# Fertility Challenges and Solutions in Women and Men with Solid Organ Transplantation: An Extensive Review of the Literature



Fatemeh Masjedi<sup>1</sup>, Niloofar Namazi<sup>2,3</sup>, Homeira Vafaei<sup>4</sup>, Sedigheh Amooee<sup>2</sup>, Saman Nikeghbalian<sup>5</sup>\*, Jamshid Roozbeh<sup>1</sup>\*

<sup>1</sup>Nephro-Urology Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

#### **ABSTRACT**

Advancements in solid organ transplantation have significantly improved patient survival and quality of life, making parenthood an achievable goal for many recipients. However, fertility restoration after transplantation presents unique challenges. In women, endocrine function and ovulatory cycles often resume quickly following kidney or liver transplants, but pregnancy outcomes are associated with higher risks, including preeclampsia, preterm birth, and low birth weight. In men, transplantation can improve hypogonadism and sperm abnormalities linked to pre-transplant conditions, although some immunosuppressive drugs, such as mTOR inhibitors or cyclophosphamide, may impair fertility. Available evidence suggests that with proper management, parenthood after transplant is safe and successful, and the risk of congenital malformations in offspring from male transplant recipients is comparable to the general population. Furthermore, assisted reproductive technologies (ART), including in vitro fertilization (IVF), have been shown to be effective in this population, though careful protocols to prevent complications like ovarian hyperstimulation syndrome (OHSS) are crucial. Emphasis on preconception counseling, family planning, and multidisciplinary care is key to minimizing risks and ensuring the health of the mother and child, and the graft function. This review presents recent evidence and practical strategies to optimize fertility outcomes in transplant recipients.

**KEYWORDS:** Solid organ transplantation; Infertility; Immunosuppression; Pregnancy; Assisted reproductive technologies

#### INTRODUCTION

dvances in solid organ transplantation have significantly improved patient survival and quality of life, making parenthood an achievable goal for many recipients [1, 2]. A substantial proportion of transplant recipients are of reproductive age [2],

\*Correspondence: Saman Nikeghbalian, MD & Jamshid Roozbeh, MD

ORCID: 0000-0003-4530-8829 ORCID: 0000-0002-4268-1727 E-mail: nikeghbals@gmail.com E-mail:roozbehj@hotmail.com weeks to months after a successful transplant. For example, women with end-stage renal disease commonly experience anovulation and amenorrhea during dialysis, but ovulatory menstrual cycles often resume shortly after kidney transplantation [3]. Similar patterns are seen in other organ failures: severe liver, lung, or heart disease can suppress fertility, whereas transplantation of those organs frequently normalizes reproductive function within months [4-6]. Consequently, many transplant recipients develop a renewed desire

and restoration of fertility often occurs within

<sup>&</sup>lt;sup>2</sup>Department of Obstetrics and Gynecology, School of Medicine, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>&</sup>lt;sup>3</sup>Infertility Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>\*</sup>Department of Obstetrics and Gynecology, School of Medicine, Maternal-fetal Medicine Research Center, Shiraz University of Medical Sciences, Shiraz, Iran

<sup>&</sup>lt;sup>5</sup>Shiraz Transplant Center, Abu-Ali Sina Hospital, Shiraz University of Medical Sciences, Shiraz, Iran

for childbearing once their health stabilizes.

However, achieving safe and successful pregnancies in this population presents unique challenges. Both female and male transplant recipients face slightly higher rates of infertility and pregnancy complications compared to the general population [7, 8]. Immunosuppressive regimens, organ dysfunction, and comorbidities can all impact reproductive health. Women with transplants are at increased risk of pregnancy complications such as preeclampsia, preterm delivery, low birth weight, and cesarean delivery [5, 9, 10]. Men may experience impaired gonadal function or sperm abnormalities related to their pre-transplant illness or medications [11]. Despite these risks, contemporary studies affirm that parenthood after organ transplantation is feasible and often successful with appropriate management [12]. Importantly, recent data indicate that paternal transplant status does not significantly increase the risk of congenital malformations in offspring [7, 13, 14], and congenital disability rates in children fathered by male transplant recipients ( $\approx 2-4\%$ ) are comparable to the general population [11].

