is rarely clinically important [11, 17].

Transplant patients on azathioprine should not discontinue it on becoming pregnant [17]. However, there have been reports of premature birth and LBW following exposure to azathioprine, particularly in combination with corticosteroids [11, 17].

Cyclosporine use during pregnancy is associated with premature birth and LBW [11]. It does not appear to have major teratogenic effects on humans. In a meta-analysis of 339 babies exposed to cyclosporine in utero, the prevalence rate of malformations (4.1%) was not substantially different from the figure typically described in population-based studies[18].

Tacrolimus use during pregnancy is associated with premature delivery and LBW[11]. It is also associated with transient neonatal hyperkalemia and renal dysfunction [19]. In a report of 100 pregnancies in mothers receiving tacrolimus, 71 pregnancies progressed to delivery and four neonates (5.6%) presented with malformations, without any consistent pattern of affected organs [19].

Few data are available on in-utero exposure to sirolimus. However sirolimus is contraindicated in pregnancy. Effective contraception must be used during treatment and for 12 weeks after stopping [16, 17]. If pregnancy is planned, the patient should be switched from sirolimus to tacrolimus or cyclosporine.

Mycophenolate mofetil (MMF) is associated with a high incidence of structural malformations [15]. In a report of 26 pregnancies with exposure to MMF, 15 ended in live births and structural malformations were reported in four of these 15 children (26.7%) [20]. It has recently been

reclassified as a Category D drug by the FDA [14]. It is contraindicated in pregnancy and at least two forms of contraceptives should be used from four weeks prior to therapy to six weeks after therapy [17].

Recommendations regarding breast feeding while on immunosuppressive medications are evolving. The American Association of Pediatrics supports breast feeding by mothers taking prednisone and warns against breast feeding by those taking cyclosporine. There are no recommendations regarding Tacrolimus and Azathioprine [21].

Management

All women of child-bearing age should be counseled regarding the possibility and risks of pregnancy after kidney transplantation. Although pregnancy after kidney transplant is feasible, complications are relatively high and this needs to be included in patient counseling and clinical decision making [9, 13, 15]. Pregnancy is likely to end in a live birth in a majority of organ transplant recipients, however in a subset of patients with higher serum creatinine before pregnancy or hypertension during pregnancy, subsequent renal function may be adversely affected [9]. In the past the recommendation was to wait two years after successful transplantation before attempting conception [21]. But the American Society of Transplantation Consensus Conference Report now states that patients may become pregnant at any time as long as graft function is optimal and immunosuppressive dosing is stable at maintenance levels [22]. Optimal graft function is defined as a serum creatinine <1.5 mg/dl, urinary protein excretion <500 mg/day and no concurrent infection. Even those who become pregnant about 6-12 months after receiving renal transplant are likely to have favorable outcome [23]. If the patient has adequate and stable graft function, is at low risk for opportunistic infections, is not taking teratogenic medications, pregnancy can be attempted one year after transplantation without concern of increased risks [22].

The immune-compromised state in transplant recipients puts them at increased risk for infections. Therefore, there is an increased risk of maternal-fetal transmission of infections and its potential risk to the mother as well as the fetus also needs to be considered. Delaying delivery until the onset of labor in patients who have had a transplant is generally thought to be the most prudent step, provided that the mother and fetus show no signs of distress. Vaginal delivery is recommended in most transplant recipient women. Caesarean section should be performed only for standard obstetric reasons [16]. Care must be taken to avoid fluid overload and infection. At the time of delivery, instrumentation should be minimized.

Since the patients are immune-compromised, in the case of any wound or incision, it is wise to use prophylactic antibiotics and careful wound closure to avoid any possible complications.

All renal transplant patients at child bearing age should be encouraged to use contraception as early as possible because ovulatory cycles may begin within 1-2 months of transplantation in women with well functioning grafts. Low dose oral contraceptives (estrogen-progesterone) and barrier methods of contraception (diaphragms, condoms, cervical sponges with spermicidal agents) are advised. Intrauterine contraceptive devices should be avoided because of potential risk for infections [6].

Conclusion

Although pregnancy is likely to end in a live birth in the majority of organ transplant recipients, there are potential risks to the graft, to the mother and to the fetus. Pregnancy in this patient population should be planned with combined care from surgeons, nephrologists, obstetricians, pediatricians and dietitians to offer the best chance of a favorable outcome in the mother and the fetus. Timing pregnancy should be based upon whether graft function is optimal and not necessarily upon the time since the transplant.

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