Kidney Medicine

Sexuality, Contraception, and Pregnancy in Kidney Transplantation

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Sexual dysfunction is defined as any abnormality in sexual arousal, libido, intercourse, orgasm, or satisfaction. It is prevalent in patients with chronic and end-stage kidney disease, with 70% to 84% of men and 30% to 60% of women reporting some form of sexual dysfunction. Although kidney transplantation improves the overall quality of life for patients receiving dialysis, it can have unexpected effects on sexual function owing to the use of immunosuppressive medications and comorbid illnesses. It is important to recognize these adverse effects and pre-emptively discuss them with patients to help mitigate consequent psychosocial discontent. Women of reproductive age will often recover fertility after kidney transplantation and therefore need to be empowered to prevent unwanted pregnancies and plan for a safe pregnancy if desired. Complications such as preeclampsia, pregnancy-induced hypertension, gestational diabetes, ectopic pregnancy, still birth, low birth weight, and preterm birth are more common in pregnant women with a kidney transplant. Careful monitoring for infection, rejection, and immunosuppressive dose adjustment along with comanagement by a high-risk obstetrician is of utmost importance. Breast-feeding is safe with most immunosuppressive medications and should be encouraged.

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SEXUAL FUNCTION IN KIDNEY FAILURE AND EARLIER STAGES OF CHRONIC KIDNEY DISEASE

Patients with chronic kidney disease (CKD) frequently have associated comorbid conditions such as diabetes, heart disease, and vasculopathies. Disorders in sexual function span both the physical and psychosocial domains. CKD and associated vasculopathies affect physical function but also have psychosocial effects through changes in hormonal balance, emotion, and socioeconomic burden.[1] Sexual dysfunction can manifest as vaginal dryness or dyspareunia in women, erectile dysfunction or premature ejaculation in men, and decreased libido and inability to achieve an orgasm in both men and women.[2]

A definitive assessment of the prevalence of sexual dysfunction in the CKD population is difficult because of the intimate nature of the topic, variable definitions, and lack of standardized registries for this data. Men with CKD have a reported prevalence of erectile dysfunction between 70%[3] and 84%.[4] Between 30% and 60% of women experience sexual dysfunction, higher in those receiving dialysis as compared with those with non–dialysis-dependent CKD.[3] Women also tend to experience premature menopause, up to 4.5 years earlier, and infertility primarily owing to estrogen deficiency.[5]

The sexual well-being of patients with CKD is underrecognized. It is neither regularly discussed by nephrologists nor reported in many "quality-of-life" trials.[6] Moreover, patients referred for kidney transplantation often do not know what to expect after transplantation with respect to their sexual function.

SEXUAL FUNCTION POST–KIDNEY TRANSPLANTATION

Kidney transplantation is recognized as the gold-standard treatment for end-stage kidney disease, offering better quantity and quality of life as compared with dialysis. Sexual health is an important quality-of-life domain in these patients. Although kidney transplantation improves the hormonal and metabolic milieu in recipients, the physical effects of the transplantation surgery can distort one's body image and hence affect sexual satisfaction.[7] The emotional and psychological distress can reduce interest in sexual activities and/or result in erectile dysfunction in men and vaginal dryness in women.[8,9] Decreased sexual satisfaction can impair overall quality of life and reduce life satisfaction.[7] Immunosuppressive agents, particularly sirolimus, can impair sexual function.[10]

Male Sexual Function After Transplantation

Libido, erectile function, orgasmic function, and sexual satisfaction are important components of male sexuality. A Dutch study reported a 48% prevalence of sexual problems in male kidney transplant recipients.[11] This was lower than in patients receiving hemodialysis (HD; 62.9%) or peritoneal dialysis (69.8%) but greater than 5 times that in the control population (8.7%). The most commonly reported problems were erectile dysfunction (74%), decreased libido (41%), and orgasm concerns (29%). Similar results have been reported from France[12] and Mexico.[9] A recent study from Portugal explored sexual function and satisfaction in male kidney transplant recipients.[13] Of the total 112 respondents, 66% had at least mild erectile dysfunction as measured by the International Index of Erectile Function (IIEF) score, 65% had desire dysfunction, 56% had orgasm dysfunction, and 76% had overall dissatisfaction with their sexual function. There was a significant negative correlation between body image satisfaction and sexual function, affecting recipients both within and more than 3 years after transplantation.

