

Original article

Management and Perspectives of Pregnancies in Solid Organ Transplant Recipients

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Abstract

Advances in immunosuppressant drugs and surgical techniques enabled pregnancies in numerous women who suffer of end-stage organ disfunction worldwide. Better tolerance to allogenic grafts, and ameliorated risk of drug toxicity created a possibility of both successful reproduction and preservation of a long-time function of a transplanted organ. 75% of pregnancies in transplant patients are registered among renal transplant recipients, followed by liver and heart transplant, all of them connected into a group of solid organ transplants (SOT). Increasing number of pregnancies emerge also from the group of patients with combined simultaneous renal-pancreatic transplant (RPT), due to treatment of an end-stage organ disfunction of diabetes mellitus Type 1, and a lung transplant, due to terminal stage of cystic fibrosis. All transplant recipients have an increased risk of miscarriage, preterm birth and fetal malformations. Renal and RPT recipients are in enhanced risk of hypertensive disorders and preeclampsia. All the immunosuppressant drugs pass the fetoplacental barrier, and pose a certain risk for embryonal and fetal development. There is no absolute safe immunosuppressant. Pregnancies of women with solid organ transplantations are high-risk pregnancies, with certain peculiarities for each of different transplanted organs. These pregnancies have to be closely monitored and supervised by multidisciplinary teams consisted of transplant medicine specialists, surgeons, maternal-fetal medicine subspecialists and neonatologists. Furthermore, SOT open a new window of ethical concerns due to reduced maternal lifespan and different moral dilemmas connected with support of their offspring.

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Introduction

Annually, around 90,000 solid organ transplant (SOT) surgeries occur worldwide (1), with 37-38% of recipients being female (2). Approximately 14% of these recipients are in their childbearing years (3). SOT candidates often experience impaired fertility, resulting from dysfunction of the hypothalamic-pituitary-ovarian axis (4), and the effects of the transplanted organ (5). Many women awaiting transplant are amenorrheic (6), and even if they conceive spontaneously, many pregnancies result in spontaneous abortion.

The primary goal for a successful pregnancy in SOT recipients is to minimize graft rejection risks and balance immunosuppressive medications to reduce teratogenicity (7), which is challenging. To avoid unintended pregnancies, all SOT candidates must be protected until they meet the criteria for conception. The hypothalamic-pituitary-ovarian axis typically resolves quickly after transplantation, with regular menstrual cycles often returning within the first post-transplant year (7). Ovulation can resume within the first few months. However, the consequences of an unexpected pregnancy for allograft function can be devastating, highlighting the importance of reproductive counseling before transplantation.

The American Society of Transplantation recommended (8) that desired pregnancies be delayed until at least one year after SOT, provided there is stable graft function and no rejection episodes during the year before conception. For lung transplant recipients, the recommendation is to delay pregnancy for two years due to elevated risks (5). Immunosuppressive medications are essential to prevent organ rejection but pose risks to pregnancy, increasing the likelihood of infections, tumors, and cardiovascular issues (1). Despite these risks, pregnancies in SOT recipients, when planned and carefully monitored, typically progress successfully, with live birth rates ranging from 64% to 75%. For pregnancies that extend past the first trimester, the live birth rate increases to 96% (9).

The primary obstetric concerns for SOT pregnancies include congenital infections (particularly Cytomegalovirus) (10), hypertension, preeclampsia, preterm birth, fetal growth restriction, low birth weight, and other comorbidities (9). However, with good, coordinated preconception and perinatal care provided by a multidisciplinary team, SOT pregnancies can result in favorable maternal and neonatal outcomes (11). The average gestational age at delivery is between 34 and 37 weeks for SOT recipients (9, 12-15).

Having children is a lifelong goal for many women, including SOT recipients. Beyond the emotional factors, each recipient and their partner must be thoroughly informed about the risks of pregnancy, the mother's life expectancy, and the implications for parenting and supporting the child (1).

