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Does Solid Organ Transplantation Affect Male Reproduction?

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Abstract

Patients undergoing solid organ transplantation have experienced increased graft survival rates over the past several decades. With increased longevity making fatherhood a viable option, many patients desire to pursue this path. However, many patients and practitioners are likely unaware of the feasibility and safety for a man on a transplant immunosuppression regimen to safely pursue fatherhood. In this review, we discuss effects of organ transplantation and posttransplantation

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treatment on male hormones, fertility, and the risk to potential offspring. Briefly, providers should be aware that organ transplant recipients may be at an increased risk for hypogonadism and erectile dysfunction, but fathering a child is a realistic and safe aspiration.

Patient summary:

In this mini-review, we discuss the effects of solid organ transplantation (such as lung, heart, kidney, and liver) on a man's sexual health, and his ability to have children. We focus on the most common problems encountered by patients after their transplant, and the effects of medications.

Keywords

Transplant; Solid organ; Erectile dysfunction; Fatherhood; Immunosuppression; Infertility

1. Introduction

Solid organ transplantation allows men previously doomed to short lifespans with organ failure to now have prolonged survival. As patient and graft survival rates increase, focusing on quality of life after transplant is imperative. Many of these men go on to have children. Given the comorbidities necessitating the transplant and the medications required after transplantation, hypogonadism and erectile dysfunction (ED) are common among this population. In this review, we evaluate the current literature regarding male fertility, hypogonadism, and sexual dysfunction after solid organ transplantation. Transplantation affects a heterogeneous population and most research comes from kidney transplantation. However, the pearls learned from available data apply to other solid organ transplants.

2. Kidney

The kidney is by far the most common solid organ transplanted, with 69 500 renal transplants performed globally in 2016. Uremia is associated with decreased testosterone, increased follicle-stimulating hormone (FSH) and luteinizing hormone (LH), decreased sperm counts, sperm quality, and fertility [1]. Patients with renal failure often have multiple comorbidities including diabetes, cardiovascular disease, hypertension, and hypercholesterolemia. Hypogonadism associated with renal failure presents similarly to adult onset hypogonadism, with symptoms including sexual and ED, low libido and overall sexual satisfaction, increased fat mass, anemia, and diminished bone mass and muscle strength [1]. The combination of uremia and associated comorbidities likely both contribute to the high prevalence of hypogonadism and sexual dysfunction. Fortunately, after transplantation, prolactin, LH, and testosterone levels, sperm counts, and testicular histology all improve [2]. In a group of 71 kidney transplant patients, Reinhardt et al [3] reported that at 1 yr after transplant, average LH levels were 5.20 IU/l, FSH levels 8.65 IU/l, prolactin levels 6.9 ng/ml, and testosterone levels 11.35 nmol/L.

Treatment of ED in the transplant patient does not vary significantly from routine therapy. ED is common after kidney transplantation and can be impacted by alteration in the pelvic vessels used for graft anastomosis. One report found ED in 65% of their kidney transplant

patients [4]. Phosphodiesterase type 5 inhibitors, intracavernosal injections, and penile prostheses are safe and effective in transplant patients [5]. Prior to therapy, practitioners must ensure that the patient is healthy enough for sexual activity.

Low testosterone at the time of transplant has been associated with decreased 3-yr graft survival, and decreased 1-yr and 3-yr patient survival after transplantation [6]. On multivariate analysis including 197 kidney transplant recipients, low testosterone (less than 220 ng/dl) was independently associated with graft loss (hazard ratio [HR] = 2.05, 95% confidence interval [CI] = 1.16–3.62) and patient death (HR = 2.27, 95% CI = 1.19–4.32) [7]. Whether this association is a marker of more severe pre-existing disease, and whether testosterone therapy has any effect on outcomes, is yet to be explored. Majzoub and Shoskes [8] reported on testosterone treatment of 15 patients with chronic kidney disease (three on hemodialysis and 12 after transplantation) and found an increase in serum testosterone and hematocrit, with no major adverse events. Studies evaluating the safety and efficacy of testosterone replacement therapy in the transplant population are lacking.

Fatherhood after kidney transplantation is common. Survey data from Ireland and China found that 14.6% ($n = 66/435$) and 3.6% ($n = 212/8515$) of patients fathered at least one child after renal transplantation [9,10]. The Transplant Registry International Annual Report shows 989 male transplant recipients who fathered children; however, this may not be all-inclusive data [11].

3. Heart, lung, and liver

Although data for other organ transplants is less robust, the same principles apply regarding fatherhood after transplant as immunosuppressant medications (Table 1) are similar. Patients needing nonrenal organ transplants have significant comorbidities and may be more critically ill prior to transplantation than patients with end-stage renal disease alone. However, healthy children have been reported from fathers with lung, liver, pancreas, and heart transplants, with birth defect rates ranging from 1.9% to 4.0%—comparable to the regular population [11]. Serra et al [12] described a series of 52 heart transplant patients of which 71% had erectile dysfunction and 34.6% had hypogonadism.