The effects of kidney transplantation on pre-existing sexual dysfunction are controversial. Previous studies have shown improvement in erectile dysfunction after kidney transplantation[14,15] but a recent study looked at both erectile and ejaculatory function prospectively in kidney transplant recipients.[16] The mean IIEF score significantly decreased at 6 months and was unchanged at 12 months after transplantation. Ejaculatory function, as assessed by the Male Sexual Health Quality-Ejaculation Disorders (MSHQ-EjD) short form, also decreased significantly at the 6- and 12-month follow-up. Age, diabetes, hypertension, smoking, and pretransplantation testosterone levels were significantly associated with posttransplantation IIEF and MSHQ-EjD scores in addition to the baseline scores.

Most (72.8%) kidney transplant recipients studied by Meuhrer et al[17] reported that sexuality was important. A total of 71% were sexually active and 80% had a regular sexual partner. Only 60% received information about posttransplantation sexuality from their health care providers and 64% of the patients who did not thought that they wanted the information. Unfortunately, less than half the patients who received the information were satisfied with it. The greatest areas of concern were communication with health care providers about sexuality and sexual pleasure. Women reported greater concerns than men.

Female Sexual Function After Transplantation

In the United States, 40% to 50% women of reproductive age have sexual concerns.[18] Hypoactive sexual desire disorder is the most prevalent concern, followed by delayed orgasm and lack of orgasm.[19] The literature on female sexual function in end-stage kidney disease and transplantation is scarce as compared with that on male sexual function. Several studies have reported a higher prevalence of sexual dysfunction in women receiving dialysis versus their counterparts without CKD, and sexual dysfunction was found in 94% of women receiving peritoneal dialysis and 100% of women receiving HD as compared with 45.8% of controls.[20] A large study conducted in Europe and South America revealed an 84% prevalence of sexual dysfunction in women receiving HD, independently associated with age, depressive symptoms, lower education, menopause, diabetes, and diuretic therapy.[21] Kurtulus et al[22] reported sexual dysfunction in 56.7%, 89.7%, and 73.9% of the control, HD, and posttransplantation female patients, respectively.

The Female Sexual Function Index, a commonly used questionnaire to assess female sexual function, improved significantly in women with a kidney transplant, specifically the lubrication, pain, and total scores.[22] Similarly, women with end-stage kidney disease followed up prospectively for 5 years posttransplantation had their mean Female Sexual Function Index score improve significantly from 17.57 ± 7.07 pretransplantation to 25.3 ± 3.28 posttransplantation, and depression scores decreased significantly from 17.91 ± 8.56 to 3 ± 4.17. Improvement in sexual function was seen in all domains including desire, arousal, lubrication, orgasm, satisfaction, and pain.[23] These studies suggest that female sexual function may improve after kidney transplantation.

Female sexual desire and satisfaction were significantly better in living donor recipients when compared with deceased donor recipients, but they were also significantly younger (38.5 vs 51.5 years) and had shorter dialysis vintage (30.5 vs 44.5 months) than deceased donor recipients. Only 34.6% of women reported discussing sexual issues with their health care providers before transplantation, whereas 73% believed it would have been important.[24]

Special Considerations With Drugs

In addition to immunosuppressive medications, transplant recipients are often receiving drugs for blood pressure, diabetes, electrolyte disorders, gastrointestinal symptoms, contraception, and mood disorders. Many of these drugs may independently affect sexual function and should be evaluated in patients presenting with sexual dysfunction. Table 1[25,26] summarizes some of these drugs and suggested alternatives.

CONTRACEPTION

Of the 23,301 kidney transplantations performed in the United States in 2019, a total of 9,133 were in women, of which 3,474 (38%) were in the child-bearing ages (18-49 years) and 301 were younger than 17 years and could potentially be pregnant in the future.[27] Ovulation and menstruation normalize within 6 to 9 months after transplantation and therefore fertility can return or increase.[28] Studies show that pretransplantation contraception counseling is often inadequate. In Brazil, although 80% of female transplant recipients were sexually active and 72% were using a contraceptive, only 49% were counseled to use contraception. This group had an unintended pregnancy rate of 93%.[29] In a report from Nebraska, 44% of female transplant recipients were unaware of pregnancy as a possibility after transplantation and only 43% of female recipients older than 13 years were counseled before transplantation about posttransplantation contraceptive use. Of these, only 50% had a specific method recommended and contraceptive pills were most commonly recommended (52%).[30]

Contraception Counseling

Important considerations for contraception counseling:

1. Patient selection: all kidney transplant recipients with child-bearing potential, current or future.
2. Counseling should begin at the time of transplantation evaluation and continue into the posttransplantation period.
3. Patients' own understanding of their sexuality, values, and beliefs about contraception and plan for pregnancy should be explored.
4. All contraceptive methods should be offered and risks and benefits discussed. The choice of contraception would depend on patients' preferences and safety