Optimizing outcomes requires careful timing and multidisciplinary planning. Current expert guidelines (e.g., from the American Society of Transplantation) recommend delaying pregnancy until at least 12-24 months post-transplant, when the graft is stable and immunosuppressive doses are minimized. In kidney transplant recipients, for instance, a commonly cited threshold is to wait  $\geq 1-2$ years after transplant with stable allograft function (serum creatinine <1.5 mg/dL, controlled blood pressure, and minimal proteinuria) before conceiving [15]. This delay must be balanced against age-related fertility decline in older patients. Counseling about contraception and family planning is therefore an essential component of pre- and post-transplant care [16]. Unfortunately, studies suggest many transplant recipients have unmet needs for reproductive counseling and may be hesitant to broach the topic with providers [17]. Integrating fertility discussions into routine transplant follow-up can prevent unplanned pregnancies and ensure that patients pursue parenthood under optimal circumstances [3].

This review critically examines the fertility challenges faced by female and male solid organ transplant recipients and discusses solutions, including timing of conception, modification of immunosuppressive therapy, fertility preservation, and use of assisted reproductive technologies (ART). We highlight recent evidence (2021–2024) and evolving practices that inform a safer approach to family building in this growing population.

# Fertility in Female Transplant Recipients

# Impact of organ failure and transplant on female fertility

Women with end-stage organ disease often experience hypothalamic-pituitary-ovarian axis dysfunction and subfertility. In chronic kidney disease (CKD), uremia and anemia contribute to anovulation and menstrual irregularity, and severe liver failure commonly causes hypothalamic amenorrhea and estrogen deficiency [18, 19]. The degree of infertility correlates with the severity of organ dysfunction. Following successful transplantation, reproductive endocrine function usually rebounds: up to ~80% of women resume regular ovulatory cycles within 6-12 months after a kidney transplant (provided graft function is good), and regular menses can return as early as 2-3 months after a liver transplant. By 7 months post-liver transplant, as many as 90% of women report regular cycles [5, 6, 20].

Restoration of fertility can be rapid; nevertheless, pregnancy is not advised immediately. As noted, a post-transplant interval of roughly 1.5–2 years is recommended to allow stabilization of the graft and adjustment of medications. This delay can be problematic for recipients in their late 30s or 40s, whose ovarian reserve may already be diminished. Indeed, one center observed that menopause occurred about 4.5 years earlier in female kidney transplant recipients than in age-matched controls [21, 22], suggesting that chronic illness or immunosuppressants might accelerate ovarian aging. Consequently, the timing of

transplantation and pregnancy should be individualized, especially in women of advanced maternal age.

# Prevalence of infertility

Precise data on infertility rates in female transplant recipients are limited, but small studies indicate the prevalence is slightly higher than in the general population [23]. In one series, approximately 11% of women with kidney transplants had persistent difficulty conceiving despite restored menses [24, 25]. Causes of infertility in this population mirror those in others: ovulatory disorders, tubal factor (e.g., from pelvic adhesions or prior infections), and male factor infertility are all reported [25, 26]. Notably, idiopathic infertility (no identifiable cause) accounts for  $\sim 25\%$  of cases in transplant patients, similar to the general idiopathic infertility rate. One hypothesized cause of unexplained infertility in non-transplant couples is immunologic incompatibility between partners (e.g., high human leukocyte antigen similarity), leading to failed implantation [23, 27]. Transplant patients, who are continuously on immunosuppressive drugs, might be less prone to such immunologic infertility factors. Overall, the absence of large epidemiologic studies makes it challenging to quantify infertility in female recipients, underscoring a need for better documentation and research.

#### Gynecologic and psychosocial considerations

Evaluation of an infertile transplant patient should proceed as it would for any woman, with added attention to graft health. A thorough workup (ovarian reserve testing, hysterosalpingography, etc.) is appropriate if conception does not occur after 6-12 months of unprotected intercourse (or sooner if the patient is >35 years old) [6]. Importantly, graft function should be optimized first, since even mild rejection or allograft dysfunction can perturb the hormonal milieu. Active medical issues (uncontrolled hypertension, unstable graft labs) should be addressed before fertility treatment. Multidisciplinary management is ideal: transplant physicians, obstetricians, nephrologists/hepatologists, and endocrinologists should collaborate on care. Psychological support is also vital. Studies indicate that

female transplant recipients experience lower overall quality of life and vitality, and face elevated risks of anxiety and postpartum depression, particularly if struggling with infertility or high-risk pregnancy [28, 29]. Ensuring access to counseling can help manage the stress of infertility and pregnancy in this context.

