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REVIEW ARTICLE

Pregnancy and Reproductive Planning in Transplanted Women

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ABSTRACT

The objective of this literature review is to provide some pregnancy results in transplanted women, proposals for preconception, prenatal and postpartum evaluation, including postpartum contraception, and therapeutic guidance during pregnancy and lactation. Based on the results found in research on PubMed without date or language limitations, we discuss the importance of reproductive planning for women with solid organ transplants and what should be done before the transplant. There are formal contraindications to pregnancy; however, when planned, within clinical and laboratory criteria, and with adequate immunosuppression and specialized prenatal care, pregnancy is possible with good perinatal results. We also highlight the importance of psychological support among pregnant women with solid organ transplants.

Descriptors: Pregnancy; Family Planning; Transplantation; Interdisciplinary Communication.

Gestação e Planejamento Reprodutivo em Mulheres Transplantadas

RESUMO

O objetivo desta revisão de literatura é trazer alguns resultados de gestação em mulheres transplantadas, propostas de avaliação pré-concepcional, pré-natal e do puerpério, incluindo a contracepção pós-parto e orientação terapêutica na concomitância da gestação e lactação. Com base nos resultados encontrados em pesquisa no PubMed sem limitação de data ou língua, discutimos a importância do planejamento reprodutivo para mulheres com transplante de órgãos sólidos e que deve ser feito desde antes da realização do transplante. Existem contraindicações formais de gestação, entretanto quando planejada, dentro de critérios clínicos, laboratoriais e uso de imunossupressão adequada e em seguimento de pré-natal especializado essa gestação é possível e com bons resultados perinatais. Salientamos também a importância do acompanhamento psicológico entre gestantes com transplantes de órgãos sólidos.

Descritores: Gravidez; Planejamento Familiar; Transplante; Comunicação Interdisciplinar.

INTRODUCTION

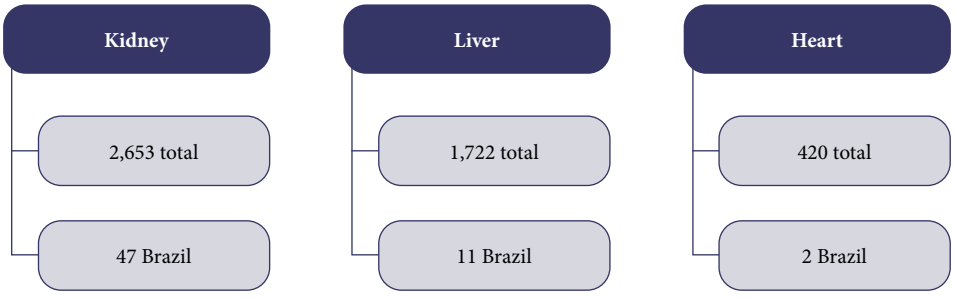
Enhancing the quality of life and health conditions of women of reproductive age with solid organ transplants (SOT) presents a new challenge to healthcare professionals responsible for their well-being. This challenge manifests in the need to engage in discussions regarding reproductive planning. When women express a desire for pregnancy, it becomes imperative to ensure the provision of comprehensive prenatal care, support during childbirth, and postpartum care of the highest quality.[1]

The SOTs with the highest incidence of pregnancy are renal (KTx), followed by hepatic (LTx). While pregnancies are infrequent for other SOTs, they remain a possibility and also necessitate specialized care. All pregnancies among women with SOTs must receive multidisciplinary care with attention from the transplant team and prenatal and postpartum care from specialized obstetric units.

METHODS

We performed an integrative review of the literature. Searches were carried out in a single database (PUBMED) with the terms "heart transplantation AND pregnancy"; "liver transplantation AND pregnancy"; "kidney transplantation AND pregnancy" in September 2023. We selected international and national articles on the topic.

The findings of the search are presented in Fig. 1. The higher frequency of KTx and LTx shows that these are the conditions most frequently associated with pregnancies, followed by heart transplantation. The literature results show that the field is rich in research that portrays the experience of groups with expertise in managing these cases, with few studies comparing interventions or follow-up strategies.



Source: Elaborated by the authors.

