Medical Science

Navigating Pregnancy After Liver and Kidney Transplantation. A review study

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To Cite:
Krasnodębska J, Stachyra K, Leśniewski M, Bieda A, Zaremba A, Borecka M, Wyskok M, Kluska M, Kwiatka P, Hanusz K. Navigating Pregnancy After Liver and Kidney Transplantation. A review study. *Medical Science* 2025; 29: e59ms3551
doi: https://doi.org/10.54905/disssi.v29i158.e59ms3551

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Peer-Review History
Received: 09 January 2025
Reviewed & Revised: 15/January/2025 to 12/April/2025
Accepted: 21 April 2025
Published: 25 April 2025

Peer-review Method
External peer-review was done through double-blind method.

Medical Science
pISSN 2321–7359; eISSN 2321–7367

DISCOVERY SCIENTIFIC SOCIETY

ABSTRACT

Pregnancy after kidney or liver transplantation is a common situation, which creates complex challenges and causes a necessity for a multidisciplinary approach. This review underlines primary problems related to pre-pregnancy counseling, pregnancy outcomes, and immunosuppression management in pregnant women who underwent liver or kidney transplantation. The study reviews the current literature on managing pregnancy in liver and kidney transplant recipients. Successful pregnancies are possible after liver or kidney transplantation but require a multidisciplinary approach involving transplant specialists, obstetricians, and other healthcare professionals. The most important factors that can help minimize the risk of complications are monitoring the mother's and fetus's health, precise risk assessment, and matched immunosuppression. A new analysis is needed to create a universal guideline for multidisciplinary teams to facilitate managing that kind of high-risk pregnancies.

Keywords: Pregnancy, liver transplantation, kidney transplantation

1. INTRODUCTION

Pregnancies following liver (LT) and kidney transplantation (KT) are more frequent and challenging for transplant physicians, obstetricians, and nephrologists. Thanks to the development of medical technology and immunosuppressive treatments, transplant recipients and their newborns may experience more favorable outcomes. However, managing pregnancy in these patients requires specialized approaches. The patients after liver or kidney transplantation are more likely to develop adverse outcomes such as preterm delivery or pre-eclampsia. This indicates careful pregnancy management, focused on monitoring kidney and liver function and measuring blood pressure and glucose levels more frequently than in women without such health issues (Deshpande et al., 2011; Deshpande et al., 2012).

Moreover, patients after kidney transplantation commonly have more

comorbidities related to diabetes and cardiovascular disease, which significantly increase the risk of maternal and fetal adverse outcomes. Other factors that can lead to pregnancy complications in transplant recipients are the advanced age of the mother, previous abdominal surgery, and exposure to long-term medical treatments, which are not indifferent to the patient's health (Davison et al., 2003).

This article aims to explore the characteristics in the management of pregnancy in these two groups of patients, focusing on pre-pregnancy counseling, care during each trimester, the teratogenic effects of immunosuppressive medications, the maternal and possible complications both groups of patients could face, and the significance of a multidisciplinary approach.

