

Liver diseases in pregnancy: Liver transplantation in pregnancy

Ghassan M Hammoud, Ashraf A Almashhrawi, Khulood T Ahmed, Rubayat Rahman, Jamal A Ibdah

Ghassan M Hammoud, Ashraf A Almashhrawi, Khulood T Ahmed, Rubayat Rahman, Jamal A Ibdah, Division of Gastroenterology and Hepatology, University of Missouri, Columbia, MO 65212, United States

Author contributions: Hammoud GM wrote and revised the manuscript; Almashhrawi AA, Ahmed KT and Rahman R were involved in reviewing the literature and collecting data; Ibdah JA provided the overall conceptual design and finalized the manuscript. Correspondence to: Jamal A Ibdah, MD, PhD, Professor, Director, Division of Gastroenterology and Hepatology, University of Missouri, 319 Jesse Hall, Columbia, MO 65212, United States. ibdahj@health.missouri.edu
Telephone: +1-573-8827349 Fax: +1-573-8844595
Received: June 17, 2013 Revised: July 30, 2013
Accepted: August 16, 2013
Published online: November 21, 2013

Abstract

Pregnancy in patients with advanced liver disease is uncommon as most women with decompensated cirrhosis are infertile and have high rate of anovulation. However, if gestation ensued; it is very challenging and carries high risks for both the mother and the baby such as higher rates of spontaneous abortion, prematurity, pulmonary hypertension, splenic artery aneurysm rupture, postpartum hemorrhage, and a potential for life-threatening variceal hemorrhage and hepatic decompensation. In contrary, with orthotopic liver transplantation, menstruation resumes and most women of childbearing age are able to conceive, give birth and lead a better quality of life. Women with orthotopic liver transplantation seeking pregnancy should be managed carefully by a team consultation with transplant hepatologist, maternal-fetal medicine specialist and other specialists. Pregnant liver transplant recipients need to stay on immunosuppression medication to prevent allograft rejection. Furthermore, these medications need to be monitored carefully and continued throughout pregnancy to avoid potential adverse effects to mother and baby. Thus delaying pregnancy 1 to 2 years after

transplantation minimizes fetal exposure to high doses of immunosuppressants. Pregnant female liver transplant patients have a high rate of cesarean delivery likely due to the high rate of prematurity in this population. Recent reports suggest that with close monitoring and multidisciplinary team approach, most female liver transplant recipient of childbearing age will lead a successful pregnancy.

© 2013 Baishideng Publishing Group Co., Limited. All rights reserved.

Key words: Liver; Pregnancy; Liver transplantation; Hemolysis elevated liver low platelets; Acute fatty liver; Cirrhosis

Core tip: This review provides an up-to-date summary of literature in the field of liver transplantation and pregnancy. It outlines the outcomes of pregnancy prior to and after orthotopic liver transplantation. Furthermore, it provides input on preconception counseling for mothers contemplating pregnancy after liver transplantation, risks of immunosuppression, and safety of breastfeeding.

Hammoud GM, Almashhrawi AA, Ahmed KT, Rahman R, Ibdah JA. Liver diseases in pregnancy: Liver transplantation in pregnancy. *World J Gastroenterol* 2013; 19(43): 7647-7651 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v19/i43/7647.htm> DOI: <http://dx.doi.org/10.3748/wjg.v19.i43.7647>

INTRODUCTION

Liver transplantation is considered to be the treatment of choice for patients with advanced liver disease. Since the first pregnancy in a transplant recipient in 1958, pregnancy in recipients of solid organ transplants has become increasingly common. In the setting of decompensated

cirrhosis, pregnancy is very uncommon as most women are infertile and have anovulation and secondary amenorrhea. However, once liver transplantation is performed, liver transplant recipients possess an improved quality of life, their hormonal imbalance return to a normal state, ovulation resumes and pregnancy may ensue if contemplated. The first successful pregnancy in a liver graft recipient was reported in 1978^[1]. Given the improving success of liver transplantation over the past two decades and decreasing levels of immunosuppression, most solid organ transplant recipients lead happy and healthy lives with an average 1-year survival rate of greater than 85% for most indications.