Table 1. Drugs Affecting Sexual Function

Drug	Sexual Side Effect	Management
Immunosuppressive Agents		
Belatacept	No direct effect.	Can consider alternatives if severe side effects outweigh benefits; alternatively, use sexual enhancers
Tacrolimus, cyclosporine	No direct effect; depression, weakness	Can consider alternatives if severe side effects outweigh benefits; alternatively, use sexual enhancers
Sirolimus, everolimus	Decreased sexual desire and erectile dysfunction in men; decreases testosterone levels	Can consider alternatives if severe side effects outweigh benefits; alternatively, use sexual enhancers
Mycophenolate mofetil	Erectile dysfunction in men; teratogenic	Can consider alternatives if severe side effects outweigh benefits; alternatively, use sexual enhancers
Azathioprine	No direct effect	
Steroids	Decreased testosterone; erectile dysfunction in men; menstrual irregularities in women	Steroid-sparing regimens when possible or lowest possible dose; alternatively, use sexual enhancers
Antihypertensive Agents		
Thiazide diuretics	Decreased libido, erectile dysfunction, and decreased ejaculation in men	Switch to loop diuretic; consider sexual enhancer
Potassium-sparing diuretics	Decreased libido, erectile dysfunction, and decreased ejaculation in men	Switch to loop diuretic; consider sexual enhancer
β-Blockers	Decreased sexual desire in men and women; erectile dysfunction in men	Consider alternative antihypertensive agents; use caution with PDE5 inhibitors in patients on antihypertensives, especially nitrates
Centrally acting α-agonist	Decreased sexual desire in men and women; erectile dysfunction in men	Consider alternative antihypertensive agents; use caution with PDE5 inhibitors in patients on antihypertensives, especially nitrates
α-Receptor blockers	May rarely decrease sexual desire in men and women	Consider using PDE5 inhibitors in combination with α-blockers and/or ARI when used for lower urinary tract symptoms in men[25]
α-reductase inhibitors (ARI)	Decreased libido, erectile dysfunction, and decreased ejaculation in men	Consider using PDE5 inhibitors in combination with α-blockers and/or ARI when used for lower urinary tract symptoms in men[25]
Angiotensin-converting enzyme inhibitors and angiotensin receptor blockers	No direct effects; extremely rare incidence of erectile dysfunction in men; teratogenic	Consider alternative antihypertensive agents; sexual enhancers
Calcium channel blockers	Rare; decreased libido in men and women; decreased penile tumescence, decreased ejaculation, and gynecomastia; galactorrhea in women	Consider alternative antihypertensive agents; sexual enhancers
Antihistamines		
Diphenhydramine, cetirizine, loratadine	Inhibited sexual arousal, vaginal dryness; erectile dysfunction	Consider timing medication away from sexual activity; use OTC lubricants for dryness
H_2-Blockers		
Cimetidine	Decreased libido, erectile dysfunction, and decreased sperm count	Use alternative agents like famotidine or ranitidine
Antidepressants		
SSRIs, eg, fluoxetine, paroxetine, sertraline	Decreased libido, erectile dysfunction; delayed orgasm; decreased sexual satisfaction	Consider alternative agents like bupropion, mirtazapine, vortioxetine; reduce dose of SSRI or consider drug holiday and/or addition of sex-enhancing drugs like sildenafil or tadalafil

(Continued)

