



Symposium on Liver & Pregnancy

Pregnancy after liver transplantationMary Eugenia Rinella¹**Abstract**

Although the transplant community has begun to gather experience in pregnancy after liver transplant, much remains to be learned about the effects of pregnancy on mother and child. Most women with end stage liver disease have amenorrhea or are unable to conceive due to medical complications. Liver transplantation offers such patients the opportunity to have children. Since libido and fertility can return fairly rapidly, it is important to discuss birth control in the early post transplant period. It is recommended that pregnancy be delayed for 1 and preferably 2 years post-transplant as pregnancies within the first year are associated with higher rates of premature birth and cellular rejection. The current evidence suggests that pregnancy is safe after transplant, however it requires close follow-up by a team of experienced physicians.

Key words: Pregnancy, liver transplantation, amenorrhea, premature birth.

Introduction

Although the transplant community has begun to gather experience in pregnancy after liver transplant, much remains to be learned about the effects of pregnancy on mother and child. National transplantation statistics indicate that women constitute approximately one-third of all liver recipients and approximately 75% of female recipients are of reproductive age. With the continued success and increase in the volume of transplants performed, issues regarding fertility are increasingly germane. Approximately 50% of women with end stage liver disease have amenorrhea or are unable to conceive due to medical complications and liver transplantation can restore libido and fertility in women of childbearing age.¹

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Since the first successful pregnancy in a liver transplant recipient in 1978,² much has been learned. Although the majority of the data on pregnancy after transplantation is extrapolated from the renal transplant literature, pregnancy is generally considered to be safe after liver transplant despite the increased risk of hypertension, intrauterine growth retardation (IUGR), premature delivery and preeclampsia in these patients.^{3,4}

Recovery of menstruation and fertility post transplantation

Amenorrhea is a common clinical problem in women with liver disease that advances enough to require liver transplantation. The hormonal basis of amenorrhea is incompletely understood, but likely involves hypothalamic-pituitary dysfunction. This is rapidly corrected in over 80% of women as evidenced by the return of normal menses within 8 months of transplantation.^{1,5,6} Therefore, women with secondary amenorrhea are likely to resume menstruation and endogenous estrogen production after transplantation and those not wishing to become pregnant should use contraception.

Libido returns fairly rapidly post transplant and women should be counseled on contraception and the avoidance of sexually transmitted diseases. In general, liver transplant recipients should be encouraged to use barrier methods during the first year post transplant to minimize the risk of venous thrombosis and sexually transmitted diseases in those who are at risk. Typically, hormonal oral contraception is avoided in the first year post transplant primarily due to these reasons. Oral contraceptives are generally appropriate after the second year but should be avoided in women with a history of Budd-Chiari or hypercoagulability.

Is pregnancy safe after transplantation?

Data from the United States National Transplantation Pregnancy Registry (NTPR) has reported on 137 pregnancies from 31 centers. Seventy percent of such pregnancies resulted in live births with good maternal and fetal outcome in the majority.⁷ A recent large series from King's college reported the outcome of 71 pregnancies in 45 women post transplant between 1988 and 2004.⁸ They too had a live birth rate of 70% with no graft loss or maternal death related to transplantation. Despite the reported safety of pregnancy after transplantation, all such patients

should be considered high risk and followed closely by the respective transplant team and ideally a specialist in high risk obstetrics or maternal fetal medicine.⁹ Transplant follow-up should be frequent during and shortly after pregnancy to ensure good allograft function and therapeutic levels of immunosuppression.¹⁰

Complications during pregnancy in the liver transplant patient

The incidence of preeclampsia, hypertension and renal insufficiency are increased after liver transplantation, particularly if renal insufficiency or uncontrolled hypertension is present at baseline.¹¹ The diagnosis of preeclampsia in the post transplant setting can be more challenging because blood pressure frequently increases after the 20th week of gestation in transplant patients and calcineurin inhibitors can increase uric acid levels, rendering an elevated uric acid level an unreliable marker of preeclampsia.^{10,12} Other markers of preeclampsia such as changes in circulating angiogenic and antiangiogenic proteins may prove helpful in this setting, though they have not been validated in this setting.¹³

Hypertension in pregnant transplant patients requires aggressive therapy.¹⁴ Methyldopa is known to be safe in pregnancy and is considered the preferred agent for the treatment of hypertension in pregnancy.¹⁵ Acceptable second-line agents include combined α and β -adrenergic blockers, calcium-channel blockers, α -adrenergic blockers, and thiazide diuretics. Drugs that interfere with the renin-angiotensin system such as angiotensin-converting-enzyme inhibitors and angiotensin-receptor blockers are teratogenic and therefore contraindicated after the first trimester.

The literature suggests that tacrolimus may offer some advantages over cyclosporine with respect to these pregnancy related complications. The incidence of hypertension and preeclampsia have recently been shown to be decreased in tacrolimus based regimens compared to cyclosporine based regimens, although tacrolimus has been associated with a higher incidence of Diabetes.^{16-18,19}

Immunosuppression

Despite earlier fears that immunosuppressive drugs would be teratogenic or lead to a worse fetal outcome,² none of the published series support this concern.^{3,19} Controversy does remain regarding the ideal immunosuppressive regimen and dose adjustments during pregnancy.