PATHOGENESIS

Women with decompensated liver disease commonly have menstrual dysfunction. In fact, menstrual abnormalities may be the first signs of chronic liver disease in females with chronic liver disease. In cirrhotic state, hypothalamic-pituitary dysfunction is associated with an inadequate response to the gonadotropin-releasing hormone agonists and clomiphene citrates as well as diminished gonadotrophin release relative to the reduced levels of circulating sex steroids^[2]. Furthermore, serum levels of estradiol and testosterone are increased in patients with portosystemic shunts. Thus pregnancy in decompensated cirrhosis is very uncommon. Obstetrical syndromes associated with transplantation may depend on several factors such as defective deep placentation, underlying maternal diseases, uterine vascular bed and effect of immunosuppressive therapy on uteroplacental arteries^[3]. Reports from the the National Transplantation Pregnancy Registry (NTPR) revealed that immunosuppressive medication is associated with an increased risk of miscarriage, prematurity, intrauterine growth retardation, and low birth weight^[4].

MATERNAL AND FETAL OUTCOMES IN PREGNANT FEMALE PATIENTS WITH ADVANCED LIVER DISEASE

Pregnancy is associated with increase in portal pressure. During pregnancy, a hypervolemic state develops leading to an increase in portal flow and elevation of portal venous pressure transmitted to the collateral veins with increased risk of esophageal variceal bleeding^[5,6]. The outcome of pregnancy in 339 patients with cirrhosis was reported in a large population-based study from 1993 to 2005^[7]. Maternal and fetal mortality were much higher than the general population (1.8% *vs* 0%, $P < 0.0001$; 5.2% *vs* 2.1%, $P < 0.0001$) respectively. The rate of hepatic decompensation occurred in 15% and patients with cirrhosis were more likely to deliver by cesarean delivery (42% *vs* 28%; adjusted OR = 1.41; 95%CI: 1.06-1.88). Similarly, the spontaneous abortion rate in cirrhotic patients is approximately 15%-20%.

MATERNAL AND FETAL OUTCOMES IN PREGNANT FEMALE LIVER TRANSPLANT RECIPIENTS

Most outcome data on pregnancy during and after liver transplantation are obtained from the NTPR. The NTPR was established in 1991 at Thomas Jefferson University in Philadelphia, Pennsylvania, to study the outcomes of pregnancies in transplant recipients in North America, including female transplant recipients and those fathered by male transplant recipients. Since then many other reports and case series have been reported and published. A retrospective study from a single institution evaluated a total of 115 gestations in 37 women with liver transplant (LT) and in 34 women with kidney transplant. The authors found 81 (70%) of all gestations were successful, 15 (13%) were terminated, and there were 19 (17%) spontaneous abortions and 2 (2%) intrauterine deaths^[8]. Deshpande *et al*^[9] reported in a systematic review and meta-analysis outcome of 450 pregnancies in 306 LT recipients in comparisons with the general United States population as well as kidney transplant recipients. The post-LT live birth rate was higher than the live birth rate for the US general population (76.9% *vs* 66.7%, 95%CI: 72.7%-80.7%). The post-LT miscarriage rate was lower than the miscarriage rate for the general population (15.6% *vs* 17.1%, 95%CI: 12.3%-19.2%). Moreover, these rates were similar to the post-kidney transplant rates. The rates of pre-eclampsia, cesarean section delivery and preterm delivery were higher than the rates for the US general population (21.9% *vs* 3.8%, 95%CI: 17.7%-26.4%; 44.6% *vs* 31.9%, 95%CI: 39.2%-50.1%; and 39.4% *vs* 12.5%, 95%CI: 33.1%-46.0%) respectively. Moreover, these rates were lower than those for post-kidney transplant recipients. The overall mean birth weight for newborns of LT recipients was less than the birth weight for the United States general population (2866 g *vs* 3298 g). More notably, the authors found that the mean gestational age and mean birth weight seems significantly greater for liver transplant versus kidney transplant recipients and the risk of hypertension during pregnancy seems also lower for liver transplant than kidney transplant recipients^[9]. In another recently published study by Alvaro *et al*^[10] from a single center in Spain, the authors analyzed the impact of pregnancy among 1341 liver transplant recipients from April 1986 to April 2011. Thirty pregnancies commenced among 18 liver transplant recipients during the follow-up. Sixteen patients (88%) became pregnant beyond a year after orthotopic liver transplantation. The post-LT live birth was 66.6% and the post-LT abortions were 26.6%. There were no maternal deaths encountered during pregnancy or the postpartum period. However, fetal deaths were observed in 6% of LT recipients. The most common maternal complications during pregnancy were preeclampsia (15%), viral reactivation (15%), acute rejection episodes (10%), infections (10%), and high blood pressure (5%)^[10]. Table 1 shows a summary of maternal and fetal outcomes in female liver transplant recipients from selected reports and studies^[11].

