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Pregnancy After Renal Transplantation

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Abstract

After receiving a kidney donation from her identical twin sister in 1956, 23-year-old Edith Helm became pregnant for the first time in 1958. She gave birth to a healthy, full-term child weighing 3300 grams through cesarean section. Wanda Foster, her twin sister, also had four healthy pregnancies after receiving the kidney [1]. Since then, several healthy pregnancies among kidney transplant patients have been documented, giving hope to women who have long wanted children. The only active registry is the National Transplantation Pregnancy Registry in the United States, which was founded in 1991. Other voluntary registries include the National Transplant Pregnancy Registry in the United Kingdom, which was founded in 1997, the European Dialysis and Transplant Association Registry, and the Australian and New Zealand Dialysis and Transplant Association Registry. All these registries are constrained by small patient populations and inevitable reporting bias [2–5]. We must keep in mind that these retrospective studies are the primary source of the majority of our present information that directs the management of pregnancy in kidney transplant patients.

Keywords: Renal Transplantation; Mycophenolate; preeclampsia; hypertension

Sexual Activity

As a result of aberrant hypothalamus-pituitary-ovarian axis, women with chronic kidney disease (CKD) experience irregular menstrual cycles, anovulation, diminished libido, and poor fertility. Women with CKD often experience menopause onset 5 years sooner than the general population [6,7]. 74% of hemodialysis female patients' experience menstrual abnormalities, and amenorrhea affects 50% of them [8]. Due to poor renal clearance, elevated levels of luteinizing hormone (LH) and follicular stimulating hormone (FSH), and decreased levels of estradiol and progesterone, women with end-stage renal disease (ESRD), particularly those with amenorrhea, have high blood prolactin levels. Anovulation is caused by chronically increased gonadotropins brought on by the lack of the LH surge and the loss of the negative feedback on the hypothalamic and pituitary centers [6,8,9]. As a result, pregnancy is uncommon among women receiving dialysis, with conception rates as low as 1 to 7%. Even after a successful conception, about 25 to 38% of pregnancies result in viable fetuses [10]. However, after a successful kidney transplant, the transient transition to hypogonadotropic hypogonadism can occur as fast as 2-3 weeks, and within 6 months, circulating sex hormones recover to normal range [11]. It is crucial that women with the ability to get pregnant begin using contraception as soon as possible following transplant since the hypothalamic-pituitary-gonadal axis returns quickly [12].

Pregnancy and Allograft Function

Normal pregnancy results in hyperfiltration, intrarenal vasodilation, and a surge in effective plasma flow without a corresponding rise in intraglomerular pressure. With a drop in the serum concentration of urea and creatinine, the glomerular filtration rate increases by roughly 50% [13]. The ability of the renal allograft to adjust to the physiological changes of pregnancy is demonstrated by a rise in creatinine clearance of about 30% in the first trimester, which is sustained with a slight decline in the second trimester and recovers to prepregnancy level during the third trimester [14]. According to Davison, healthy women's increases in 24-hour creatinine clearance were equivalent to those of allograft patients at 39% against 35% of gestation at 11 weeks. Additionally, compared to healthy women, allograft recipients have a higher 24-hour protein excretion, which rises throughout pregnancy, triples by the third trimester and regularly exceeds

500 mg (versus 200 mg in healthy women), and then returns to pre-pregnancy levels at three months after delivery [15]. Never ascribe proteinuria in pregnancy to typical pregnancy-related changes; instead, screen out common comorbidities such urinary tract infection and preeclampsia.

Risk of complications during pregnancy

Preeclampsia and hypertension: It has been observed that 51% to 70% of kidney transplant patients had hypertension. Preeclampsia is six times more common in kidney transplant patients than the general population and ranges from 24% to 38% of the time [4] [16–18]. Because preeclampsia frequently raises blood pressure beyond 20 weeks in previously normotensive women and hyperfiltration-related worsening of preexisting proteinuria, it can be challenging to differentiate it from hypertension in renal transplant patients. Since kidney transplant recipients frequently take calcineurin inhibitors, which raise uric acid levels, hyperuricemia becomes a less useful indicator for identifying preeclampsia [19].

Acute rejection is also accompanied by a considerable rise in proteinuria and a rapid worsening of hypertension, which further complicates the diagnosis of preeclampsia. Preterm birth, intrauterine development retardation, and the likelihood of graft loss are all made more likely by hypertension during pregnancy [18].