Discussion

Women with end-stage organ failure awaiting solid organ transplantation commonly experience amenorrhea, and more than half do not use contraception; approximately 40% rely on methods with high typical-use failure rates such as condoms, withdrawal, or rhythm tracking (16). As a result, one-third of pregnancies following transplantation are unplanned (6). Combined hormonal contraception is considered safe for most patients; however, estrogen-progestin formulations warrant caution in women with comorbidities such as diabetes mellitus, dyslipidemia, or thrombotic risk, particularly when interacting with immunosuppressants. Women receiving mycophenolate mofetil (MMF) are required to use highly effective contraception during treatment and for six weeks after discontinuation due to its teratogenic potential (1).

Pregnancy in solid organ transplant (SOT) recipients is uniformly classified as high risk. Maternal risks include graft dysfunction, rejection, hypertension, and infection; fetal risks include medication-related toxicity, prematurity, and growth restriction, with incidences far exceeding those in the general population (17).

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The likelihood of allograft rejection during or after pregnancy necessitates maintaining adequate immunosuppression (18). Calcineurin inhibitors (cyclosporine and tacrolimus), azathioprine, and prednisone are generally considered compatible with pregnancy, although dose adjustments are often required. Because immunosuppressive dosing is most intensive during the first post-transplant year, conception should be deferred until the lowest stable therapeutic dosing is achieved (6).

Tacrolimus is the most frequently used calcineurin inhibitor during pregnancy in transplant recipients. Due to its high protein and erythrocyte binding, pregnancy-related hemodilution decreases whole-blood drug concentrations, necessitating dose increases of approximately 20–25% to maintain target trough levels (19). Careful monitoring is essential because excessive dose escalation increases the risk of nephrotoxicity, neurotoxicity, and hypertension. For patients who experience tacrolimus-related toxicity even at low serum levels, supplemental immunosuppression with steroids or azathioprine may be required (10). MMF and mycophenolic acid are contraindicated because of their strong teratogenicity. In addition, sirolimus, everolimus, and belatacept should be avoided due to insufficient human pregnancy data (6). Thus, preconception counseling and contraceptive planning are fundamental for all SOT recipients.

Obstetric complications are frequent. Preterm delivery is the most common, occurring in more than 75% of pregnancies, followed by hypertension (60%), infections, and preeclampsia (30%) (7). Premature contractions may occur spontaneously or be precipitated by hypertensive disorders. Among kidney transplant (KT) recipients, nearly half of infants demonstrate intrauterine growth restriction (IUGR) or low birth weight, largely attributable to underlying kidney disease, hypertension, or superimposed preeclampsia (7). Although congenital malformation rates do not differ significantly from those in the general population (20), children of KT recipients have higher rates of acute bronchitis, systemic lupus erythematosus, and behavioral hyperactivity

disorders. Overall long-term morbidity is otherwise comparable (20).

Hypertensive disorders occur more frequently in transplant recipients than in non-transplant pregnancies. The physiologic plasma volume expansion of pregnancy may exacerbate pre-existing hypertension or graft-related vascular sensitivity (21,22). Estrogen and progesterone induce systemic vasodilation and increase glomerular filtration, partially counterbalancing hypertensive tendencies (23). Maintaining blood pressure $\leq 130/80$ mmHg is recommended (24). Nifedipine, amlodipine, labetalol, hydralazine, and methyldopa remain first-line agents; in contrast, ACE inhibitors and angiotensin receptor blockers must be avoided due to fetal renal failure and other malformations (25,26). These medications should be discontinued preconception or immediately upon pregnancy recognition (10).

Preeclampsia (PE) is significantly more prevalent in SOT recipients (14%–37%) compared to the general population (2%–8%) (27). It is most common in KT and pancreas–kidney transplant (PKT) recipients due to long-standing hypertension and endothelial injury (10). Risk factors include serum creatinine $\geq 125 \mu\text{mol/L}$ before conception, chronic hypertension, and prior PE (21). Low-dose aspirin initiated between 12–16 gestational weeks reduces the incidence of PE (28,29), based on moderate evidence extrapolated from high-risk, non-transplant pregnancies (30,31).