# Immunosuppressive medications and female fertility

Most maintenance immunosuppressants are not inherently sterilizing to women, but certain agents can affect menstrual regularity or pose teratogenic risks. Glucocorticoids, calcineurin inhibitors (tacrolimus and cyclosporine), and azathioprine have no direct adverse effect on female fertility; indeed, these drugs are generally considered compatible with pregnancy (they are not associated with infertility and can be continued during gestation with appropriate monitoring) [30, 31]. Mycophenolate mofetil (MMF), in contrast, is highly teratogenic to embryos (causing a welldocumented pattern of birth defects). It does not appear to impede a woman's ability to conceive, but MMF is absolutely contraindicated in pregnancy and should be replaced with a safer alternative (usually azathioprine) at least 6 weeks before attempting conception [32]. Female transplant recipients must be counseled on stringent contraception while on MMF. mTOR inhibitors such as sirolimus and everolimus can disrupt ovarian function: they have been linked to anovulatory cycles and elevated gonadotropin levels in women, consistent with an ovarian suppression effect [33]. In clinical practice, some centers avoid mTOR inhibitors in women desiring pregnancy or will withdraw them to allow a return of ovulation. Cyclophosphamide, an alkylating agent used for certain transplant indications (e.g., treatment of rejection or concurrent autoimmune disease), is highly gonadotoxic. Even at relatively low doses, cyclophosphamide can cause premature ovarian failure in women; when indicated, its use should be accompanied by discussions of fertility preservation (such as embryo or oocyte cryopreservation) if time permits [34, 35]. Finally, many transplant medications can complicate a pregnancy's course even if they don't prevent conception. For example, calcineurin inhibitors often cause hypertension and gestational diabetes, and must be closely monitored in pregnant women [36]. Angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs), frequently used for post-transplant blood pressure control, are contraindicated in pregnancy due to fetotoxicity and must be substituted before conception [22]. In summary, with proper adjustments—such as switching teratogenic drugs to pregnancy-safe alternatives and ensuring stable graft function—most female transplant recipients can attempt pregnancy without an excessive risk of infertility from their transplant medications.

## Pregnancy outcomes

When pregnancy does occur in a woman with a solid organ transplant, rigorous monitoring is required. Overall live birth rates are quite favorable, on the order of 70-80% in kidney transplant recipients [15]. A 2019 meta-analysis of 6712 pregnancies in kidney transplant patients reported a live birth rate of 73%, only slightly lower than the general population. Miscarriage rates (~15%) and stillbirth rates  $(\sim 5\%)$  were modestly higher than in healthy women. Pregnancy complications, however, are substantially more frequent. In the metaanalysis, nearly 25% of pregnant kidney recipients developed pregnancy-induced hypertension, and 21.5% developed pre-eclampsia. By comparison, pre-eclampsia occurs in <5-10% of pregnancies in the general population. Similarly, preterm birth (<37 weeks) occurred in 43% of transplant pregnancies, far above the ~10% baseline risk. The average gestational age at delivery was only ~35 weeks, and the mean birth weight was ~2.5 kg, highlighting the tendency toward prematurity and growth restriction. Cesarean delivery is also markedly elevated in this group (reported in 60-80% of cases), driven by the high-risk nature of these pregnancies and complications like pre-eclampsia [37]. These outcomes underscore that while fertility is often restored, post-transplant pregnancies should be considered highrisk and managed by experienced maternal-fetal medicine teams. Notably, pregnancy risks vary by organ type: kidney and liver transplant recipients generally tolerate pregnancy well if the graft is stable [22], whereas heart or lung transplant recipients face additional cardiopulmonary stresses and higher maternal-fetal risk, including a risk of graft rejection precipitated by the hemodynamic shifts of pregnancy [38]. Despite these challenges, maternal mortality during pregnancy does not appear to be higher in transplant recipients than in non-pregnant transplant patients [39]. With careful supervision, the vast majority of transplant pregnancies result in healthy mothers and babies.