If the blood pressure is continuously more than 140/90 mmHg, antihypertensives should be started. The conventional medications that have been used safely to regulate blood pressure during pregnancy include hydralazine and alpha methyldopa. Beta-blockers and calcium channel blockers are additional antihypertensives that are safe to take during pregnancy. The link between angiotensinogen converting enzyme inhibitors and pulmonary hypoplasia and oligohydramnios in fetuses makes them contraindicated. All recipients of kidney transplants should take low dosage aspirin since it lowers the incidence of preeclampsia in high-risk populations [20].

Allograft function

Without risk factors, pregnancy does not enhance the rate of graft loss. At a follow-up of 10 years, there was no difference in the graft failure rate between pregnant women and nonpregnant allograft patients (19% versus 21%) [14]. History of drug-treated hypertension, prepregnancy creatinine 1.4 mg/dL, and proteinuria are risk factors for graft loss. Out of 133 female renal transplant recipients, 20 lost their grafts within five years, and it was shown in the NTPR registry that these patients had higher serum creatinine levels before pregnancy (1.6 mg/dL versus 1.1 mg/dL), higher serum creatinine levels after pregnancy (2.2 mg/dL versus 1.3 mg/dL), and higher rejection rates during or within three months of pregnancy (45% versus 4.6%).

Pregnancy creatinine levels >1.4 mg/dL and >1.7 mg/dL were associated with 3.5- fold and 7.6 -fold greater risks, respectively, of allograft failure at 5 years [4]. In all 7 of the women who experienced graft loss within two years after delivery, prepregnancy creatinine was more than 1.5 mg/dL, according to [21]. In a case-control research, Sibanda et al. found no indication of increased renal allograft loss during pregnancy; nevertheless, the 2-year post-pregnancy graft survicase-control researchplant recipients with hypertension than in those without (100% versus 87%). It is advised that proteinuria in renal transplant patients be less than 500 mg prior to conception because nephrotic range proteinuria increases the risk of spontaneous abortion, intrauterine growth retardation, and preterm in pregnant women [22].

Rejection Risk and Its Management

It is possible that the antigenic stimulation produced by the fetus may also cause graft rejection. Pregnancy is a condition of immunological tolerance linked with immunodepressant activity of lymphocytes, which builds tolerance to the fetus and may help the kidney allograft. Additionally, due to the restoration to normal immunosurveillance state during the postpartum period, acute rejection may be more common [23]. High blood creatinine levels, rejection prior to pregnancy, and fluctuating doses of immunosuppressive medications are risk factors that raise the likelihood of rejection, but varied immunosuppression regimens do not [24].

The diagnosis of rejection is challenging since the condition is typically accompanied by a little increase in creatinine and may be confused by the pregnancy-related reduction in creatinine owing to hyperfiltration. To detect rejection in an allograft during pregnancy, ultrasonography guided renal biopsy is safe [25]. High dosage steroids continue to be the primary line of therapy for allograft rejection during pregnancy. There are few studies and no concrete recommendations about the use of additional medications for treating pregnancy-related rejection, such as antithymocyte globulin and rituximab [26].

Infections

Due to the use of immunosuppressive drugs, pregnant kidney transplant recipients are more susceptible to infections, particularly bacterial urinary tract infections (UTI) and severe pyelonephritis. Up to 30% of women get UTI because of reflux, moderate hydronephrosis following transplant, and pregnancy-related dilatation of the ureters and renal collecting ducts. Every visit should include a urine dipstick screening for UTIs, and every four weeks, urine cultures should be taken. Antibiotics should be administered to asymptomatic bacteria for two weeks, after which prophylaxis should be continued the entire pregnancy. Nitrofurantoin and cephalexin are two antibiotics that are used to treat UTIs [22]. While secondary infection has a lesser chance of harming fetuses (2%), primary cytomegalovirus (CMV) infection leads in 45–50% transmission to fetus with 6–19% of them being symptomatic at birth. The amniotic fluid is cultured to determine the presence of fetal CMV.

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It has not been proven that treating the mother with ganciclovir or CMV hyperimmunoglobulin will stop fetal CMV illness [27]. Herpes simplex infection in the mother is linked to a higher risk of miscarriage and can be passed from mother to child during delivery. Acyclovir is used as a form of treatment, and caesarean sections are favored since they reduce the risk of newborn herpes. Hepatitis B immunoglobulin and the hepatitis B vaccination should be administered to infants whose mothers have the virus in order to avoid neonatal infection, which protects more than 90% of newborns.