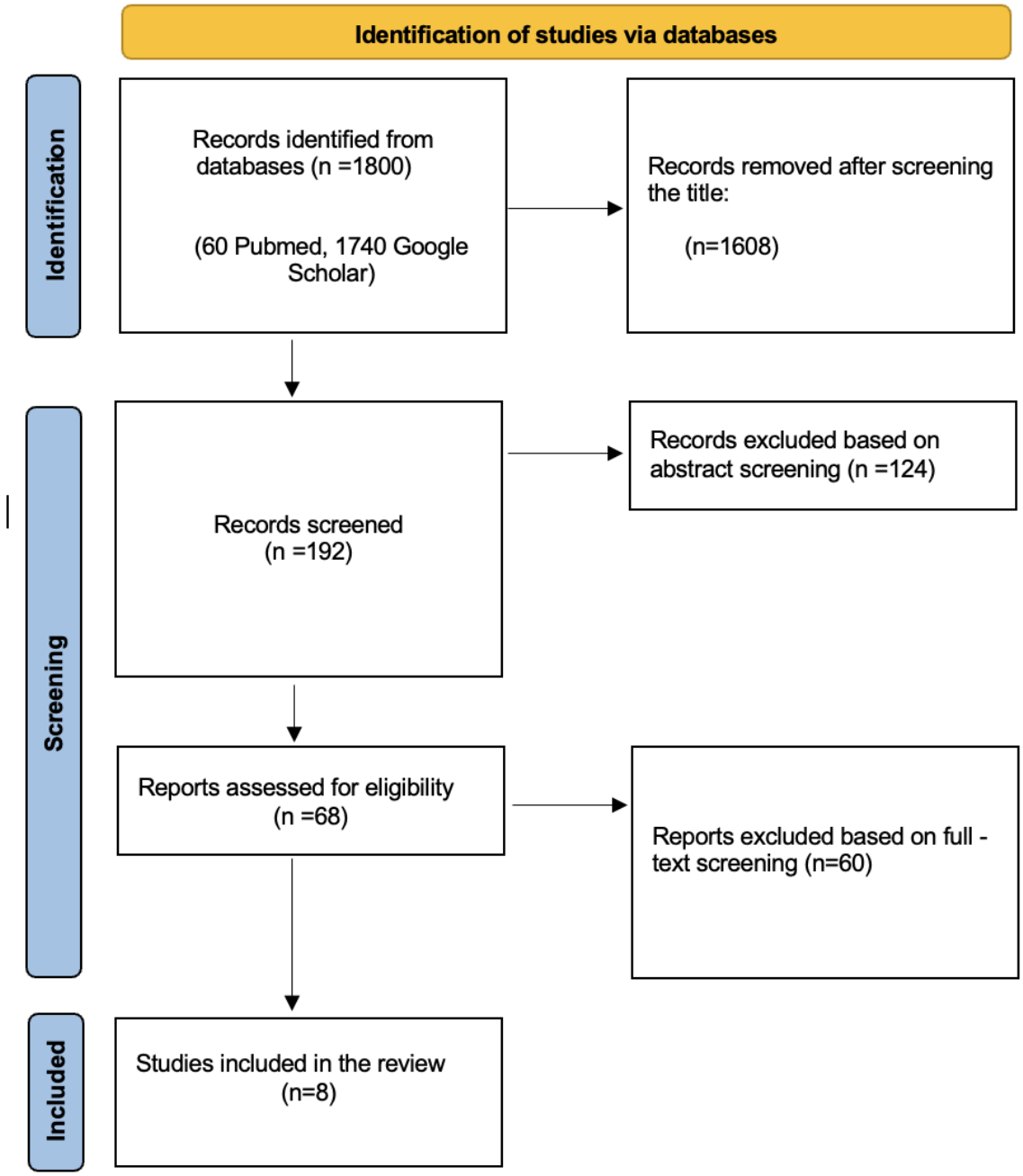

Figure 1. PRISMA flow diagram

2. METHOD

The article is an overall review of the literature on current approaches to managing pregnancy in patients after liver and kidney transplantation. Phrases such as "pregnancy after liver transplantation," "pregnancy after kidney transplantation," "liver transplantation," and “kidney transplantation” were used in the PubMed and Google Scholar databases to search articles published between 2019 and 2024. The review included randomized controlled trials, crossover, retrospective, follow-up, and population studies. The review screening was performed according to the Preferred Reporting Items for Meta-Analyses (PRISMA) 2020 guidelines (figure 1). The study’s main aim was to compare the two groups of patients in terms of differences and similarities in challenges, occurrence of adverse events, and impact on allograft.

3. RESULTS & DISCUSSION

Fertility before transplantation

Around 30%-50% of women suffering from chronic liver disease experience amenorrhea. The underlying causes of liver disease, nutritional status, and metabolic or endocrine dysfunctions all contribute to the development of this stage. Hormonal imbalances in liver disease result from hypothalamic-pituitary axis disruption, impaired liver processing of sex hormones, altered androgen circulation, and increased peripheral conversion of androgens to estrogens. Early liver disease may be associated with elevated estrogen levels (Rahim et al., 2020).

End-stage renal disease (ESRD), which is known as the last, chronic stage of renal failure, is one of the most common indications of kidney transplantation. It affects fertility, often leading to functional menopause in female patients. Studies have reported infertility rates reaching up to 92% in women with ESRD (Alalawi et al., 2023). Women of reproductive age on renal replacement therapy have significantly reduced fertility (approximately ten times lower than the general population) due to reproductive dysfunction manifested as low libido, irregular menstruation, and amenorrhea, frequently associated with elevated prolactin levels. Women who underwent kidney transplantation experienced a significant fertility improvement. Studies of pregnancies following kidney transplantation show live birth rates (LBR) comparable to the general population, although these pregnancies carry a heightened risk of complications (Mohammadi et al., 2017).