Table 1 (Cont'd). Drugs Affecting Sexual Function

Drug	Sexual Side Effect	Management
SNRIs, eg, venlafaxine, desvenlafaxine, duloxetine	Decreased libido, erectile dysfunction; delayed orgasm; decreased sexual satisfaction	Consider alternative agents like bupropion, mirtazapine, vortioxetine; reduce dose of SSRI or consider drug holiday and/or addition of sex-enhancing drugs like sildenafil or tadalafil
Monoamine oxidase inhibitors, eg, isocarboxazid, phenelzine, selegiline, tranylcypromine (used infrequently)	Decreased libido, erectile dysfunction; delayed orgasm; decreased sexual satisfaction	Consider alternative agents like bupropion, mirtazapine, vortioxetine; reduce dose of SSRI or consider drug holiday and/or addition of sex enhancing drugs like sildenafil or tadalafil
Tricyclic antidepressants, eg, amitriptyline, nortriptyline, clomipramine, doxepin	Decreased libido, erectile dysfunction; delayed orgasm; decreased sexual satisfaction	Consider alternative agents like bupropion, mirtazapine, vortioxetine; reduce dose of SSRI or consider drug holiday and/or addition of sex enhancing drugs like sildenafil or tadalafil
Antipsychotics		
Prolactin-elevating agents, eg, haloperidol, risperidone, amisulpride	Decreased libido, impaired arousal, and impaired orgasm; may also cause erectile dysfunction, delayed ejaculation in men; poor vaginal lubrication in women	Decreased dose or switch to alternate agent (prolactin-sparing) and/or addition of sex-enhancing drugs
Prolactin-sparing agents, eg, olanzapine, clozapine, quetiapine, aripiprazole	Same as above but much lesser frequency and severity[26]	Decreased dose or switch to alternate agent (prolactin-sparing) and/or addition of sex enhancing drugs
Antianxiety Agents		
Lorazepam, diazepam	Decreased arousal, libido, and delayed orgasm	Cognitive behavioral therapy; decreased dose and/or addition of sex-enhancing drugs
Hormonal Birth Control		
Combined contraceptive pills, progestin-only pills, depo-MPA	Decreased arousal and libido	Use nonhormonal methods like barriers or vaginal ring

Abbreviations: ARI, 5 α-reductase inhibitors; depo-MPA, depo medroxyprogesterone acetate; OTC, over-the-counter; PDE5, phosphodiesterase type 5; SNRI, serotonin and norepinephrine reuptake inhibitor; SSRI, selective serotonin reuptake inhibitor.

profiles based on other medical comorbid conditions and graft status.

5. Implications of unintended pregnancy while receiving immunosuppressive agents should be discussed, including teratogenicity associated with mycophenolate.
6. If patient intends to become pregnant, preconception counseling is essential to avoid adverse outcomes for the kidney transplant, the patient, and the child, and multidisciplinary care should be initiated as discussed later.

Methods of Contraception

The World Health Organization published guidelines (Medical Eligibility Criteria for Contraceptive Use) for contraceptive use in women with specific comorbid conditions. In the United States, the Centers for Disease Control and Prevention adapted and issued guidelines.[31] Contraceptive methods are classified into the following 4 categories: (1) no restriction for use of method, (2) advantages generally outweigh theoretical or proven risks, (3) theoretical or proven risks usually outweigh the advantages, and (4) unacceptable health risk (method not to be used).

Solid-organ transplant recipients are considered complicated in the setting of acute or chronic graft failure, rejection, or cardiac allograft vasculopathy. Uncomplicated solid-organ transplant recipients can initiate any contraceptive method (all are category 2), whereas complicated solid-organ transplant recipients may safely initiate treatment with progestin pills, progestin implant, and progestin injection. Complicated recipients may also continue to use a previously inserted intrauterine device (IUD; category 2), but insertion of new IUD is not advisable (category 3). Combined hormonal contraceptives are defined as category 4 (unacceptable) for complicated solid-organ transplant recipients.

Permanent Sterilization

Irreversible birth control includes male vasectomy and tubal ligation. The failure rate is <1%[32] (Table 2).

Intrauterine Devices

Local hormonal (levonorgestrel IUD) or nonhormonal (Copper T) T-shaped devices can be placed inside the

uterus during a short office procedure.[32] Rare risks include pelvic inflammatory disease and uterine wall perforation.[33]

Levonorgestrel IUD (eg, Mirena, Bayer). A small amount of progestin is released and makes the intrauterine milieu unsuitable for implantation. This device is safe, effective, long lasting, and reversible and does not have any significant interaction with immunosuppressive medications or systemic effects. Impressively, failure rates range from 0.1% to 0.4%.[32] Recent case series in organ transplant recipients have quelled previous concerns and established the safety and efficacy of the levonorgestrel IUD in these patients.[34,35]

Copper T

The Copper-T is nonhormonal but shares the same benefits as a progestin-based IUD and can be used for up to 10 years. The failure rate is 0.8%.[32]

Progestin-Based Implant (etonogestrel)

A thin rod is inserted under the skin in the upper arm. It slowly releases progestin for up to 3 years. The benefits include decreased menstrual blood losses and protection against endometrial cancer. There is a risk for abnormal uterine bleeding, headaches, and weight gain.[33] The etonogestrel implant (Nexplanon, Organon) is considered the most effective progestin-only contraceptive method. The typical failure rate is 0.1%.[32]

Progestin-Based Injection (depot medroxyprogesterone)

This injection in the buttock or arm needs to be repeated every 3 months. Benefits are similar to progestin implants but risks include decreased bone mineral density in addition to abnormal uterine bleeding, headaches, and weight gain.[33] The failure rate is up to 4%, commonly due to delay in repeat injections.[32]

