


Research Article

Fertility and Conception Following Kidney Transplantation: A Narrative Review

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Abstract

Individuals with chronic kidney disease often experience sexual disorders and infertility, which can significantly impact their quality of life. The cause of infertility in CKD patients is multifactorial, resulting from sexual dysfunction, hormonal disturbance, and uraemia-induced gonadal toxicity. Kidney transplantation can significantly improve this pathological state, although complete restoration of fertility may not occur. Conceiving after kidney transplantation carries a slightly higher maternal and fetal risk compared to the normal population, with neonates of kidney-transplanted mothers showing an increased risk of prematurity and low birth weight. The use of steroids in infants was found to be safe, while mycophenolate mofetil was associated with fetal and infant toxic events and is, therefore, not recommended for breastfeeding mothers following kidney transplantation. Nevertheless, studies have indicated the safety of using azathioprine in breastfeeding kidney-transplanted mothers. Notably, limited data is available on the use of immunosuppressive drugs during pregnancy and poses an area for further research.

Keywords: Kidney transplant; Infertility; Posttransplant conception; Immunosuppressive interactions; Ictal complications; Graft rejection

Introduction

If pregnancy cannot be established after 12 months of frequent, unprotected sexual activity, this is described as infertility [1]. Sexual disorders along with infertility are complications frequently observed in under-favoured individuals affected with chronic kidney disease. It affects both genders and impacts their quality of life. As the staging of chronic kidney disease progresses, the extent of infertility increases [2]. Endocrine system impairments, physical damage to the ovaries, and testicles brought on by high level urea, erectile disorders, and depression are a few variables that disrupt fertility in individuals with chronic kidney disease. Although not completely restored, kidney transplantation was found to be associated with a notable improvement in sexual function, libido, and ovulatory cycles. After around 6 months following transplantation, reproductive potential may operate effectively. A period of up to twenty-four months after a kidney transplant is the ideal window for conception [3]. This review aims to provide a comprehensive summary of the effects of chronic kidney disease on both male and female fertility, as well as the impact of kidney transplantation on reproduction. The review also covers the possibilities and outcomes of conception following kidney transplantation, along with related topics such as immunosuppressant medications, contraception methods, and lactation, all

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of which are discussed in relation to fertility and conception after transplant. The goal is to make this information easily accessible to all medical professionals.

Effect of CKD on fertility

Sexual dysfunction

This is noted to occur in 70-80% of males with chronic kidney disease [4, 5]. Likewise, females have a significant fall in libido and a parallel decline in their capacity to attain orgasm. Both psychological and organic factors are contributors to the pathogenesis of sexual dysfunction. CKD patients commonly exhibit depression [6, 7]. Depression as well as antidepressants thus are important culprits of sexual functionality in CKD. If not the initial causes of CKD, cardiovascular diseases, diabetes, and hypertension commonly co-exist with CKD. Therefore, in addition to their medications, these comorbidities are another contributor to impaired sexual functionality in CKD. Other causes of sexual dysfunction are said to be the sequence of CKD itself, such as anemia, zinc deficiency, and erythropoietin therapy.

Hormonal disturbance

The main hormonal changes in men with chronic kidney disease can be summarized as follows; levels of total and free testosterone experience a significant decrease in concentration, while binding globulin to sex hormones remains within normal levels [8]. On the contrary, serum luteinizing hormone (LH) levels are noted to experience an increase due to uremia. This results in a state of hypogonadotropic hypogonadism. Due to the role of testosterone in normal functioning and morphology of the penis, a decrease in its level can thus also contribute to erectile dysfunction [9]. Although the correlation between serum TT concentration and CKD stage, there was no association in the severity of sexual dysfunction in men compared to CKD stage and/or serum TT [10]. A decrease in testosterone level can also be treatment induced. Cinacalcet, which is used to decrease parathyroid levels in CKD patients, thus decreasing bone resorption, is noted to cause further reduction in testosterone levels [11]. Females with CKD have a very low chance of becoming pregnant, especially as the condition advances to stage 5. These women reach menopause roughly 4 years earlier than healthy women do [12, 13]. In women with CKD, there may be a derangement in the synthesis, secretion, or metabolism of hormones. These effects lead to an anovulatory menstrual cycle and infertility. The changes in the hypothalamic-pituitary-ovarian axis start early in CKD and progress along the course of the disease, especially after the initiation of RRT [14].