# Fertility in Male Transplant Recipients

# Recovery of gonadal function

For male patients, successful organ transplantation can markedly improve reproductive hormonal status and sexual function. End-stage organ disease—especially chronic kidney failure—often causes hypogonadism characterized by low testosterone and elevated luteinizing hormone (LH) and follicle-stimulating hormone (FSH) levels, along with reduced libido and erectile dysfunction. Uremia in particular is toxic to Leydig cells and the seminiferous epithelium, leading to decreased sperm counts and impaired sperm motility [40]. After kidney transplantation, these abnormalities tend to improve: studies have documented significant increases in serum testosterone and normalization of FSH/LH within 6-12 months post-transplant in many male recipients [41]. Another study reported that 50% of male renal transplant recipients recovered from hypogonadism (based on testosterone levels) in the first year after transplant [42]. Sperm parameters (counts, motility, morphology) also show improvement within months of transplantation in those with previously severe uremia [43]. However, not all damage is reversible. If a male patient experienced prolonged renal failure during puberty or adolescence, the insult to the developing testes may result in irreversible germ cell loss [41]. One report found that men who endured teenage years with uremia did not see improved semen quality after transplant, presumably due to permanent spermatogenic damage inflicted before or during puberty [41]. Regardless, the ability of transplant recipients to father children is well documented and generally considered safe. Large series have reported hundreds of men successfully fathering children post-transplant, with no higher rate of birth defects or cancer in their offspring than in the general population. A comprehensive review in 2018 concluded that "fathering a child is a realistic and safe aspiration" for solid organ transplant recipients, despite the potential challenges of hypogonadism and medication effects [11].

## Contributing factors to male infertility

Apart from the reversible uremic hypogonadism discussed above, male transplant candidates/recipients may have multiple other factors affecting fertility. Comorbid conditions like diabetes, hypertension, and cardiovascular disease are common in transplant populations and are each associated with reduced semen quality and erectile performance \( \grace{44}, \) 45]. Medications used to manage these conditions can also play a role; for instance, certain antihypertensives (notably beta-blockers) and antidepressants can cause erectile dysfunction or decreased libido [46, 47]. Erectile dysfunction itself is prevalent in men with organ failure (one study noted erectile dysfunction in 65% of male kidney transplant candidates) and often persists after transplant to some degree [48, 49]. Phosphodiesterase-5 inhibitors (like sildenafil) are generally effective and safe in transplant patients and can be used to treat erectile dysfunction if not contraindicated by cardiac status [50, 51]. Another consideration is that low serum testosterone pre-transplant may predict worse outcomes: low testosterone has been associated with poorer graft and patient survival in kidney transplant recipients [52], although whether supplementation improves outcomes is unclear. From a fertility standpoint, if hypogonadism (low testosterone) remains after transplant, men may experience suboptimal spermatogenesis and reduced sexual desire. If clinically indicated, endocrine evaluation and possibly testosterone therapy (or use of gonadotropins in those desiring fertility) could be considered. However, exogenous testosterone must be used cautiously because it can suppress intratesticular testosterone and actually worsen spermatogenesis [53]. Each case warrants individualized assessment by a urologist or reproductive specialist.

# Immunosuppressive drugs and male reproductive health

Transplant recipients typically require lifelong multidrug immunosuppression, and understanding the impact of these agents on male fertility is crucial. It can be challenging to isolate the effect of any single drug, since patients are often on combinations, but current evidence offers several insights:

Glucocorticoids (Prednisone) - Corticosteroids in high doses can suppress the hypothalamic-pituitary-gonadal axis by feedback inhibition, leading to reduced LH/FSH release and lowered testosterone production [54]. Steroids may also act directly on Leydig cell glucocorticoid receptors, impairing testosterone synthesis [55]. In practice, the impact of steroids on fertility appears dose-dependent and often transient. Heart transplant patients on intensive early post-transplant steroid taper showed a significant drop in testosterone in the first month. Still, levels rebounded to normal by one year as doses were reduced [56]. Maintenance prednisone at moderate doses is generally compatible with fatherhood, and no increase in malformation rates has been linked to paternal steroid use [57]. Thus, while highdose steroids can cause temporary infertility via hypogonadism, the typical low-dose regimens used chronically are not a major barrier to male fertility.

Calcineurin Inhibitors (Tacrolimus and Cyclosporine A) – CNIs are cornerstone immunosuppressants. Most clinical studies have found that neither tacrolimus (TAC) nor cyclosporine A (CsA) causes overt gonadal failure at standard doses [58]. Serum testosterone levels usually remain normal in men on CNIs, and some reports even document improved sperm quality after transplantation despite CNI use. Sperm parameters appear to correlate inversely with CsA blood concentration, and withdrawal of the drug can lead to recovery of sperm counts. Tacrolimus is considered somewhat less gonadotoxic than cyclosporine; men with kidney transplants

who switched from CsA to TAC showed better sperm motility and morphology outcomes [59]. Animal models corroborate that tacrolimus at therapeutic doses causes only mild sperm count reduction without histological testicular damage [60, 61]. Overall, CNIs do not prohibit paternity, but prudence dictates using the lowest effective CNI dose in men who are trying to conceive. Some adjunct medications can potentiate CNI toxicity – for example, calcium-channel blockers like diltiazem (often given to boost CsA levels) were shown to aggravate CsA-induced testicular injury in rodents [62]. Clinicians should be aware of such interactions.