Progestin-Only Pill

Also known as the "mini-pill," this pill has only a single hormone, progestin. It needs to be taken at the same time every day and is better for women with contraindications to the estrogen component of combined contraceptives. Side effects include abnormal bleeding, headaches, and weight gain.[33] The typical failure rate is 7%.[32]

Combined Hormonal Contraceptives

These contraceptives include pills, patches, or vaginal rings. They release both estrogen and progestin hormones and can reduce uterine bleeding, dysmenorrhea, acne, hirsutism, and risks for ovarian and endometrial cancer. Risks include venous thromboembolism, hypertension, stroke, and heart attacks. These risks are greater in tobacco smokers, women older than 35 years, and those with a family history of blood clots.[33] The typical failure rate is 7%.[32]

Female Barrier Methods

Female condom (failure rate, 21%), diaphragm, or cervical cap (failure rate, 17%) and vaginal sponge with spermicide (failure rate, 14%-27%) are types of female barrier methods.[32] Risks include sepsis and toxic shock syndrome if left for longer periods.[33] A major benefit of barrier methods is protection against sexually transmitted diseases.

Male Condom

A condom needs to be used consistently by the male partner to prevent unintended pregnancies. The failure rate with typical use is 13%, and like female barrier methods, these also provide protection against sexually transmitted diseases.[32,33]

Spermicides

Spermicides are chemicals that kill sperm in the female reproductive tract. They can be in the form of gels, creams, foam, suppository, tablet, or film. Ideally, spermicides should be used in conjunction with barrier methods. The typical failure rate for spermicides is 21%.[32] Risks include local vaginal irritation and/or allergic reactions.[33]

The least effective methods include withdrawal, fertility awareness–based methods (failure rate, 2%-23%), and lactational amenorrhea.[32]

Contraception Guidance for Mycophenolate Exposure

Given the increased risk for first-trimester pregnancy loss and congenital malformations associated with mycophenolate exposure, the US Food and Drug Administration (FDA) requires a *Risk Evaluation and Mitigation Strategy* (REMS).[36] As part of mycophenolate REMS, female kidney transplant recipients have 3 acceptable options for contraception use, as follows: option 1, standalone use of IUD or tubal ligation or male partner with vasectomy; option 2, one hormonal and 1 barrier method; and option 3, two barrier methods (male or female condom and female diaphragm or cervical cap with spermicide or a contraceptive sponge).

MANAGEMENT OF POSTTRANSPLANTATION PREGNANCY

The first successful pregnancy in a kidney transplant recipient was reported in 1958.[37] The delivering team opted for elective caesarean section for fear of damage to the allograft from fetal vertex. Since then, more than 14,000 pregnancies in kidney transplant recipients have been documented in the literature.[38] Most of the data about pregnancies in the transplant population are available through case reports, single-center case series, and voluntary registries such as the Transplant Pregnancy Registry International (TPRI, formerly National Transplant Pregnancy Registry) and the Australia and New Zealand Dialysis and Transplant Registry (ANZDATA).

Physiologic Changes During Pregnancy

An increase in cardiac output and blood volume and decrease in systemic vascular resistance lead to an increased glomerular filtration rate and decreased serum creatinine level. In pregnant women who have undergone transplantation, glomerular filtration rate can increase by up to 34% in the first trimester and returns to prepregnancy levels by the third semester.[39] Urinary protein levels increase during pregnancy and can exceed 500 mg/24 h by the third trimester before returning to normal within 3 months postpartum. Other common causes of proteinuria include urinary tract infections and preeclampsia.

Preconception Counseling

The first question that prepregnant transplant recipients and their health care providers face is regarding the timing of pregnancy. When is it safe to become pregnant? In 2005, the American Society of Transplantation published their report on the Consensus Conference of Reproductive Issues and Transplantation. The consensus statement advised a transplantation-to-conception interval of at least 1 year.[38] The timing of pregnancy should be individualized based on risk for rejection, fetotoxic infections such as cytomegalovirus, concomitant use of teratogenic medications, and overall graft function. Conception is considered safe with no rejection in the past year, adequate stable graft function (creatinine < 1.5 mg/dL), no or minimal proteinuria, no fetotoxic infections, and a stable immunosuppressive regimen.

A recent study using Medicare claims from the US Renal Data System reported the probability of kidney graft failure from any cause (including death) as 9.6%, 25.9%, and 36.6% at 1, 3, and 5 years after pregnancy.[40] Women who became pregnant in the first 2 posttransplantation years had higher risk for death-censored graft loss as compared with their nonpregnant counterparts (hazard ratio, 1.25 in year 1 and 1.26 in year 2); pregnancy in posttransplantation year 3 was not associated with increased risk for graft failure.