Gestational diabetes mellitus (GDM) is especially common in lung transplant (LuT) recipients (32%), three to four times higher than in other SOT populations, largely due to underlying cystic fibrosis (CF) and pancreatic insufficiency (10). GDM occurs in approximately 8% of KT and liver transplant (LT) recipients and 11% of heart transplant (HT) recipients (32,33). ACOG recommends a pre-pregnancy HbA1c $< 6\%$ to minimize malformations, which approach baseline population levels when glycemic control is optimized (10).

SOT does not inherently necessitate cesarean delivery; labor management follows standard obstetric indications. Because transplanted

kidneys and pancreas grafts are placed extraperitoneally, they do not mechanically interfere with uterine expansion or fetal descent. Although cesarean delivery carries some risk of graft injury, it is not contraindicated; however, surgeons must be familiar with graft anatomy (6).

Parenthood remains a major psychosocial milestone for many SOT patients emerging from prolonged illness. Nevertheless, patient counseling must address the finite life expectancy associated with transplantation. Median survival after lung transplantation for CF is 9.9 years (34), while kidney transplant survival is 19.2 years for living-donor and 11.7 years for deceased-donor grafts (35). Responsible reproductive decision-making requires transparent discussion of maternal health prognosis, caregiving capacity, and potential pregnancy-related risks.

Pregnancy Considerations by Organ Type

Kidney and Pancreas-Kidney Transplants (KT, PKT)

In end-stage renal disease, >90% of women have anovulatory cycles or amenorrhea, frequently exacerbated by dialysis (36). Prior to conception, KT and PKT recipients must meet standardized criteria: serum creatinine <1.5 mg/dL, minimal proteinuria, absence of recent rejection, and well-controlled hypertension and diabetes (10,37). Conception may be considered as early as six months post-transplant if all clinical parameters are stable (38). Multidisciplinary management with maternal-fetal medicine is

essential. When appropriately selected and monitored, approximately 75% of KT and LT recipients achieve successful live births (39,40).

Liver Transplant (LT)

Approximately 75% of LT candidates experience secondary amenorrhea due to chronic liver disease (41). Pregnancy in LT recipients carries increased risks of hypertension, preeclampsia, anemia, preterm birth, and cesarean delivery, but does not elevate the likelihood of acute rejection, graft loss, or maternal mortality (11). A conception delay of 1–2 years post-transplant is advised, with strict adherence to effective contraception during this interval (11).

Heart, Lung, and Heart-Lung Transplants (HT, LuT, H-LuT)

Pregnancies in HT, LuT, and H-LuT recipients are increasingly encountered. Most HT recipients tolerate pregnancy-related hemodynamic changes relatively well. In contrast, LuT recipients have the highest complication rates, including graft rejection, infection, and adverse perinatal outcomes. Importantly, overall graft survival is limited, with approximately 50% mortality at five years post-transplant, which must be considered when counseling patients about long-term parenting capacity (18). More than half of LuT recipients conceive using assisted reproductive technologies (ART), owing largely to CF-related infertility from cervical mucus obstruction and ovulatory dysfunction (42). ART is often combined with pre-implantation genetic diagnosis to avoid transmission of CFTR mutations (43).

Summary of Key Guidelines for Management of Pregnancy in SOT Recipients

(Adapted from Society of Maternal-Fetal Medicine recommendations) (44):

1. Provide prepregnancy counseling to all transplant candidates and recipients.
2. Defer pregnancy for ≥ 1 year post-transplant (≥ 2 years for LuT recipients) or after acute rejection.
3. Ensure stable graft function and well-controlled comorbidities before conception.
4. Use highly effective contraception when receiving MMF or other teratogenic immunosuppressants.