Characteristics of pregnancy outcomes, obstetric complications and delivery outcomes of pregnancy in liver transplant recipients

Marson et al., (2020) conducted a systematic review and meta-analysis of 28 studies, including 1496 pregnancies in 1073 liver transplant patients. The percentages for live births, miscarriages, abortions, stillbirths, and ectopic pregnancies were 83.3%, 7.8%, 5.7%, 3.3%, and 1.7%, respectively. In women undergoing liver transplantation, pregnancy-induced hypertension (PIH) was observed in 14 studies, with a rate of 18.2% in patients. The authors reported preeclampsia in 15 studies with a rate of 12.8%. Gestational diabetes mellitus appeared in 13 studies, with an incidence of 7.0%. A survey by Marson et al., (2020) described the incidence of C-section and vaginal delivery as 42.2% and 42.4% reported by 26 and 22 studies, respectively. The researchers noted a preterm birth in 23 studies with a rate of 27.8%. Moreover, gestational age and birth weight were mentioned in 19 and 20 studies, respectively, with an average of 37.1 weeks and 2,783 g.

Sciarrcione et al., (2022) reported 60 liver transplant recipients with 62 pregnancies. The median age at conception was 31, and the median between transplant and conception was 8 years. Four women experienced pregnancy-related complications requiring hospitalization. All pregnancies resulted in live births, but 25 of the 62 newborns were premature, and eight newborns had low birth weight. A study by Marzec et al., (2021) reported 14 pregnancies in 10 liver transplant recipients. These women had an average age of 28.5 at the time of transplantation and an average age of 32 years at the time of pregnancy. The average time between transplant and conception was 4.07 years, with an average gestational age at delivery of 36.67 weeks. Valentin et al., (2021) analyzed 38 studies encompassing 1,131 pregnancies in 838 liver transplant recipients, revealing an average maternal age of 27.8 years at conception, with an average of 59.7 months between transplant and pregnancy. The live birth rate was 80.4%, and the average gestational age at delivery was 36.5 weeks. Miscarriage rates (16.7%) were comparable to the general population. However, the number of preterm births (32.1%), preeclampsia incidence (12.5%), and cesarean sections (42.2%) were significantly higher than national averages (Sciarrone et al., 2022).

Characteristics of pregnancy outcomes, obstetric complications, and delivery outcomes of pregnancy in kidney transplant recipients

A retrospective study by Kaatz et al., (2023) showed that 39 out of 46 pregnancies resulted in a live birth, with a maternal survival rate of 100%. The median gestational age at delivery or pregnancy termination was 35.15 weeks. The seven pregnancy losses consisted of two very early abortions (before 12 weeks; the authors excluded them from analysis), one abortion at 12 weeks, two induced

abortions at 19 and 22 weeks due to significant fetal anomalies, one miscarriage at 20 weeks due to membranes, which broke prematurely and one stillbirth at 25 weeks due to severe preeclampsia.

Schwarz et al., (2022) performed a retrospective observational study of 92 pregnancies in 67 women after renal transplantation from 1972 to 2019. Live births occurred in 90.5% of pregnancies (9 fetal deaths). Maternal complications included preeclampsia (24%, resulting in one graft loss and three fetal deaths), graft rejection (5.4%, one graft loss), hemolytic uremic syndrome (2%, one graft loss and one fetal death), maternal hemorrhage (2%, one fetal death), and urinary tract obstruction (10%). 76% of cases ended with cesarean delivery. Fetal complications were frequent, with low gestational age (average 34.44 ± 5.02 weeks) and low birth weight (average 2322.26 ± 781.98 g).

Kovic's study examined 22 pregnancies in 18 women (aged 26–39), an average of 78 ± 37 months post-kidney transplant. No transplant rejections occurred during pregnancy, but three occurred within the first nine postpartum months. The median pregnancy length was 37 weeks. 4 women developed preeclampsia, and two developed severe eclampsia. 19 (86%) deliveries were by cesarean section. One child was born with Down syndrome (trisomy 21), and three had minor congenital disabilities (Kovač et al., 2021).

Caretto et al., (2020) performed studies describing 109 pregnancies after pancreas-kidney transplantation in the period between 1991 and 2018. 70% of pregnancies resulted in live births, with one neonatal death due to extreme prematurity. The primary maternal adverse events were hypertension – 58%, infections – 39%, diabetes - % graft rejection – 5%, and congenital malformation – 1%. The rate of preterm delivery (<37 GW) was 76%, and the mean gestational weeks at birth was 34.2 ± 3.1. 69% of pregnancies ended with cesarean section.