Pregnancy in a transplant recipient is considered high risk and therefore should be managed in consultation with a high-risk obstetrician if available. The goal is to maintain stable allograft function, allow for a normal metabolic milieu, and avoid complications such as preeclampsia, eclampsia, preterm birth, fetal growth restriction, and intrauterine fetal demise.

Our approach to preconception counseling is as follows:

- Begin before transplantation and carry discussions into the posttransplantation period
- Discuss the timing of pregnancy based on individual factors as described previously
- Discuss data on pregnancy outcomes and set realistic expectations
- Encourage partner participation throughout counseling
- Refer to a high-risk obstetrician
- Medication management: for patients receiving mycophenolate, we check for donor-specific antibodies before stopping mycophenolate therapy[41] and recommend contraception for 6 weeks after switching from mycophenolate to azathioprine. If there is no concern for rejection during these 6 weeks, conception can be attempted
- Address the need for postpartum birth control and discuss spacing between pregnancies as appropriate

Pregnancy Outcomes and Complications

An international study evaluated 6,712 pregnancies in 4,174 kidney transplant recipients with a mean maternal age of 29.6 ± 2.4 years and mean transplantation-to-conception interval of 3.7 years.[42] Overall, pregnancies in kidney transplant recipients appeared to be safe with acceptable maternal, fetal, and graft outcomes. The live birth rate (72.9%) is comparable to that in the general US population. The following complications in pregnant transplant recipients are higher than in the general US population: stillbirth rate (5.1% vs 0.6%), ectopic pregnancies (2.4% vs 1.4%), preeclampsia (21.5% vs 3.8%), pregnancy-induced hypertension (24.1% vs 5-9%),[43] gestational diabetes (5.7% vs 2%-10%),[44] and cesarean section delivery (62.6% vs 31.9%). Preterm birth (48%) and low birth weight (53%) were significantly higher in kidney transplant recipients than in the general population.[45] Acute kidney rejection occurred in 9.4% during pregnancy as compared with 9.1% in the US nonpregnant transplant population, and 9.2% of women lost their graft in the first 2 years following delivery. Creatinine level showed a small but significant elevation after pregnancy, from 1.23 ± 0.16 to 1.37 ± 0.27 mg/dL. A transplantation-to-conception interval of 2 to 3 years was unfavorable as compared with less than 2 or more than 3 years in terms of spontaneous abortion, neonatal deaths, caesarean section, live birth rate, and preeclampsia.[45] Creatinine level > 1.3 mg/dL, proteinuria with protein excretion > 500 mg per day, diastolic blood pressure > 90 mm Hg, and more than 1 kidney transplant were associated with poor pregnancy outcomes.[46]

Acute Rejection During Pregnancy

Acute kidney rejection can occur in pregnancy with rates similar to that in the nonpregnant population. Patients with elevated prepregnancy creatinine levels and fluctuating immunosuppressive drug levels are at higher risk for rejection. Preeclampsia and acute pyelonephritis are important differentials. If rejection is suspected, an ultrasound-guided kidney biopsy should be performed. When rejection is confirmed, corticosteroids are preferred in addition to augmentation of baseline immunosuppression. Data with intravenous immunoglobulin, antithymocyte globulin, plasma exchange, and rituximab are sparse.