Uremia-induced gonadal damage

Testicular injury in CKD patients is attributed to uremia. As will further be explained, it has been noted that testicular injury synchronously relates to many hormonal changes experienced by CKD patients. Hormones produced by Sertoli

cells such as Inhibin and AMH are decreased following testicular injury [15]. Inhibin is a hormone that negatively affects FSH production produced by the pituitary gland. Thus, failure of inhibin production due to testicular injury results in a state of high FSH along with the already increased LH level as mentioned above. Although the high level of FSH and LH levels, there is a lack of normal LH cycle surge [16, 17, 18, 19, 20]. This, in addition to uremia-induced testicular injury, results in low testosterone levels. The combination of impaired hormonal function, as well as testicular injury, is furthermore a cause of impaired spermatogenesis in CKD patients.

In women with CKD, there is a concomitant decrease in the ovarian reserve of follicles due to uremic toxins. A clinical study conducted to compare the reserve volume of follicles in hemodialyzed women with regular menstrual cycles and in age-matched regularly menstruating females showed a marked decline in the ovarian reserve of hemodialyzed women. Kidney transplantation in females improves sexual function and menstrual cycle disorders. It normalizes hormone synthesis, secretion, and metabolism. Although kidney transplantation alleviates hypothalamus-pituitary-ovarian axis disorders, it does not restore the ovarian reserve [17]. Therefore, infertility, which is to some extent still present after kidney transplantation, is caused by the derangement of ovarian function.

Review

Conception Post-Kidney Transplantation

Most pregnancies in women who have had kidney transplants are associated with positive outcomes and typically result in live births. Adverse maternal and fetal events are prevalent, nevertheless. The frequency of preeclampsia, stillbirth, and delivery by cesarean section was increased compared with the general population. Preterm labor, at least once, stillbirth, and infant death are serious pregnancy problems that have been reported. Following kidney transplantation, these issues were observed in 25% of expecting mothers [21]. The incidence of preeclampsia increased. Its frequency was six times higher compared with general population [22]. Research has identified a higher rate of gestational diabetes in pregnant transplant recipients, most likely as a result of the immunosuppressive medications they were given to ensure graft survival [13]. There was an increased rate of delivery by cesarean section. Deliveries by cesarean section were found in more than three-quarters of pregnant women with kidney transplants. However, a renal indication for cesarean section was found in only 3% of those patients [23]. There were no adverse events found concerning birth via vaginal delivery. In most women with kidney transplantation, the birth canal is not obstructed by the pelvic allograft [13]. Regarding the fetus, there was an increased incidence of premature birth compared to the general population. It was seen in 50% of live births [24]

Table 1: Prevelant complications in female patients after kidney transplantation [24]

| Complication | Percentage |
|---------------------------|------------|
| Hypertension | 53% - 64% |
| Preeclampsia | 30% - 32% |
| Type 2 diabetes mellitus | 5% - 12% |
| Rejection | 1% - 2% |
| Graft loss within 2 years | 6% - 9% |

Table 2: Pregnancy outcomes in female patients after kidney transplantation [24]

| Pregnancy Outcomes | Percentage |
|------------------------|------------|
| Spontaneous abortion | 12% - 25% |
| Live birth | 71% - 77% |
| Prematurity < 37 weeks | 52% - 53% |
| Cesarean delivery | 43% - 57% |