The pregnancy impact on graft survival

Impact on graft survival after LT

Jain et al., (2003) described one patient who experienced ischemic graft injury during labor and another patient who lost her allograft due to recurrent autoimmune hepatitis and chronic rejection shortly after Pregnancy. In the work of Dei Malatesta et al., (2006) an acute rejection rate was 10%. However, the authors did not provide information about the time of acute rejection or the administered treatments. Nagy (2003) documented 4 cases (out of 24 live births) of biopsy-confirmed graft rejection, with an overall rejection rate of 17% for the 24 live births. Still, no instances of graft loss were reported.

Impact on graft survival after KT

Among women with initially good kidney function before pregnancy, 20% experienced decreased function during pregnancy. In total, 33.9% of women experienced a decline in kidney function during pregnancy. Of these, 63.2% did not recover to baseline levels within one to two years postpartum. Additionally, 30% of women developed new or worsening kidney function problems within the first one to two years after delivery (Mohammadi et al., 2017). In Stavart et al., (2023) studies, no transplant rejections occurred during pregnancy in this group. However, they reported two confirmed and one suspected/possible case of rejection within two years of postpartum follow-up.

Similarities in the management of pregnancy in kidney and liver transplant recipients

All female transplant recipients should receive counseling regarding obstetrical options from their transplant physicians. The health team, which includes an obstetrician and a transplant specialist, should manage pregnant transplant recipients. Counseling should begin before liver and kidney transplantation and continue both after the transplant and before conception. The recommendation is to wait at least 12–24 months after a before trying to conceive. Additionally, patients who become pregnant are required to be screened for diabetes and hypertension. If possible, the type of delivery should be planned, preferably a cesarean section or induced labor.

Immunosuppressive treatment in patients undergoing liver and kidney transplantation

There are various possibilities for using immunosuppression in pregnant women. The medical team should match the treatment individually and consider the patient's needs and tolerance for immunosuppression. The safest immunosuppression during Pregnancy is Prednisolone, azathioprine, cyclosporine, and tacrolimus (EASL, 2016). Mycophenolate mofetil (MMF) and the less frequently used sirolimus are contraindicated during pregnancy. Studies indicate that the use of MMF at the beginning of pregnancy may cause pregnancy loss, with spontaneous abortion rates ranging from 33% to 45% and malformations such as cleft lip and palate (Alisi et al., 2016).

The optimal interval between liver/renal transplantation and pregnancy

The definitive interval between liver transplantation and pregnancy has not been defined; the recommendations are to wait at least one year after transplantation. This may help to stabilize the graft function and to match an appropriate dose of immunosuppression (Armenti et al., 2006; Josephson et al., 2007). Nonetheless, it is essential to remember that this is a general recommendation, and a multidisciplinary team should always consider the optimal time frame on a case-by-case basis. A National Transplant Registry (NTPR) study of 128 pregnancies in liver transplant recipients found that waiting more than two years post-transplantation before conceiving was associated with a lower incidence of neonates born with low birth weight, transplant rejection, and loss of the allograft (Coscia et al., 2009).

Pais et al. showed that the most favorable time for pregnancy was 12-24 months after KT. This period is related to decreased risk of urinary tract infections, fetal growth restrictions, premature delivery, and low birth weight. Recent advances in immunosuppression and concerns about decreasing childbearing years due to increasing average maternal age contributed to the shortage, from 2 years to one year, of the waiting period before pregnancy after transplantation by the American Transplant Society (Pais et al., 2018). Study summaries are mentioned in table 1.