Azathioprine (AZA) – Azathioprine is an antimetabolite immunosuppressant that is often used as a safer alternative to MMF when a patient wishes to conceive. Available data suggest that azathioprine has minimal impact on male fertility. It may inhibit testosterone synthesis slightly, but studies in inflammatory bowel disease and transplant patients have found no significant changes in sperm count or motility in men on AZA [63, 64]. A prospective study of 23 men on azathioprine for 3+ months showed no deterioration in semen parameters. Theoretical mutagenic effects (due to AZA metabolites interacting with DNA) prompted earlier concerns, but reassuring clinical data exist. Notably, pregnancies fathered by men on azathioprine did not show higher miscarriage or congenital disability rates than those in the general population [65]. Based on these findings, azathioprine is considered compatible with male fertility – men can continue taking it when trying to conceive, as the benefits (avoiding rejection) outweigh any unproven risks. Some experts still recommend sperm banking before starting AZA in young men as a precaution, but this is not routinely necessary.

Mycophenolate Mofetil (MMF) – In contrast to its severe effects in pregnant women, paternal exposure to MMF has not been linked to adverse outcomes in children. Earlier, due to MMF's genotoxic potential, regulatory agencies recommended that men on MMF use contraception or discontinue the drug for

3 months before conception. But growing evidence has dispelled much of this concern. A 2017 analysis of 205 pregnancies fathered by 152 male transplant recipients on mycophenolic acid found no increase in malformations or miscarriage compared to baseline populations. Rates of prematurity (~11%), miscarriage  $(\sim 7\%)$ , and congenital disabilities  $(\sim 3\%)$  were in line with normal expectations [66]. These data have led transplant guidelines to ease restrictions on paternal MMF; for instance, the American Society of Transplantation no longer mandates men to stop MMF when trying to conceive, though they advise discussing potential (theoretical) risks [67]. Overall, the consensus is that MMF does not significantly affect male fertility or offspring health, but paternal counseling is warranted.

#### mTOR Inhibitors (Sirolimus/Everolimus)

- mTOR inhibitors have well-documented anti-proliferative effects on the testis. These drugs tend to lower serum testosterone and raise FSH/LH levels in men, consistent with induction of hypogonadotropic hypogonadism. Sirolimus can impede the recovery of normal gonadal function even after a kidney transplant, and animal studies indicate it may cause testicular atrophy by inhibiting germ cell proliferation [68]. Clinically, men maintained on sirolimus after transplant have shown significantly impaired sperm parameters (low count, poor motility, and morphology) and dramatically reduced fertility rates. Zuber et al. reported that male kidney recipients on sirolimus had a fatherhood rate of only 5.9 per 1000 patient-years, compared to 92.9 per 1000 patient-years in those not on sirolimus – roughly a 15-fold difference. Fortunately, these effects appear to be reversible in most cases upon discontinuing the mTOR inhibitor [69]. Given these findings, male patients of reproductive age should be counseled about the potential for reversible infertility on sirolimus/everolimus therapy. If a man on sirolimus wishes to conceive, transitioning him to an alternative immunosuppressive regimen (when medically permissible) is advisable to improve his chances. In practice, many centers avoid mTOR inhibitors in younger male patients unless absolutely indicated.

Cyclophosphamide and Other Cytotoxic Agents - Cyclophosphamide (CYC) is occasionally used in transplant patients (for treating severe rejection or concomitant autoimmune disease). It is one of the most gonadotoxic drugs for males. CYC can destroy proliferating spermatogonial stem cells and cause long-term oligospermia or azoospermia, depending on the dose. Over half of men receiving chronic CYC may develop lasting gonadal dysfunction. Cumulative dose is critical: high total doses are associated with permanent infertility and even Leydig cell dysfunction (low testosterone). If CYC must be given to a young male patient, sperm cryopreservation before starting therapy is strongly recommended [70].