Fetal complications

In allograft patients, the live birth rate varies from 72 to 80%, which is equivalent to the general population [4,18]. According to reports, preterm birth happens more frequently because of maternal or fetal impairment than from spontaneous preterm labor, with rates as high as 45 to 55% compared to 6 to 20% in the general population [4]. Preterm birth is predisposed by maternal hypertension and a high blood creatinine level of 1.6 mg/dL [18]. They also frequently have preterm delivery (52–53%), low birth weight (42–46%), and IUGR (30–50%) [4,23,28]. According to research by Bramham et al. [17], receivers of renal allografts have a 12-fold greater risk of preterm births, a 10-fold higher risk of low-birth-weight newborns, and a 7-fold higher risk of small for gestation babies compared to the general population. A newborn's gestational age is 34.5 weeks on average, and their birth weight is 2270 grams on average [16]. Although there is a greater risk of perinatal death in the absence of risk factors such as hypertension, proteinuria, and poor allograft functioning, the miscarriage incidence varies from 10 to 27% (compared to 9 to 10% in the general population) [4,17,18].

Predictors of the Outcomes of Pregnancy

Hypertension, high prenatal creatinine >1.4 mg/dL, proteinuria, and history of >2 renal transplants are risk factors linked to poor pregnancy outcomes. According to a study by Bramham et al. [17], there was an approximately 6-fold increased risk of adverse fetal outcomes (stillbirth, miscarriage, neonatal death, birth 32 weeks, and congenital anomalies) in women with high prenatal creatinine and high diastolic pressure during the second and third trimesters. Pregnant women who have nephrotic range proteinuria have an increased risk of spontaneous abortion, intrauterine growth restriction, and preterm [22]. Therefore, a favorable pregnancy outcome is connected with prenatal creatinine 1.4 mg/dL, the absence of hypertension, and low proteinuria 500 mg.

The Ideal time to conceive

The best period of time to get pregnant following a kidney transplant is still up for debate. According to recommendations made by the American Society of Transplantation, women who have had a kidney transplant should wait between one and two years before trying to get pregnant. Following transplantation, deferring pregnancy for two years is advised by European best practice standards [22,29]. However, as long as the graft function is steady and the women are not using teratogenic drugs, it is safe to get pregnant even six months after receiving a kidney transplant. Conception within two years after receiving a transplant increases the chance of a viable fetal outcome [16]. Waiting longer may potentially cause postpartum renal dysfunction that is worsened and may not recover, along with already deteriorating renal function as a result of chronic allograft nephropathy. Recent research found that while pregnancy in the third posttransplant year was not linked to a higher risk of mortality censored graft loss, it was linked to an increased risk of allograft failure in the first and second posttransplant years [30].

Immunosuppression

Table 1: Immunosuppressant drugs used in transplantation.

	FDA category
Induction	
Basiliximab	B
Alemtuzumab	C
Antithymocyte globulin	C
Methylprednisolone	C
Maintenance	
Azathioprine	D
Cyclosporine	C
Tacrolimus	C
Mycophenolate mofetil	D
Sirolimus, rapamycin	C
Prednisone	B
Belatacept	C
Leflunomide	X
Treatment of rejection	
Antithymocyte globulin	C
Basiliximab	B

Due to the possible teratogenic risk and side effects, managing immunosuppression in pregnant kidney transplant patients is crucial. All immunosuppressive medications pass the maternal-fetal circulation and have been found in fetal circulation to varying degrees [31]. A (no human danger), B (animal studies suggesting risk but no evidence of human risk), C (human risk not ruled out), D (evidence of human risk), and X (completely prohibited) are the medication classifications used by the Food and medication Administration (FDA) to determine how safe they

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are during pregnancy. Most medications come under category C, where risk and benefits must be balanced. Table 1 [32] provides a summary of the most popular immunosuppressive medications used by kidney transplant patients as well as information on their pregnancies.

Calcineurin inhibitors

Tacrolimus and cyclosporine are two examples of calcineurin inhibitors that are regarded as safe to use while pregnant. The blood levels of calcineurin inhibitors found in the fetus are roughly half those of the mother because they cross the placenta and enter the fetal circulation [33]. About 4 to 5% of women on calcineurin inhibitors had significant congenital structural malformations, which is equivalent to the reported frequency of 3 to 4% in the general population [4,34]. Cyclosporine has been demonstrated to promote thromboxane and endothelin production, increasing vascular bed resistance and contributing to the pathophysiology of preeclampsia. In prenatal treatment to calcineurin inhibitors results in immature T cells, deformed peripheral lymphatic organs, and ineffective T cell reactivity, according to animal studies [35].