Figure 1. Total number of academic articles and number of Brazilian academic articles covering pregnancy and the most frequent SOT (PubMed, Sep. 2023)

RESULTS

Particularities of the different types of SOT and pregnancy

Kidney

The association of pregnancy with RT is the most frequent and oldest in the world and also in Brazil, according to data from the Brazilian Transplant Registry. After kidney transplantation, the rapid normalization of the hypothalamic-pituitary-ovarian axis facilitates the return of ovulatory cycles, enabling pregnancies.[1] Consequently, it becomes imperative to offer reproductive guidance either before or immediately after transplantation to mitigate the risk of unplanned pregnancies, ensuring a suitable timeframe post-normalization of graft function.

While kidney transplantation does not stand out as the most severe among pregnancy-related kidney complications, especially if adequate pre-conception guidance is given and pregnancy is appropriately timed, certain risks must be acknowledged. These include an elevated risk of pre-eclampsia, asymptomatic bacteriuria, and urinary infection, as well as the lifespan of the graft, as pregnancy is characterized by increased glomerular flow.[2]

There are several large center or association studies on perinatal outcomes post-kidney transplant, such as the Transplant Pregnancy Registry International (TPR), UK Transplant Pregnancy Registry, European Renal Association - European Dialysis and Transplant Association (ERA-EDTA) and Dialysis and Transplant Australia and New Zealand (ANZDATA).[3]

Generally, the rate of live births in pregnant women with KTx is comparable to the general population. Vaginal birth is recommended, yet cesarean deliveries predominate (43 to 72%), and the most frequent indications for cesarean section are changes in fetal well-being, previous cesarean section, and deterioration of kidney function; during labor, the most frequent indication is the occurrence of acute fetal distress. The risk of maternal mortality is limited to women with immunological disorders, such as active systemic lupus erythematosus or systemic vasculitis.[2]

Regarding perinatal outcomes, premature birth in women with KTx is more prevalent than in the general population (43% versus 10%), and its predictors are concomitant hypertension during pregnancy and serum creatinine > 1.7 mg/dL before pregnancy.[4] Similarly, the risk of low birth weight (<2500 g) and fetal growth restriction (weight below the 10th percentile for gestational age) is more significant in transplant recipients with pre-gestational hypertension, proteinuria, and use of calcineurin inhibitors.[4]

The occurrence of spontaneous abortion is the same as in the general population, except if mycophenolate was used. The use of mycophenolate is contraindicated among pregnant transplant recipients, and it is essential to suspend it if the woman is planning a pregnancy.[5] The occurrence of stillbirths is slightly higher than in the general population. Still, it depends much more on the quality of prenatal care in detecting changes in fetal vitality than any direct relationship with the transplant.

A national case series with 22 transplants and 25 pregnancies had an average transplant–pregnancy time interval of 5 to 6 years. In this group, 65% had some form of high blood pressure (hypertensive syndrome) during pregnancy, 47% had premature births, and 88% had cesarean sections. Among postpartum women, 82% received some postpartum contraception, with tubal ligation performed in 1/3 of cases.[6]

Liver

Liver diseases of any etiology are always a challenge for monitoring pregnancy, as situations of extreme severity in obstetrics, such as HELLP syndrome and fatty liver of pregnancy cholestasis, can overlap with the underlying disease, making diagnosis and therapeutic approach difficult and increase maternal risks. In LTx, it is no different, as the situations described above can occur and must be differentiated from graft rejection episodes. Contrary to what was described above about KTx, the loss of the liver graft, which has no replacement therapy, means that rejection episodes during pregnancy can be fatal.[7]

Approximately 1 in 12 women undergoing LTx are of reproductive age. Pre-LTx infertility rates are high due to cirrhosis, and LTx reverses this cirrhosis-induced infertility. Post-LTx pregnancy is associated with increased rates of hypertension, preeclampsia, preterm birth, low birth weight, postpartum hemorrhage, and the need for cesarean section. Altered renal function in LTx affects pregnancy outcomes with declining glomerular filtration.

There is no evidence of increased fetal or maternal mortality or allograft loss in post-LTx when conception occurs after six months of transplantation. Women are advised to delay conception until one year after LTx due to the increased risk of immunosuppression instability and infection during this period, as the occurrence of these events increases the risk of acute rejection.