Newer Biologic Agents – As transplant regimens evolve, biologics such as rituximab (anti-CD20), abatacept (T-cell co-stimulation blocker), and interleukin-1 inhibitors occasionally come into use. Data on their effects in males are sparse but generally reassuring. Rituximab does not target reproductive organs and is considered safe for fatherhood, with only a few cases reported and no apparent issues. Limited case series of men on anakinra (an IL-1 inhibitor) showed no adverse impact on pregnancies conceived. Likewise, no increase in malformations or miscarriage was seen with paternal abatacept exposure in available data [58, 71]. While experience is limited, no major red flags have emerged regarding biologics and male fertility. When using these agents, the decision is usually driven more by the underlying condition than by fertility concerns.

In summary, male transplant recipients typically recover good reproductive potential after transplant, but some immunosuppressants (notably sirolimus and CYC) can significantly hinder fertility. Clinicians should review each patient's drug profile when counseling about family planning. If a man is struggling to conceive, it is reasonable to check hormone levels (testosterone, FSH, LH) and semen analysis, and consider modifications like discontinuing sirolimus or switching MMF to AZA, if feasible. In all cases, the multidisciplinary

approach is key: input from transplant physicians, urologists, and fertility specialists will yield the best strategy for balancing rejection risk with reproductive goals.

## Fertility outcomes for male recipients

The ability of male transplant recipients to father children has been documented across all organ types. For example, the Transplant Pregnancy Registry International (TPR) reports nearly one thousand male kidney transplant patients who have reported fathering children [72]. Outcomes for these pregnancies are generally positive. A large Scandinavian study of 121 pregnancies fathered by male kidney or liver transplant recipients found no increase in stillbirth or congenital anomaly rates, though a slight increase in pre-eclampsia among their partners was noted [13]. A recent multicenter survey (2024) highlighted that the live birth rate for partners of male transplant recipients was lower than that for female recipients, and significantly fewer of those pregnancies were conceived spontaneously. In that study, only 64% of pregnancies in partners of male recipients were spontaneous sothers requiring in vitro fertilization (IVF) or intrauterine insemination (IUI), compared to >80% spontaneous conception in transplanted women [11]. This suggests that while men can safely have children post-transplant, some may require assisted reproductive techniques, possibly reflecting residual subfertility from immunosuppressive effects or age/comorbid factors in male recipients. Nonetheless, the overall picture is optimistic: fatherhood after transplant is achievable, and with proper medical guidance, the health outcomes for partners and children are comparable to the general population in most respects.

# Infertility Management and Assisted Reproductive Techniques (ART)

For transplant recipients with ovulatory dysfunction or mild male factor infertility, firstline therapy often involves ovulation induction with oral agents (clomiphene citrate or letrozole) or injectable gonadotropins, with or without IUI. The limited literature suggests that these approaches are as effective in transplant patients as in the general infertility population. Clomiphene and gonadotropins have not shown any deleterious effect on transplanted organs in clinical practice [73].

One consideration is that women with a history of thrombosis or hereditary thrombotic risk (sometimes present in transplant patients who lost organs to thrombotic events) should be carefully monitored if using gonadotropins, as the high estrogen levels can promote thrombosis [74]. Intrauterine insemination can be offered for mild male factor or unexplained infertility when at least one fallopian tube is open. There is no contraindication to IUI in female transplant recipients, and although specific success rates in this population are not well documented, they are expected to be similar (~10-20% per cycle, depending on age) under appropriate conditions [75]. If several cycles of ovulation induction ± IUI fail, or if more significant infertility factors are present, patients should be escalated to IVF.

IVF is the most advanced and effective fertility treatment and has been successfully performed in many transplant recipients, though mainly reported in case studies and small series. Indications for IVF in this population are the same as in others: significant tubal disease, severe male factor infertility, or failure of simpler treatments. Additionally, IVF may be chosen to bypass time constraints in older patients or to enable preimplantation genetic testing (for hereditary conditions). Notably, one recent case used heterologous IVF (donor oocytes) in a 47-year-old kidney transplant recipient to prevent transmission of a genetic kidney disease (autosomal dominant polycystic kidney disease); this resulted in the birth of a healthy child, illustrating the expanding scope of reproductive options for transplant patients [76].