Table 2. Contraceptive Methods

Method	Pros	Risks	Failure Rate
Permanent Sterilization			
Female tubal ligation	Single, 1-time procedure	Risk for infection, bleeding, tubal ectopic pregnancy	<1%
Male vasectomy	Single, 1-time procedure	Risk doe infection, bleeding Waiting period before efficacy	<1%
IUDs			
Levonorgestrel IUD	Long-lasting (up to 5 y), reversible	Irregular bleeding, pelvic pain	0.1%-0.4%
Copper-containing IUD	Long-lasting (up to 10 y), reversible	Pelvic inflammatory disease, bleeding, uterine perforation	0.8%
Hormonal implant (etonogestrel-based)	Lasts up to 3 y, easy insertion, decreased bleeding	Weight gain, abnormal uterine bleeding, breast tenderness	0.1%
Depot medroxyprogesterone	Decreased bleeding	Needs to be injected every 3 mo, decreased bone mineral density, abnormal uterine bleeding, weight gain, headaches	4%
Oral Contraceptives			
Progestin-only pill	No estrogenic side effects	Irregular bleeding, headaches, breast tenderness, nausea	7%
Combined contraceptive pill	Regulate menstrual cycle, predictable bleeding, reduction of dysmenorrhea, acne, hirsutism Decreased ovarian and endometrial cancer risk	Estrogenic thrombotic risks including VTE, stroke, MI	7%
Vaginal or Exterior Contraceptives			
Vaginal ring	Can self-insert and remove when desired	Irritation, bleeding, risk for infection	7%
Combined contraceptive patch	Self-administration	Higher estrogen exposure than other hormonal methods; VTE, hypertension, stroke, MI	7%
Barrier Methods			
Female condom	Ease of use, self-insertion	Irritation, allergic reaction, sepsis, and toxic shock	21%
Diaphragm or cervical cap	Ease of use, self-insertion	Irritation, allergic reaction, sepsis, and toxic shock	17%
Vaginal sponge with spermicide	Ease of use, self-insertion	Irritation, allergic reaction, sepsis, and toxic shock	14%-27%
Male condom	Protection against STIs	Allergic reaction	13%
Spermicides	Can be used in combination with other methods	Allergic reaction, irritation	21%

Abbreviations: IUD, intrauterine device; MI, myocardial infarction; STI, sexually transmitted infection; VTE, venous thromboembolism.

Urinary Tract Infections During Pregnancy

Asymptomatic bacteriuria can be seen in 2% to 15% of uncomplicated pregnancies and more so in transplant recipients. If untreated, up to 30% can progress to acute pyelonephritis.[47] Given the anatomy of the transplanted ureter, this risk is significantly higher in transplant recipients. Therefore, we recommend screening for asymptomatic bacteriuria with urinalysis every 2 to 4 weeks and treating with antibiotics based on culture results if infection is present.

Immunosuppressive Drug Management During Pregnancy

Calcineurin Inhibitors

Calcineurin inhibitors are considered safe for the mother and fetus during pregnancy and should be continued throughout pregnancy. Calcineurin inhibitor blood levels may fluctuate due to the physiologic expansion of blood volume, changes in intestinal motility, changes in metabolic enzyme activity, and gastrointestinal losses with vomiting (Table 3). A 20% to 25% dose increase may be

Table 3. Various Agents Used for Maintenance Immunosuppression in Kidney Transplant Recipients and Special Considerations During Pregnancy and Breastfeeding

Immunosuppressive Agent	Monitoring	Special Considerations With Pregnancy	Special Considerations With Breast-feeding
Calcineurin-inhibitors (tacrolimus, cyclosporine)	Blood trough level every 2-4 wk	Expansion of blood volume, changes in intestinal motility and increased metabolic enzyme activity may necessitate 20%-25% dose increase	Breast-feeding is safe; <1% maternal weight-adjusted dose exposure to infant through breast milk
Mycophenolate compounds	Blood cell counts for cytopenias	Must be stopped at least 6 wk before conception; Mycophenolate REMS program	Known teratogen; breast-feeding not recommended if mycophenolate is being used
Azathioprine	Blood cell counts and liver enzymes	Safe alternative to mycophenolate	Breast-feeding is safe
Corticosteroids	Blood glucose, blood pressure	Low doses used for maintenance are not associated with adverse fetal effects	Breast-feeding is safe; infant only receives 0.1% of maternal dose through breast milk
Sirolimus	Blood trough levels every 2-4 wk	Fetal defects seen in animal studies; sirolimus should be stopped 6-12 wk preconception if possible	Breast-feeding not recommended due to delayed wound healing and lack of evidence demonstrating safety
Everolimus	Blood trough levels every 2-4 wk.	Sparse data	Breast-feeding not recommended due to delayed wound healing and lack of evidence demonstrating safety
Belatacept	Blood cell counts and electrolytes every 4 wk	Only few case reports of pregnancy with belatacept	Data are lacking

required to maintain therapeutic levels. Tacrolimus circulates in unbound and bound form to albumin and white and red blood cells.[48] Therefore, titrating dose to whole-blood tacrolimus levels can increase the free tacrolimus level and cause drug toxicity in women with low albumin levels and blood cell counts. Plasma tacrolimus levels may better reflect therapeutic levels (free unbound drug concentration) but are not generally available in clinical practice. Tacrolimus crosses the placenta and can cause reversible nephrotoxicity and hyperkalemia in the fetus, but placental P-glycoprotein lowers fetal exposure by active efflux of tacrolimus back into the maternal circulation.[48]