The best perinatal outcomes occur with adequate immunosuppression, stable allograft function, and sufficient control of medical comorbidities. Given its efficacy and safety, Tacrolimus is considered the ideal immunosuppressant during pregnancy. Acute rejection should be treated similarly to that in a non-pregnant person. Historically, breastfeeding has been discouraged due to a lack of safety data. Recent data have demonstrated no adverse events in infants breastfed by mothers who received tacrolimus after transplantation and, likewise, the use of azathioprine is safe given negligible concentrations of its metabolites, 6-mercaptopurine (6-MP) and 6-TGN, in breast milk.[8,9]

Reports of 5 cases followed up at the State University of Campinas by a multidisciplinary team show promising results, with pregnancies between 2 and 11 years after LTx. Even so, there was a premature birth, an episode of acute genital herpes, in addition to a liver hematoma in a pregnant woman using anticoagulation due to a history of venous thrombosis. Despite complications, all five pregnancies were successful. The average gestational age at birth was 35.2 weeks. No structural malformations or early complications were observed in the neonates. All cases had stable liver parameters.[9] Recently, there was a case of maternal death on the 51st day postpartum after acute rejection of the graft during pregnancy, with a sequence of complications resulting from rejection during the postpartum period, which determined the occurrence of maternal death (not yet published).

Heart

The physiological changes of pregnancy impose cardiac overload, and this must be considered in the face of any heart disease or dysfunction, including transplantation. Therefore, the functionality of the graft, as well as the assessment of the risk of rejection when using immunosuppressants that can be maintained during pregnancy, are the first step in thinking about preconception guidance.

There are reports of success, such as an Australian series that reports five pregnancies in 3 heart transplant recipients, all with excellent results with vaginal birth, full-term pregnancies, and breastfeeding. These cases described share pre-conception guidance, right ventricular ejection fraction > 55%, more than 2 years of transplant-pregnancy interval, and adjustment of immunosuppressive therapy before pregnancy. All three used tacrolimus and azathioprine during pregnancy, and one also used prednisone.[10]

However, another issue that must be considered is that, despite the improvement in the quality of life of transplanted people who can become pregnant, the more effective therapy in preserving grafts and the more significant number of transplants over time, an extensive study on heart transplantation involving 157 cases shows a reduction in the number of pregnancies over almost four decades of observation (1982-2017), and one of the hypotheses for this is better counseling from pre-transplantation and clarification of maternal-fetal risks when discussing the possibility of pregnancy.[11] This same study points to less satisfactory results, such as 31% of pregnancy loss, 63% of low birth weight, 59% of prematurity, 23% of pre-eclampsia, and 9% of graft rejection up to 3 months after childbirth, in addition to corroborating by showing an increase in congenital disabilities among pregnant women who continued to use mycophenolate during pregnancy (3 cases, corresponding to 23% of users).

Preconception assessment

Preconception assessment should be part of reproductive planning in any situation, but among people with SOTs, it is essential. It must be carried out by a multidisciplinary team specialized in dealing with immunosuppressive medication, which must be adjusted to drugs that can be used during pregnancy, in addition to controlling other associated comorbidities, such as high blood pressure and autoimmune diseases. After medication adjustment, graft stability must be assessed with specific laboratory and imaging evaluation before pregnancy.[5,12]

The proposed minimum time between SOT is one year as long as there is no occurrence of acute rejection and no fetal-risk infections for kidney, liver, and heart transplants and two years for lung transplants. Another vital issue is up-to-date vaccinations before pregnancy, although some vaccines must be administered during pregnancy (dTP-A, influenza).

No less critical is psychological support, which must be offered before the transplant, but also in the pregnancy decision and planning phase. People with chronic illnesses who are pregnant have a lot of ambiguity in their feelings and a sense of guilt during this period and need all the support from the team.[13]

Prenatal, childbirth, and postpartum

Prenatal care is an opportunity to promote health. In cases of pregnancy in people with SOTs, adequate reproductive counseling and the pre-pregnancy condition directly influence the care routine and perinatal outcomes. All prenatal practices must be maintained in people with SOTs, and prenatal care must be adapted according to the need to evaluate the graft or specific clinical situations the person presents. It is essential that monitoring is shared between the specialized obstetric team and the transplant team, with the sharing of clinical information, in addition to the adjustment between the pregnant woman's expectations and the possibilities imposed by the clinical situation.