IVF in transplant recipients can achieve pregnancy rates comparable to those of agematched infertility patients, but it carries additional risks. Perhaps the most concerning is ovarian hyperstimulation syndrome (OHSS), a complication of fertility medications that causes fluid shifts and third-spacing. OHSS can be especially dangerous for women with

renal or hepatic allografts, as it may precipitate graft dysfunction [77]. A classic example is a case where a kidney transplant recipient underwent IVF, developed severe OHSS, and suffered acute renal impairment due to enlarged ovaries compressing the transplanted kidney and intravascular volume depletion [78]. To mitigate this risk, modern IVF protocols for high-risk patients employ controlled ovarian stimulation strategies: using lowerdose stimulation or an antagonist protocol with GnRH agonist trigger to reduce OHSS incidence, and adopting a "freeze-all" approach (cycle segmentation) to defer embryo transfer until the patient's condition stabilizes [79]. In practice, many transplant patients undergoing IVF will have all embryos cryopreserved and perform embryo transfer in a non-stimulated cycle, virtually eliminating the risk of OHSS while still achieving success rates.

Another critical strategy is to avoid multiple gestations. Twin pregnancies are dangerous in any context, but more so in transplant recipients who cannot afford the heightened cardiovascular strain and complication rate. Therefore, elective single-embryo transfer (eSET) should be the standard of care in transplant patients undergoing IVF [80]. By transferring only one embryo at a time, the nearly 30-40% twin rate that would result from doubleembryo transfer can be avoided. Indeed, many reported cases of IVF in transplant recipients have involved twin pregnancies (since earlier practice often transferred multiple embryos), and while outcomes mainly were positive, complications like pre-eclampsia, preterm delivery, and graft dysfunction were noted [78, 81, 82]. We now know these risks can be minimized with eSET and meticulous obstetric care.

Published data on IVF in solid organ transplant recipients, though limited, are encouraging. Table 1 summarizes the key findings from reported cases and series of IVF pregnancies in female transplant recipients (mainly kidney, with a few liver or combined kidney-pancreas recipients). Early reports from the 1990s and 2000s were isolated case reports, while more recent years have seen small case series and

Table 1: Published data about IVF pregnancies in solid organ recipients.					
Authors (Year)	Transplanted Organ	Cause of Infertility	Fetuses	Complications	Gestational Age
Lockwood et al. (1995) [86]	Kidney	Tubal factor	2 (twins)	DVT, PROM	29 weeks
Furman et al. (1999) [87]	Kidney (2 cases)	Anovulation (Case 1)	2 (twins)	Preeclampsia	33 weeks
		Anovulation (Case 2)	$3 \rightarrow 2$ (reduced to twins)	None	36 weeks
Khalaf et al. (2000) [78]	Kidney	Tubal factor	2 (twins)	OHSS, AKI	30 weeks
Case et al. (2000) [88]	Liver	Male factor	2 (twins)	Preeclampsia	34 weeks
Tamaki et al. (2003) [89]	Kidney	Not stated	1 (single)	Not stated	35 weeks
Ulug et al. (2005) [90]	Liver	Male factor	1 (single)	Preterm delivery	31 weeks
Fichez et al. (2008) [91]	Kidnay & Pancreas	Tubal factor	1 (single)	Hypertension	34 weeks
Nouri et al. (2011) [92]	Kidney	Male factor	1 (single)	None	37 weeks
Choi et al. (2013) [93]	Liver	Male factor Endometriosis	1 (single)	None	38 weeks
Norrman <i>et al.</i> (2015) [94]	Kidney (7 women) (8 IVF)	Not stated	2 (twins)	Hypertension, Anemia	30 weeks
			1 (single)	None	40 weeks
			1 (single)	Transient kidney dysfunction	39 weeks
			1 (single)	None	38 weeks
			1 (single)	Transient kidney dysfunction	36 weeks
			1 (single)	Hypertension	38 weeks
			1 (single)	Severe preeclampsia, IUGR	27 weeks
			1 (single)	None	38 weeks
Pietrzak et al. (2015) [95]	Kidney	Tubal factor	1 (single)	Preeclampsia, IUGR, Anemia	34 weeks
Warzecha et al. (2018) [96]	Kidney (2 cases)	Idiopathic infertility	1 (single)	Gestational diabetes	36 weeks
		Tubal factor	1 (single)	Preeclampsia	34 weeks
Gastañaga-Holguera <i>et al.</i> (2021) [83]	Kidney	Autoimmune problem	1 (single)	None	38 weeks
Huang et al. (2023) [84]	Kidney	Male factor (oligospermia)	1 (single)	Preterm delivery (C-section)	35 weeks
Liu et al. (2024) [85]	Kidney	AMA/DOR	2 (twins)	None (C-section)	34 weeks

Abbreviations: IVF = in vitro fertilization; DVT = deep vein thrombosis; PROM = premature rupture of membranes; OHSS = ovarian hyperstimulation syndrome; AKI = acute kidney injury; IUGR = intrauterine growth restriction; AMA = advanced maternal age; DOR = diminished ovarian reserve

even a cohort of transplant couples. Table 1 includes outcomes up to early 2024, illustrating the evolving experience.