Pregnancy's effects on transplant survival

Kidney transplant has been one of the most exceptional methods to give women with end-stage renal disease the opportunity to successfully become pregnant. However, one of the major concerns is the numerous side effects associated with the transplant. The effective renal plasma flow (ERPF) and glomerular filtration rate (GFR) are set on a continuous sequence during and after gestational [25]. Despite this, the allograft develops compensatory kidney hypertrophy. This can result in renal hyperfiltration, and the risk of adverse maternal and fetal complications is regarded as a significant challenge [13]. Moreover, pregnancy causes physiological changes in the allograft and cardiovascular systems. These changes include peripheral vasodilation and a 50% increase in glomerular filtration ratio (GFR), while intraglomerular pressure remains constant. The renal allograft can adapt to these changes by increasing GFR during the first trimester, decreasing slightly in the second trimester, and returning to preconception levels in the third trimester [13]. In the preconception risk assessment, episodes of rejection are used as a predictor of graft survival. When there are no episodes of acute rejection within 28 days, the patient is considered low risk. In the absence of adverse predictive factors, pregnancy following kidney transplantation is not found to be associated with an increased rate of graft loss. The graft failure rate were not differed compared with any pregnant recipient at 10 years of follow-up [13]. Furthermore, there is a strong link between transplantation, pregnancy, and age, and one study found that a younger age at transplantation and pregnancy was linked to a higher chance of success of having a live birth [26].

Proteinuria of more than 0.5 gm/day was found to be associated with an increased risk of graft dysfunction in kidney-transplanted women, especially if it is associated with

increased serum creatinine [27]. Studies found that serum creatinine can be used as a predictor for graft survival. Serum creatinine of less than 1.3 was found to be associated with favorable allograft outcomes. Moderate graft dysfunction (serum creatinine 1.3 to 1.9) was found to be associated with worse allograft outcomes, which often leads to a severe decline in allograft function. Severe allograft dysfunction (serum creatinine of more than 1.9) was found to be associated with a severe decline in allograft dysfunction, which progresses to end-stage renal disease [27]. Concomitant allograft dysfunction and proteinuria were found to be associated with an increased risk for irreversible graft damage and loss, especially if serum creatinine is more than 1.5 and proteinuria is more than 500 mg/24hr. In addition, studies have found that the presence of the following risk factors is associated with an adverse allograft outcome: hypertension, preconception proteinuria, decreased allograft function, and a short transplant to conception interval time. The optimal timings for conception after kidney transplantation were prescribed by the guideline as follows: an interval of more than one year between kidney transplantation and conception, as well as an interval of more than one year between conception and the last episode of acute rejection. Furthermore, the serum creatinine level should be less than 1.5 mg/dl, there should be no acute infection, and the immunosuppressant used for maintenance should be stable and non-teratogenic [13].

Immunologically, pregnancy is considered an immunological tolerance condition in which lymphocytes are suppressed in their activity to achieve tolerance to the fetus, which may be beneficial to the kidney allograft. The fetus, on the other hand, may provide an antigenic stimulus, which can result in allograft rejection. Furthermore, because of the return to normal immunity status, the rate of acute rejection increases in the postpartum period. During pregnancy and the first three months after delivery, the acute rejection rate is comparable to that of no pregnant kidney transplant recipient. It ranges from 1% to 14.5%. Rejection before conception, increased serum creatinine, and changes in immunosuppressant levels are all predictive factors for an increased risk of acute rejection. The diagnosis of rejection during pregnancy is difficult because it is associated with a small increase in serum creatinine, which can be confounded by the hyperfiltration-associated decrease in serum creatinine during pregnancy. During pregnancy, ultrasound-guided allograft biopsy can be performed safely [13]. Acute rejection during pregnancy can be successfully treated with steroids, which is the first-line protocol of treatment. There is limited research on the use of ATG and rituximab to treat acute rejection [13, 28].

The use of immunosuppressive drugs increases the risk of infection, particularly urinary tract infections (UTIs), in pregnant kidney transplant recipients. UTI occurs in 40% of pregnant women due to reflux (mild hydronephrosis occurs

after transplantation and pregnancy-related dilatation of the renal collecting system and ureter. UTI should be screened at every visit, and urine cultures should be performed every four weeks. Antibiotics should be used to treat asymptomatic bacteria for two weeks, and then prophylactic treatment should be continued throughout the pregnancy [13].