Cyclosporine may generate immature T cells and a deficiency in B cells in newborn humans, which may eventually result in the emergence of autoimmunity [36]. Children who were exposed to cyclosporine in utero and had a mean age of 4.4 years had developmental impairments in 16% of cases [37]. The long-term effects of calcineurin inhibitor exposure in utero are still poorly understood, and there is little data on pediatric neurodevelopmental follow-up [38,39]. First trimester, second trimester, and third trimester cyclosporine trough levels typically decline by 23%, 39%, and 29%, respectively [40]. We advise more regular monitoring of the whole blood trough level during pregnancy, with measurements taking place every two weeks during the first and second trimesters, once a week during the third trimester, and once more within a week after delivery.

Azathioprine

Even though the FDA has classified azathioprine as a class D medicine, it is safe to use as immunosuppressive during pregnancy since it quickly breaks down into 6-mercaptopurine. Although 6-Mercaptopurine enters the fetal blood, the fetus is spared from its harmful effects because the fetal liver lacks the enzyme inosinate pyrophosphorylase needed to convert it to the active metabolite thioinosinic acid [41]. If the mother's white cell count is higher than 7500/mm3, it is also linked to dose-related myelosuppression in the baby, albeit newborn leukopenia is often uncommon [42].

Corticosteroids

Prednisone (category B) and methylprednisolone (category C) are two steroids that are often administered to kidney transplant recipients [16,22,32]. 90% of the maternal dosage of corticosteroids is efficiently broken down in the placenta before it reaches the fetus. The ratio of maternal to cord blood is around 10:1 [43]. At dosages more than 20 g/day, sporadic occurrences of fetal adrenal immunosuppression, thymic hypoplasia, and cleft palate have been documented [44].

Mycophenolate Mofetil

The category D medicine mycophenolate mofetil is linked to an increased risk of spontaneous abortion and congenital deformity. The most frequent congenital abnormalities are limb and facial anomalies, which include microtia, hypoplastic nails, short fifth fingers, cleft lips and palates, congenital diaphragmatic hernias, and congenital heart problems [45]. Mycophenolate mofetil should be stopped six weeks before conception as it is not recommended during pregnancy. Mycophenolate-using transplant patients do not increase the risk of abnormalities in their offspring [46].

Sirolimus

A category C medication is sirolimus. In animal investigations, it has been linked to higher fetal mortality, lower fetal weights, and delayed ossification of skeletal structure, although no teratogenicity has been shown [26]. Human exposure data are few, however sirolimus should be stopped six weeks before conception because it is not recommended for use during pregnancy [22,47].

Labor and Delivery

The ideal method of birth is vaginal delivery, and obstetric reasons are the only times a cesarean section is recommended. The false pelvis, where the renal allograft is situated, is not obstructing the course of the fetus' delivery. If there are no obstetrical difficulties, spontaneous labor may continue up to 38 to 40 weeks. High-risk obstetricians, neonatologists, and transplant nephrologists should be part of a multidisciplinary team to treat pregnancies in renal transplant recipients [22]. We advise close follow-up visits every two weeks with a transplant nephrologist during prenatal care.

Conclusion

A successful pregnancy requires meticulous preparation and a renal transplant to restore fertility. Primary care physicians and nephrologists should exert more effort to discuss menstruation and reproductive difficulties with kidney transplant recipients. The transplant team should provide thorough information and counseling to women of reproductive age who are considering pregnancy.

The criteria for kidney transplant recipients who are contemplating about pregnancy are summarized as follows [29,32]:

i. at least six months following transplant.

ii. Allograft stability and a creatinine level under 1.4 mg/dL

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iii. No current instances of severe rejection

iv. 140/90 mmHg or lower blood pressure

v. No or little proteinuria, less than 500 mg per day.

vi. less than 15 mg of prednisone every day

vii. less than 2 mg/kg/day of azathioprine

viii. 6 weeks before pregnancy, stop taking sirolimus and mycophenolate mofetil.

Throughout pregnancy, a multidisciplinary approach by the transplant nephrologist and maternal-fetal medicine is crucial and can provide positive outcomes for mother and child.

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