Vaccination of pregnant women is routinely carried out with dTPa and Influenza during each pregnancy, in addition to the opportunity for vaccines such as COVID-19. Vaccines for hepatitis B, pneumococcus, and meningococcus can be administered if they are overdue. Still, if there has been good reproductive planning, they should be up to date when pregnancy occurs.[14]

The prenatal laboratory routine, which includes serology (HIV, Hepatitis B and C, Syphilis, and Toxoplasmosis), CBC, urine summary and urine culture, blood glucose, and blood typing, should include screening for cytomegalovirus, which can reactivate and cause vertical infection. For transplant recipients, there is also guidance on prophylaxis for urinary tract infections throughout pregnancy, as they have a single kidney.

The increase in plasma volume and weight expected during pregnancy makes it essential, whenever possible, to monitor the serum level of immunosuppressants and adjust the dose. We remind you once again that the use of mycophenolate is contraindicated during pregnancy and should be discontinued.[5]

Due to the increased incidence of pure or superimposed pre-eclampsia in SOT (29% in kidney transplants, 21% in liver transplants), pre-eclampsia prophylaxis with acetylsalicylic acid 100 mg per day and calcium carbonate is recommended (1 – 1.5 g per day) since the 1st trimester, including among kidney transplant recipients.[5]

Due to the risk of fetal growth restriction due to the use of immunosuppressants or associated comorbidities such as high blood pressure and lupus, there is a need for serial surveillance of fetal growth and vitality using all available investigations such as ultrasound, cardiotocography, and serial Doppler flowmetry.[15]

Delivery must occur obstetrically, except in cases with portal hypertension, where the indication is an elective cesarean section, or in cases in which pregnancy resolution occurs before 32 weeks, when the severe maternal or fetal clinical condition that indicated delivery may give rise to concerns about the duration of labor induction.

Even among people with SOTs, the unplanned pregnancy rate is high, and reproductive planning and the choice of postpartum contraception must be carried out during prenatal care so that there is a greater possibility of choosing effective methods, greater ease of access, and there is no risk of subsequent pregnancy with a short intrapartum interval.

The recommendation to screen for depression and anxiety exists in all pregnancies. In cases of SOT, this is imperative; in addition to screening, routine psychological follow-up is recommended.[5,16]

Postpartum follow-up cannot be neglected, with contraception, breastfeeding, return to baseline treatment, provision of contraception if it was not provided during birth, and psychosocial conditions being assessed during this period.

Immunosuppression

The immunosuppressive agents most used in SOTs are Corticosteroids, Azathioprine, Calcineurin Inhibitors (Ciclosporin and Tacrolimus), Mycophenolate, B and T cell inhibitors (Sirolimus Everolimus), T-selective cell inhibitors (Betacept) - below you can see the main characteristics of the medication and its use during pregnancy and breastfeeding (Table 1).

Table 1. Immunosuppressive therapy in SOT and use during pregnancy and breastfeeding.

Immunosuppressant	Mechanism of action	Adverse effects	Use during pregnancy	Use in breastfeeding
Corticosteroids	Multiple effects	palate defects (conflicting and scarce data), FGR, GDM,	Low risk	Compatible
Azathioprine	Inhibits purine synthesis, DNA replication, and B and T cells	No evidence of FD, FGR, Prematurity	Low risk	Compatible
Ciclosporin Tacrolimus	Inhibitors of interleukin II and T cell activation	No evidence of FD, FGR, Prematurity Dose-dependent maternal reactions	Low risk	Compatible
Mycophenolate	Purine synthesis inhibitor	1st-trimester abortion Teratogenic (facial, cardiac, CNS defects, esophageal atresia	Contraindicated Discontinue six weeks before pregnancy	No data; should be discouraged
Sirolimus Everolimus	B and T cell inhibitors	Scarce data, there are descriptions of congenital disabilities	Contraindicated Discontinue 12 weeks before pregnancy	No data
Betacept	T-selective cell inhibitors	No data	No data	No data