Management of the immunosuppressant in pregnant transplant females

Studies found that immunosuppressants can cross the placenta to a variant degree. They carry teratogenic and fetotoxic effects. Some of them are associated with an increased risk of maternal diseases. Furthermore, they have an obstetric impact (24). Careful planning of pregnancy is not a contraindication in women with organ transplants. Most of the drugs used are classified by the FDA as category C. However, no sufficient data were found on the effect of drugs on pregnancy and the fetus. This imposes an area for further research.

The main immunosuppressant drugs used postrenal transplant are corticosteroids, CNI, MMF, and mTOR inhibitors [29]. In a study conducted on women with recurrent miscarriages, prednisolone in a dose below 20 mg was noted to increase fertilization [30]. However, high exogenous long-term use of glucocorticoids was still associated with a risk of maternal hypertension, preeclampsia, maternal diabetes, and prematurity [30]. Minimal studies link the use of prednisolone to oro-facial cleft risk, adrenal insufficiency, and dysfunction of the fetal hypothalamic-pituitary-adrenal axis with irreversible damage [31].

CNIS such as tacrolimus and cyclosporine are other immunosuppressive medications used in organ-transplanted patients. Concerning fertility, cyclosporine was found to increase the live birth rate in women with unexplained recurrent miscarriages. However, a study conducted on rats treated with cyclosporine showed irreversible testicular damage and a decrease in sperm count. Tacrolimus reaches the fetal circulation at a rate of approximately 71% and is not metabolized by the fetus due to lack of liver maturity and enzymes [31]. The use of tacrolimus during pregnancy has been shown to increase the possibility of congenital malformations by 5-6%, preterm birth by 30%, and low birth weight by 32% [32]. Both CNIs can induce renal fibrosis, reversible nephrotoxicity, and hyperkalemia in newborns. Overall, maternal-fetal outcomes are not only linked to the use of CNI but rather the initial obstetric conditions of the mother [31].

Azathioprine is the most commonly used immunosuppressant agent in pregnant women posttransplant, as it was found to be the safest following steroids. Only the inactive form of azathioprine crosses the placenta [31]. Clinical studies, although limited, did not show an excess of congenital malformations in women exposed to azathioprine during

pregnancy. More than a thousand pregnancies conceived by men exposed to azathioprine or 6-mercaptopurine were not shown to have any teratogenicity. Yet, during the treatment and for a year after it was stopped, chromosomal abnormalities in the spermatozooids of male participants have been reported. Some studies recommended stopping the drug 3 months before conception [32]. Mycophenolate Salts, however, are classified as category D drugs and are associated with increased first-trimester abortion and fetal teratogenic effect [31]. It was found to be associated with an increased risk of abortion, intrauterine growth retardation, and preterm delivery. In kidney-transplanted women, mycophenolate mofetil should be switched to azathioprine six weeks before conception [33]. Such is the case with leflunomide, the medication is contraindicated during pregnancy as it is highly teratogenic. It should be stopped a year before planning to conceive. mTOR inhibitors such as sirolimus may alter the normal functioning of the hypothalamic-pituitary-gonadal axis and lower serum testosterone levels as well as affect spermatogenesis in men. An animal study with sirolimus showed a reduction in the size of the ovary and ovulatory cycles [32]. Overall, there is no adequate data concerning the safety of using mTOR in pregnant transplanted women. Therefore, they should be switched to CNI six weeks before conceiving [32].

Managing non-immunosuppressive medications during pregnancy

Most patients receiving kidney transplants also have coexisting hypertension. These individuals have a higher prevalence of preeclampsia during pregnancy. Therefore, it is essential to monitor blood pressure levels as well as provide adequate knowledge and understanding of preeclampsia and its symptoms. ACE inhibitors during pregnancy are associated with an increased risk of fetal teratogenicity. The recommendation is to review antihypertensive medications before conception due to the potential negative effects they may have during pregnancy and lactation. Because methyl dopa has no effect on the fetal circulation or the uteroplacenta's hemodynamic condition, studies suggest using it to treat moderate cases of hypertension in pregnant women. While utilizing hydralazine, nifedipine, or labetalol for severe hypertension is advised [34]. Contraception in kidney transplant females: Contraception is a method that enables women to avoid unwanted pregnancies safely. Every woman who undergoes kidney transplantation should receive counselling on the risks of pregnancy following the procedure, the optimal time to conceive, and the appropriate type of safe and effective contraception based on her health condition. To avoid all the risks associated with pregnancy loss and rejection of the transplanted kidney, women should not plan pregnancy for at least one year after kidney transplantation. [35, 36]. Contraception can be categorized into two main types: temporary and permanent. The permanent methods of