Table 1 Summary of important fetal and maternal outcomes in liver transplant recipients from selected publications

Author, reference, number of pregnancies	Live birth rate (%)	Preterm (%)	Graft dysfunction (%)	Cesarean section rate (%)	Spontaneous abortions (%)	Low birth weight < 2500 g (%)	Maternal/neonatal deaths (%)
Nagy <i>et al</i> ^[12] , n = 38	63	29	17	46	NA	17	17/0
Jain <i>et al</i> ^[13] , n = 49	100	4	25	47	0	9	10/6
Armenti <i>et al</i> ^[14] , n = 205	73	35	7	35	19	34	/0
Christopher <i>et al</i> ^[15] , n = 71	71	NA	17	40	19	20	4/0
Dei Malatesta <i>et al</i> ^[16] , n = 285	78	31	10	43	NA	23	/4
Sibanda <i>et al</i> ^[17] , n = 16	69	50	NA	62	13	57	NA
Coffin <i>et al</i> ^[18] , n = 206	70	27	5	38	5	NA	0/6
Jabiry-Zieniewicz <i>et al</i> ^[19] , n = 39	100	31	8	80	0	20	/0
Dashpande <i>et al</i> ^[9] , n = 450	76.9	39.4	NA	44.6	6.2 (including intrauterine fetal death)	NA	NA
Alvaro <i>et al</i> ^[10] , n = 30	66.6	NA	10	42	26.6	NA	0/6

NA: Not available.

Table 2 Food and drug administration pregnancy categories of common immunosuppressive therapy

Medicine	Pregnancy category
Corticosteroids	B
Azathioprine	D
Cyclosporin	C
Mycophenolate mofetil	D
Tacrolimus	C
Sirolimus	C

PRECONCEPTION COUNSELING

Pregnancy after liver transplant should be considered as a high-risk pregnancy and should be monitored closely by a team of a transplant hepatologist and experts in obstetrics and fetal medicine. Female liver transplant recipients who are planning of becoming pregnant should be counseled on optimal timing of pregnancy, mode of delivery and risks associated with immunosuppressive therapy. Furthermore, they should also be counseled on methods of contraception if pregnancy is not contemplated. Immunosuppressive agents are at their nadir one-year post liver transplantation and thus risk of allograft rejection is low. Furthermore, renal and liver functions tend to be stabilized during that period and thus it is ideal to delay pregnancy till patient is on a maintenance immunosuppression 1 to 2 years after transplantation to minimize fetal exposure to high doses of immunosuppressants^[14,20].