5. Optimize immunosuppressive regimens before conception and stabilize dosing prior to pregnancy.
6. Monitor drug levels closely during pregnancy and postpartum.
7. Provide all indicated vaccinations before and during pregnancy.
8. Complete necessary cytomegalovirus prophylaxis or treatment before conception.
9. Prescribe daily low-dose aspirin to reduce the risk of preeclampsia and renal allograft injury.
10. Screen for depression and ensure access to mental health services.
11. Perform fetal growth assessments every 4–6 weeks.
12. Initiate antenatal surveillance at 32 weeks, or earlier if indicated.
13. Assess renal function early in pregnancy for all SOT recipients.
14. Individualize delivery timing; generally recommend delivery between 37+0/7 and 39+6/7 weeks.
15. Reserve cesarean delivery for standard obstetric indications.
16. Maintain blood pressure $\leq 130/80$ mmHg in renal transplant recipients with chronic hypertension.
17. Screen monthly for asymptomatic bacteriuria in KT recipients.
18. Manage PKT pregnancies similarly to KT pregnancies.
19. In LT recipients, assess the underlying disease and baseline renal function.
20. Provide multidisciplinary cardiovascular management for HT recipients.
21. Use delivery strategies that minimize hemodynamic stress and provide continuous ECG monitoring.

Several domains remain insufficiently defined in counseling SOT recipients, including the role of panel-reactive antibodies, noninvasive immunologic monitoring, prior rejection history, and the long-term impact of preeclampsia on graft survival (10). Current evidence largely derives from registries, observational cohorts, and case reports rather than randomized trials, limiting the certainty of recommendations. Counseling should be individualized and grounded in shared decision-making with

patients and their partners. Adolescents and young adults—particularly vulnerable to unplanned pregnancies—require targeted, developmentally appropriate counseling about risks and graft preservation (45). All counseling must remain objective, evidence-based, and free of bias to support informed reproductive choices.

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Vođenje i izgledi trudnoća kod trudnica s transplantiranim solidnim organima

Sažetak

Napredak u razvitku imunosupresivnih lijekova i kirurških tehnika omogućio je diljem svijeta trudnoće kod brojnih žena koje boluju od terminalne disfunkcije organa. Bolja tolerancija alogeničnih presađaka te smanjen rizik od toksičnosti lijekova stvorili su mogućnost uspješne reprodukcije uz očuvanje dugotrajne funkcije transplantiranog organa. Čak 75 % trudnoća kod transplantiranih pacijentica zabilježeno je kod primateljica bubrežnih presađaka, a slijede trudnoće nakon transplantacije jetre i srca, koje zajedno čine skupinu transplantacija solidnih organa (SOT). Sve je veći broj trudnoća i kod pacijentica s kombiniranom, istovremenom transplantacijom bubrega i gušterače (RPT), kao terapijom terminalne disfunkcije organa uzrokovane dijabetesom tipa 1, te kod transplantacija pluća zbog završnog stadija cistične fibroze. Sve primateljice transplantata imaju povećan rizik od spontanog pobačaja, prijevremenog poroda i fetalnih malformacija. Bubrežne i RPT primateljice su pod dodatnim rizikom od hipertenzivnih poremećaja i preeklampsije. Svi imunosupresivni lijekovi prolaze fetoplacentarnu barijeru i predstavljaju određeni rizik za embrionalni i fetalni razvoj. Ne postoji apsolutno siguran imunosupresiv. Trudnoće kod žena s transplantiranim solidnim organima spadju u visokorizične, te imaju određene specifičnosti, ovisno o vrsti transplantiranog organa. Takve trudnoće moraju se pomno pratiti i voditi od strane multidisciplinarnih timova koji uključuju stručnjake transplantacijske medicine, kirurge, subspecijaliste fetalno-maternalne medicine i neonatologe. SOT otvara i nova etička pitanja zbog potencijalno skraćenog životnog vijeka majke, te moralnih dilema vezanih uz budućnost njihove djece.

Ključne riječi: transplantacija solidnih organa, trudnoća, imunosupresivni lijekovi, alogeni presađci