Table 1. Characteristics of published studies on pregnancy after liver or kidney transplantation

Study	Population and duration	Outcome measure	Results
Marson et al., 2020	1496 pregnancies in 1073 liver transplant recipients	live birth rate, induced abortions, miscarriages, stillbirths, obstetric complications, hypertension, preeclampsia and gestational diabetes, delivery outcomes for cesarean section and pre-term birth	live birth rate (85.6%), induced abortions (5.7%), miscarriages (7.8%), stillbirths (3.3%), obstetric complications: hypertension (18.2%), preeclampsia (12.8%) and gestational diabetes (7.0%), cesarean section (42.2%), preterm birth (27.8%)
Sciarrone et al., 2022	62 pregnancies in 60 LT recipients between 1990 and 2018	maternal complications with hospital admission, live birth rate, prematurity, low birth weight	maternal complications with hospital admission (66%), live birth rate (100%), prematurity (40%), and low birth weight (13%)
Marzec et al., 2021	14 pregnancies in 10 women (12 childbirths, one induced abortion due to fetal death in the first trimester, one pregnancy is still ongoing)	Maternal complications (increase in aspartate transaminase and alanine transaminase, anemia, and hyperthyroidism), preterm birth, delivery outcomes	maternal complications included an increase in aspartate transaminase and alanine transaminase (20%), anemia (40%), hyperthyroidism (20%), preterm birth (50%), spontaneous labor (50%), cesarean delivery (70%)
Kaatz et al., 2023	40 women after single or combined pancreas–kidney transplantation between 2003 and 2019	maternal survival rate, pregnancies ended up with live born baby, adverse pregnancy events (preeclampsia with severe end-organ dysfunction)	maternal survival rate (100%), pregnancies ended up with a live born baby (85%), adverse pregnancy events - preeclampsia with severe end-organ dysfunction (39%)

Schwarz et al., 2022	92 pregnancies in 67 women after renal transplantation from 1972 to 2019	live births, maternal complications of pregnancy, fetal complica- tions	live births (90.5%), maternal complications: preeclampsia (24%), graft rejection (5.4%), maternal hemorrhage (2%), urinary obstruction (10%,) cesarian section (76%), fetal complica- tions: low gestational age (34.44 ± 5.02 weeks), low birth weight (2322.26 ± 781.98 g)
Kovač et al., 2021	22 pregnancies in 18 women	the median duration of pregnancies, preeclampsia, severe eclampsia, cesarean section, congenital defects	median duration of pregnancies - 37 weeks, preeclampsia (22%), severe eclampsia (11%), cesarian section (86%), fetal complica- tions: trisomy of chromosome 21 (4.5%) and minor congenital anomalies (13.6%)
Caretto et al., 2020).	109 pregnencies in combined pancreas–kidney recipients, including a few multiple pregnancies	live birth, hypertension, infections, diabetes, graft rejection, congenital malformations, preterm delivery, mean birth weight, cesarian cection	live birth (70%), hypertension (58%), infections (39%), diabetes (3%), graft rejection (5%), congenital malformations (1%), preterm delivery (76%), mean birth weight (2142 ±726 g), cesarian cection (69%)
Jain et al., 2003	49 pregnancies in 37 women	mean gestational period, cesarian section, mean birth weight	mean gestational period (36.4±3.2 weeks), excluding two premature deliveries at 23- and 24-weeks gestation, cesarian section (46.9%), mean birth weight (2,797±775 g)

4. CONCLUSION

Our review confirms that delivering a healthy infant after KT or LT is possible. This involves close collaboration between transplant specialists (hepatologists and nephrologists), obstetricians, and other relevant healthcare professionals. Each pregnancy needs careful evaluation of maternal and fetal risks based on the type of transplantation, graft function, immunosuppression regimen, and co-morbidities. Systematic screening of blood pressure, kidney and liver functions, and blood glucose levels is necessary. Additionally, monitoring of fetal growth should be conducted with special attention. This review emphasizes the importance of further research to establish the most reliable recommendations for patients who wish to become pregnant after undergoing liver transplantation, as most analyses were associated with substantial heterogeneity.

Authors' Contributions

Conceptualization, J.B.K, and A.Z.; Methodology, J.B.K., M.L.; Software, P.K.; Validation, M.L., A.Z. and M.B.; Formal Analysis, A.B, M.B., A.M., K.H.; Investigation, M.K., M.K.; Resources, K.S., M.B.; Data Curation, P.K., K.S., K.H.; Writing – Original Draft Preparation, A.B., M.L., A.M., K.H. and A.Z.; Writing – Review & Editing, M.B., P.K., M.K., K.H. and J.B.K.; Supervision, A.B., A.M.; Project Administration, A.B., J.B.K., A.Z., M.L., P.K., K.S., M.K., A.M., K.H, M.B.

Informed Consent

Not applicable.

Ethical approval
Not applicable.

Funding
This study has not received any external funding.

Conflict of interest
The authors declare that there is no conflict of interests.

Data and materials availability
All data sets collected during this study are available upon reasonable request from the corresponding author.

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