There are extensive data on the use of tacrolimus and cyclosporine. Despite increased reported rates of prematurity, there have not been an increased incidence or specific pattern of fetal malformations.¹⁸ There are less data for other immunosuppressive drugs. In animals, mycophenolate mofetil (MMF) can lead to malformations during organogenesis.²⁰ Some have reported successful preg-

nancies in patients on MMF that did not give birth to children with major malformations.²¹ There is, however, a case report of fetal malformations similar to those seen in animals on MMF, in a patient receiving MMF in the renal transplant literature.²² Thus, the European practice guidelines for renal transplantation recommend that ideally MMF should be changed to an alternative agent 6 weeks prior to conception due to the potential for teratogenicity and its long half-life if pregnancy is anticipated.²³ However, the current experience does not suggest that immunosuppressive regimens containing MMF should be altered if the patient becomes pregnant and is stable on an MMF containing regimen. The data on sirolimus are even more scarce, however a few case reports document the absence of birth defects.^{24,25} More data are needed to determine the safety of sirolimus and MMF in order to establish guidelines for their use. Therefore, all centers are encouraged to report pregnancies with exposures to these agents to the NTPR.²⁴ The unknown risk of teratogenicity of these newer compounds must be balanced against the risk of rejection of the allograft when deciding which drugs to use.

Management of immunosuppression

The NTPR reported that in renal transplant recipients, those that took higher doses of immunosuppressant medication before and during pregnancy had better graft function than those who took lower doses.²⁶ In contrast, Jain et al. reported no renal allograft dysfunction in patients whose dose had not been adjusted during pregnancy despite sub-therapeutic trough levels.²⁷ Nevertheless, the current experience with pregnancy after liver transplantation suggests that sub-therapeutic immunosuppression can precipitate acute cellular rejection with its known complications such as graft failure and infection ;e.g. cytomegalovirus (CMV).⁸ Therefore, most agree that it is important to maintain adequate levels of immunosuppression to avoid the risk of rejection and other complications.

In general, it is best to avoid changing immunosuppression during pregnancy if the patient is stable on a regimen prior to pregnancy. Target trough levels are not different from those in non-pregnant transplant patients. Serum levels should be followed closely and maintained in the therapeutic range (50-150 g/L for cyclosporine and 4-8 for tacrolimus), particularly in the second and third trimester where levels can fluctuate more due to changes in circulating blood volume.^{23,28}

Pregnancy related rejection is a rare event. The risk of graft loss within the first 2 years of pregnancy is approximately 3-9% after liver transplant, compared to a higher incidence in renal transplant recipients; 4-14%.^{14,29} With the exception of cases where immunosuppression was sub-therapeutic, allograft rejection is uncommon, in fact the current evidence illustrates that rejection rates are no different between pregnant and non-pregnant transplant patients.^{23,30}

Timing and management of pregnancy after transplantation

The NTPR and most centers recommend delaying pregnancy until at least 1 year and preferably 2 years after liver transplantation. Several studies have demonstrated increased rates of prematurity, IUGR and low birth weight in fetuses of women becoming pregnant within the first year of liver transplantation.^{4,31,32} In a recent series, outcomes of women who conceived within the first 12 months of transplantation were compared to those who conceived after the first year. Although the rates of live birth, abortion, renal failure, hypertension and preeclampsia were no different between the groups, 33% of patients in the early group developed acute cellular rejection compared to 14% in the late group. The early pregnancy group also had a much higher Cesarean section rate compared to those who conceived > 1 year after transplantation; 50% and 24%, respectively.⁸

Furthermore, during the early post-transplant period higher levels of immunosuppression may be required and this increases the patient's susceptibility to infections such as CMV and herpes simplex virus (HSV). After the first year post-transplant, opportunistic infections are less common. In contrast, the early post transplant period is associated with a higher risk of CMV infection and this risk is augmented after treatment for acute cellular rejection.¹¹ CMV infection is among the most ominous infections leading to catastrophic consequences in both mother and fetus.³³

Conclusion

Although pregnancy outcomes are generally good for both mother and child after liver transplant, morbidity and mortality can be increased either as a result of pregnancy or more typically, related to complications from recurrent liver disease or graft dysfunction. No formal guidelines exist for pregnancy in liver transplant recipients, however a recent consensus conference concluded that pregnancy is typically safe after the first year provided that there was no history of rejection during the preceding year and allograft function is stable.³⁴

Patients wishing to conceive should be encouraged to do so, preferably more than 1-2 years after transplantation if their allograft is functioning well and they are clinically stable. At this time the risk of rejection is generally low, the dose of immunosuppressive medication is at its nadir, viral prophylaxis has been completed, and the patient is generally stable, thus, optimally pregnancy should be delayed until this point. Nevertheless, if the patient does become pregnant within the first 12 months one can still expect a high probability of a good outcome and express cautious optimism to the patient. In conclusion, successful pregnancy after liver transplantation can be expected, however the management of the patient must be meticulous and multidisciplinary in its ap-

proach in order to ensure the best possible outcome for mother and child.

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