Table 3: Summary of Contraception Methods [37]

| Contraception Methods | |
|---|---|
| Temporary | Permanent |
| Copper and progestin intrauterine devices | Female tubal ligation Male vasectomy |
| Oral contraceptive pill | |
| Transdermal patch | |
| Vaginal ring | |
| Progesterone only Implant | |
| Diaphragm with spermicide | |
| Cervical cap with spermicide | |
| Contraceptive sponge | |
| Male condom | |
| Female condom | |

contraception are tubal ligation in females and vasectomy in males. Although vasectomy is a more invasive procedure, it completely eliminates the risk of ectopic pregnancy and may be a suitable option for those who have made a conscious decision to not have children. [37]. Temporary methods include, combined hormonal contraceptives, intrauterine contraceptive devices (IUCD), subcutaneous implants, vaginal rings, barriers, and natural methods like coitus interrupts. The most commonly used method of contraception is combined hormonal contraceptives, which are effective. Although they are contraindicated in women at high risk of thrombosis and cardiovascular events. Studies have indicated that utilizing both copper IUD and levonorgestrel-releasing intrauterine device is a secure and efficient method and it is not associated with an increased risk of infection [37]. Subcutaneous implants are a new contraception option that is safe, effective, and reversible. They can result in less reduction of bone mineral density, which is a common concern after transplantation due to the impact of steroids on bones. Other methods used are barrier methods such as spermicides, cervical caps, and condoms. Condoms are a simple and effective method that also prevent sexually transmitted diseases. When used in combination with spermicides, the success rate increases to 97%. However, their efficacy may be reduced in kidney transplant recipients due to a high rate of failure when misused. [37, 38].

Lactation in Kidney Transplant Females

The American Academy of Pediatrics suggests that exclusive breastfeeding for six months should be followed by the gradual introduction of complementary foods. Breastfeeding offers various physiological benefits, such as reducing the risk of necrotizing enterocolitis, improving enteral feed tolerance, lowering the risk of infections, enhancing oxygen saturation levels, promoting cognitive development, and reducing the likelihood of allergies in later life. [39, 40]. Low birth weight and preterm neonates are possible pregnancy outcomes following kidney transplantation. These neonates require additional nutritional and emotional support which can be provided by breastfeeding. However, the excretion of immunosuppressive agents into breast milk at varying

levels is a significant concern. To minimize the potential direct effects of these drugs on the child, modifications can be made based on their excretion level into breast milk and their direct toxicity. [39]. Post-transplanted women who become pregnant should know the benefits of breastfeeding as well as the adverse events that occur upon their child's exposure to immunosuppressant drugs (41).

Conclusion

Chronic kidney disease reduces fertility in both men and women. Kidney transplant leads to improved fertility in both sexes as well as the ability to reproduce. Women who have transplants need a period of time, at least a year before considering conceiving. Women need to familiarize themselves with contraception methods, their efficacy and their interactions with immunosuppressive drugs. Choosing the right contraception needs precision. Women should be aware of the risks associated with pregnancy following transplantation, as well as how to prepare for it. Within at least six weeks of conception, immunosuppressive medications should be changed to better suit the period of conception. Pregnancy in this group of patients is considered critical and requires to be followed up by a multidisciplinary team. Breast feeding is important for this category of neonates, as they more frequently suffer from prematurity and low birth weight. They need tenderness and good nutrition to strengthen their immunity. While breast feeding mothers need to review their immunosuppressive drugs so that unsuitable drugs for neonates are eliminated. Although challenging, pregnancy and lactation post kidney transplanted is achievable.

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