Mycophenolic Acid and Mycophenolate Mofetil

Mycophenolic acid (MPA) and mycophenolate mofetil (MMF) are contraindicated in pregnancy and must be stopped at least 6 weeks before conception. This is based on the black box warning issued by the FDA when it changed its pregnancy category for MPA/MMF from C to D in 2007. MPA and MMF products are associated with increased risk for spontaneous abortions and structural birth defects such as hypoplastic nails, shortened fifth digit, microtia, and cleft lip and palate.[49] This risk has not been observed when MPA/MMF are taken by the father.[50]

The FDA mandated the Mycophenolate REMS program to educate health care providers and patients about the risks associated with MPA/MMF and pregnancy and to help women plan for pregnancy in a safe and effective manner.[51] As part of the program, all women of reproductive age should receive a urine pregnancy test immediately before initiating MPA/MMF treatment and again in 8 to 10 days. They should be counseled about the risks of pregnancy with MPA/MMF and the importance of using acceptable contraception (described previously) during and for 6 weeks after stopping MPA treatment. As per the 2019 Annual Report of TPRI, there are 142 reported pregnancies with MPA exposure. In these, the live birth rate was 48% as compared with 78% in the group that stopped MPA treatment 6 weeks before conception (n = 302) and miscarriages occurred in 48% versus 20%. There was no significant difference in mean gestational age, prematurity, mean birth weight, or birth defects, although 11.6% of pregnancies with MPA exposure resulted in birth defects as compared with 5.7% without exposure.[45]

Azathioprine

Azathioprine is considered safe in pregnancy and is the alternative of choice for patients receiving MPA/MMF. The fetal liver does not convert azathioprine to its active metabolite and hence teratogenicity is usually not seen.[52] Complete blood cell counts and liver chemistry test results should be monitored in the mother and dose should be adjusted accordingly.

Corticosteroids

Low-dose corticosteroids used in maintenance immunosuppression have not been associated with adverse fetal

effects.[53] Breast-fed infants have minimal exposure to prednisone and therefore breast-feeding is considered safe with prednisone use.[54]

Sirolimus and Everolimus

Sirolimus exposure during pregnancy has not been associated with significantly different outcomes than pregnancies without sirolimus exposure.[45] As per TPRI, 74% of pregnancies with sirolimus exposure resulted in live births and 24% had miscarriages. However, given the structural defects seen in animal studies, many centers choose to stop sirolimus treatment 6 to 12 weeks preconception and switch to azathioprine. Data about everolimus exposure are sparse, with 71% of 6 reported pregnancies resulting in live births.

Belatacept

Belatacept is a newer immunosuppressive agent that selectively blocks the costimulatory pathway in T-cell activation. There are only a few case reports of pregnancy with belatacept exposure; 2 successful pregnancies in kidney transplant recipients and 1 in a liver transplant recipient.[55,56]

Breast-feeding

The American Academy of Pediatrics recommends exclusive breast-feeding for 6 months, followed by gradual introduction of complimentary foods. There are no definite guidelines on breast-feeding with immunosuppressive medications but the TPRI has not received any reports of adverse effects in breast-fed infants whose mothers were receiving prednisone, azathioprine, cyclosporine, and tacrolimus.[45] MPA is a known teratogen and sirolimus/everolimus are associated with decreased wound healing. Therefore, breast-feeding with these agents is not recommended due to theoretical concerns and limited data.[54] Infant exposure to drugs through breast milk is far less than in utero. For example, tacrolimus concentrations in umbilical blood can reach 71% of maternal whole blood concentrations but <1% of maternal weight-adjusted dose in breast milk.[55,57] Similarly, prednisolone exposure through breast milk is 0.1% of maternal dose, which is <10% of the infant's endogenous corticosteroid production.[54] Given the higher prevalence of preterm birth and low birth weight in transplant recipients, breast-feeding assumes a greater therapeutic role. Breast milk reduces the risk for infections and necrotizing enterocolitis and can increase mental, motor, and behavioral development at ages 18 and 30 months in preterm infants.[58–60]

The benefits of breast-feeding generally outweigh the risks to the infant and therefore we encourage breast-feeding among our transplant recipients. During the past 3 decades, there has been a modest increase in transplant recipients breast-feeding their infants as per the TPRI report.[54]

CONCLUSIONS

Sexual dysfunction is common in patients with kidney failure and earlier stages of CKD. Kidney transplantation improves overall sexual function and fertility. Women of reproductive potential can regain fertility after transplantation and therefore need to be empowered to plan for a pregnancy that is safe for the fetus and mother, as well as the kidney graft. Counseling should start at the time of transplantation evaluation and carry into the post-transplantation period. Breast-feeding is safe and should be encouraged.

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