From these reports, we observe that IVF is indeed a viable option for transplant recipients with infertility. Across the published cases up to 2019, there were 21 IVF-conceived pregnancies in 20 women (some women underwent IVF twice), resulting in 21 live-born deliveries (including six twin gestations). Notably, outcomes in those early reports were largely positive and comparable to those of transplant recipients who conceived naturally. The majority of pregnancies resulted in live births of healthy infants, and grafts generally remained stable. Hypertensive disorders (including preeclampsia) were the most common complications, affecting roughly 20-30% of cases, which is in line with overall transplant pregnancy statistics. Preterm delivery was frequent, especially in twin pregnancies, but with appropriate neonatal care, most infants did well (see Table 1). Since 2019, additional IVF successes have been documented. Gastañaga-Holguera et al. (2021) reported a kidney transplant patient with multiple autoimmune comorbidities who underwent IVF and delivered a healthy baby; they emphasized the importance of individualized decision-making in such complex cases [83]. Huang et al. (2023) described four Chinese transplant couples (both husband and wife had kidney transplants) achieving pregnancies; in one couple with male-factor infertility, IVF was used successfully and resulted in a singleton live birth. That series highlighted that with careful preconception evaluations (including switching the female partner from MMF to AZA and ensuring tacrolimus levels were low therapeutic) and intensive monitoring, even couples both on immunosuppression can have outcomes comparable to single-transplant pregnancies [84]. Most recently, Liu et al. (2024) reported the first case of an older kidney transplant recipient (mid-40s) giving birth to healthy twins via IVF [85]. This case is remarkable because advanced maternal age plus transplant was once considered nearly insurmountable for pregnancy, yet through IVF with careful management, the patient avoided major complications. These contemporary reports reinforce that with modern ART and medical care, even the more challenging scenarios (advanced age, dual-transplant couples) can sometimes be overcome.

In conclusion, transplant recipients of childbearing age face unique but surmountable challenges to fertility. With modern immunosuppression and interdisciplinary care, female and male solid organ transplant patients can often successfully conceive and have children, but achieving this outcome requires careful planning and management. Key considerations include choosing the optimal timing for pregnancy (generally at least 1-2 years post-transplant with a stable graft), adjusting medications to minimize teratogenic risks (for example, avoiding mycophenolate in women and using alternatives to mTOR inhibitors in men), and diligently monitoring for complications during pregnancy. The process of infertility evaluation and treatment in transplant patients mirrors that in the general population, encompassing hormonal assessment, imaging, and use of ART when indicated. However, it must be undertaken in the context of the patient's overall health status, with close coordination between transplant specialists and fertility experts. Assisted reproductive techniques, including IVF, are acceptable and can yield favorable results in this population, as long as patients are managed prudently to prevent iatrogenic complications. This means employing strategies like single-embryo transfer to avoid multiples and using modified stimulation protocols to reduce OHSS risk. The growing number of reported IVF successes in transplant recipients is a testament to the advances in both transplantation and reproductive medicine over the past decade. Equally important is the role of contraception and counseling - by addressing reproductive plans early, healthcare providers can empower transplant patients to make informed choices, avoid unintended pregnancies, and pursue fertility treatments at the right time. Ultimately, the goal is a healthy parent and a healthy child. Achieving pregnancy in a transplant recipient should never compromise the transplanted organ's viability or the patient's life, and with proper precautions, it

need not do so. As more transplant recipients enter their reproductive years, it is incumbent on the medical community to collect data and refine guidelines in this area. The current literature is still primarily based on case reports and retrospective studies, indicating a need for prospective research and perhaps registrybased tracking of fertility outcomes. Nonetheless, the evidence to date is reassuring: parenthood after solid organ transplantation is possible and often very successful, providing immense psychosocial benefit to patients who have already overcome the challenges of organ failure. With individualized, multidisciplinary care, transplant recipients can be supported in their desire to build a family without compromising their own health or their graft. The collaborative approach – involving transplant physicians, obstetricians, gynecologists, perinatologists, and mental health professionals - is essential to navigate the complexities of these cases and ensure the best outcomes for both generations.

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