FGR: fetal growth restriction; DMG: Gestational diabetes Mellitus; CNS: Central nervous system. Source: Adapted from Society for Maternal-Fetal Medicine Consult Series #66: Pregnancy evaluation and pregnancy management of patients with solid organ transplants, 2023.[5]

Summary of recommendations

Recently, the Society for Maternal-Fetal Medicine published a series of recommendations that compiles previous studies and recommendations from various medical societies on the topic (Table 2).[5] Recommendations follow the degrees of scientific evidence (GRADE)

Tabela 2. Summary of recommendations for pregnancy in people with SOTs

N°	Recommendation for receivers	Degree
1	People with SOT who are capable of becoming pregnant should receive preconception counseling as part of the pretransplant evaluation and before posttransplant pregnancy.	Good habits
2	Delay pregnancy for at least 1 year after SOT (except for lung transplant, in which case the recommended delay is 2 years) or any episode of acute cellular rejection.	1B
3	Stable allograft function and optimal control of chronic diseases before pregnancy.	1B
4	SOT recipients of reproductive age should use highly effective contraceptive methods when using mycophenolate or other immunosuppressive agents with a known teratogenic risk.	1A
5	SOT recipients who wish to become pregnant must first transition to an immunosuppressive regimen that can be maintained throughout pregnancy and establish stable medication dosage and allograft function.	1C
6	Close monitoring of serum drug levels during pregnancy and postpartum to guide dosing of immunosuppressive therapy.	1C
7	Pregnant women or those intending to become pregnant must receive all recommended vaccines before and during pregnancy	1C
8	Due to the fetal and neonatal risk of vertical CMV infection, treatment or prevention with antivirals must be carried out before pregnancy, in addition to screening during pregnancy.	2B
9	Use of ASA for Preeclampsia Prevention	1C
10	Access to mental health care with specialists and depression screening during pregnancy and the postpartum period	Good habits
11	Systematic ultrasound assessment for the risk of fetal growth restriction (every 4 to 6 weeks)	1C
12	Assessment of fetal vitality based on fetal viability	2C
13	Pre-pregnancy or early pregnancy renal function assessment for any SOT	1C
14	Elective termination of uncomplicated pregnancies at term (37 – 39+6 weeks)	2B
15	Spontaneous or induced vaginal birth is the most indicated, with less risk for the graft and cesarean section must follow obstetric indications	1C
16	Kidney transplant recipients with AH should follow the recommendations for any pregnant woman with chronic CAH (<130/80mmHg)	1C
17	Screening for asymptomatic bacteriuria with monthly urine culture for kidney transplant recipients and treatment whenever urine culture is positive to protect the graft	1C
18	Pancreas-kidney transplant cases must follow the recommendations for kidney transplant	1C
19	Characterize the condition that led to liver transplantation and evaluate renal function in all cases	1C
20	Due to the cardiovascular changes during pregnancy, heart transplant cases require multidisciplinary care with cardiologists and anesthesiologists.	Good habits
21	Birth planning to minimize hemodynamic stress and continuous intrapartum or intraoperative electrocardiographic monitoring in cases of heart transplantation.	1C

Recommendations for SOT Recipients who wish to conceive. Source: Adapted from Irani et al.[5]

CONCLUSION

People with SOTs who wish to become pregnant should be advised regarding the possibility of pregnancy, risks for both graft health and perinatal results, and the importance of choosing the lowest risk moment with adequate reproductive planning in a multidisciplinary way with a transplant team and gynecologist-obstetrician They must also receive psychological support from the transplant planning, preconception period, pregnancy and postpartum period. Furthermore, access to highly effective contraceptives is essential when pregnancy is not desired.

CONFLICT OF INTEREST

Nothing to declare.

AUTHOR'S CONTRIBUTION

Substantive scientific and intellectual contributions to the study: Surita FG, Guida JPS, Juliato CRT, Boin IFSF; **Conception and design:** Surita FG, Boin IFSF; **Data analysis and interpretation:** Surita FG, Guida JPS, Juliato CRT; **Article writing:** Surita FG, Guida JPS; **Critical revision:** Surita FG, Guida JPS, Juliato CRT, Boin IFSF; **Final approval:** Surita FG.

DATA AVAILABILITY STATEMENT

All dataset were generated or analyzed in the current study.

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