4. Medications

Post-transplant medications can affect fertility at the level of the testis and the hypothalamic-pituitary-gonadal axis. The intensity of immunosuppression differs between different transplanted organs, which may lead to differences in fertility and hormonal changes. Though different transplant centers may vary in their practice patterns, it is generally true that heart and lung transplant patients are more immunosuppressed than kidney transplant patients, with higher target serum tacrolimus levels. Medications commonly used after transplant include cyclosporine, tacrolimus, sirolimus, mycophenolate, azathioprine, and prednisone (Table 1). A typical regimen includes a corticosteroid (eg, prednisone), an antimetabolite (mycophenolate or azathioprine), and a calcineurin inhibitor (tacrolimus or cyclosporine), though not every component is always necessary or tolerated. In the early 2000s, the use of cyclosporine began to decline and has been replaced with tacrolimus.

Similarly, mycophenolate has become the more common antimetabolite used. The practicing urologist should be generally familiar with these medications' effects on male reproduction. Cyclosporine decreases sperm counts, testosterone level, and fertility while increasing LH and FSH in male rats [13]. Tacrolimus results in reduced sperm counts and decreased fertility in mice [13]. However, findings in humans have been mixed, with some studies showing worse parameters and some showing semen parameters similar to healthy individuals [14]. Sirolimus, an mTOR inhibitor, decreases testosterone, with resulting increases in FSH and LH, and also decreases pregnancy rate when compared to transplant patients not taking sirolimus. This effect may be because mTOR is a key regulator of spermatogonial proliferation.

Of the transplant medications, mycophenolate has been the most concerning for teratogenicity. In mothers exposed to mycophenolate during pregnancy, an "embryopathy" has been described, which includes external ear, lip/palate, and eye abnormalities including: hypoplastic pinna, complete absence of pinna, cleft lip (with or without cleft palate), iris or chorioretinal coloboma, and anophthalmia/microphthalmia [15]. This phenotype has not been documented for children of fathers taking mycophenolate, and birth defect rates were similar to the children of transplanted men not taking mycophenolate in a study of 350 children [15]. In 2015, the Food and Drug Administration published guidelines requiring medications to have specific labeling regarding the drug's effect on male fertility; consequently, mycophenolate now includes a warning that therapy needs to be discontinued 90 d prior to having unprotected sex (even if the patient has undergone a vasectomy) [13]. The evidence for this recommendation is lacking, and any benefit of altering immunosuppression should be weighed against the risk of organ rejection. A summary of medication effects on male reproduction and recommendations based on the present work's review of the literature, medication safety guidelines, transplant center publications, and a previous review by Semet et al [13] is summarized in Table 1.

In addition to medication-specific effects, an increased risk of preeclampsia and pre-term delivery has been found in pregnancies fathered by solid organ transplant recipients, with risk of pre-term delivery decreasing significantly after 2 yr post-transplant [10,16].

5. Conclusions and clinical recommendations

Given the increased volume and success of solid organ transplantation internationally, urologists will encounter these patients in their practice. Fatherhood is possible for these patients, with appropriate counseling regarding medication effects. Outcomes are improved approximately 2 yr after transplantation, when immunosuppressive dosages are reduced. A high index of suspicion for hypogonadism and ED is warranted in male transplant patients, and therapy seems preliminarily to be safe and effective. Any and all interventions in transplant patients with complicated medication regimens should be performed in a multidisciplinary fashion with risks and benefits in mind, and both the transplant team and primary care physician should be well informed of all changes.

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Table 1

Medication effects on the male reproductive system

Medication	Medication class	Effects on male reproductive system	Recommendations
Tacrolimus	Calcineurin inhibitor	Reduces sperm counts and decreases fertility	Can continue when trying for pregnancy
Cyclosporine	Calcineurin inhibitor	Decreases sperm counts, testosterone level, and fertility while increasing LH and FSH in male rats	Can continue when trying for pregnancy
Sirolimus	mTOR inhibitor	Decreases testosterone, with resulting increases in FSH and L H, and also decreases pregnancy rate when compared to transplant patients not taking sirolimus Hypothetical teratogenic effect	Discuss risks and benefits of continuing vs stopping medication prior to attempting conception
Mycophenolate	Antimetabolite	No known direct sperm effects, but hypothetical teratogenic effect from paternal exposure	Discuss risks and benefits of continuing vs stopping medication prior to attempting conception

FSH = follicle-stimulating hormone; LH = luteinizing hormone.