As per mode of delivery, vaginal delivery appears to be safe. However, high rates of cesarean section have been reported in female liver transplant patients (45.8%^[12], 71%^[21], 35%^[22], 38%^[18] and 44.6%^[9]) signifying the high rates of prematurity in this population. It is not known whether a particular immunosuppressive therapy is associated with increased rate of cesarean section. If pregnancy is not contemplated in young females of childbearing age, contraceptive method is advised particularly in the first few months post liver transplantation. Barrier methods possess low risk of systemic side effects. Intrauterine devices are generally discouraged due to their

potential infection complications. Furthermore, oral contraceptives did not appear to impair liver function or glucose metabolism after its introduction within 6 mo to 7 years post transplantation^[23].

IMMUNOSUPPRESSION IN LIVER TRANSPLANT PREGNANT RECIPIENTS

There is no consensus on the optimal maintenance regimen for transplant recipients. The use of immunosuppressive therapy after liver transplantation is unavoidable. Therefore, women planning to conceive after transplantation should be counseled about the risks such therapy may pose on them and their fetuses. All immunosuppressive medication cross the placenta and enter fetal circulation and could potentially have deleterious effects in utero. Despite the fact that immunosuppressive agents such as Azathioprine, Cyclosporine, and Mycophenolic acid, were teratogenic in animals, the risk of birth defects was not statistically different between those who received immunosuppressive medications and those who did not. Birth defects have been reported with Calcineurin inhibitors^[8,12,19]. Renal dysfunction and rates of pre-eclampsia appears higher with cyclosporine therapy^[12,24]. No matter what immunosuppressive therapy is chosen based on maternal allograft function and laboratory assay, patients treated with either calcineurin inhibitors cyclosporine or tacrolimus should have serial blood tests in pregnancy to follow medication levels and to assess hepatic and renal function while avoiding unnecessary toxicity. Table 2 shows the food and drug administration classification of risk of medication and their categories in pregnancy^[25].

BREASTFEEDING IN FEMALE LIVER TRANSPLANT RECIPIENTS ON IMMUNOSUPPRESSIVE THERAPY

The American academy of pediatrics advises that breast-

feeding mothers can use prednisone and other glucocorticoids safely. Infant exposure to tacrolimus in milk is very low and that maternal tacrolimus therapy may be compatible with breastfeeding. Data collected from the NTPR indicated no adverse outcomes in infants who were breastfed during maternal cyclosporine use. There is insufficient evidence in the literature to suggest that women taking azathioprine should refrain from breastfeeding. Nevertheless, mothers may be discouraged to breast feed in the first few months post transplantation where immunosuppressive therapy is at high serum level.

CONCLUSION

Pregnancy after liver transplantation, although considered a high risk pregnancy, has an acceptable outcome for both mother and baby. With the return of fertility following transplantation, accurate family planning advice is essential. To date there is no evidence of specific structural malformations among children born to female liver transplant recipients, but there appears to be increased risk of prematurity and low birth weight after solid organ transplantation. Multidisciplinary team approach is of utmost importance to ensure smooth pregnancy. The NTPR data and others have revolutionized our understanding of the outcomes of pregnancy in this high risk population. We encourage physicians in the field to continue to report their outcome to the transplant registry.

REFERENCES

- 1 **Walcott WO**, Derick DE, Jolley JJ, Snyder DL. Successful pregnancy in a liver transplant patient. *Am J Obstet Gynecol* 1978; **132**: 340-341 [PMID: 360844]
- 2 **Van Thiel DH**, Lester R. The effect of chronic alcohol abuse on sexual function. *Clin Endocrinol Metab* 1979; **8**: 499-510 [PMID: 389488 DOI: 10.1016/S0300-595X(79)80028-6]
- 3 **Brosens I**, Pijnenborg R, Benagiano G. Risk of obstetrical complications in organ transplant recipient pregnancies. *Transplantation* 2013; **96**: 227-233 [PMID: 23466636 DOI: 10.1097/TP.0b013e318289216e]
- 4 **Coscia LA**, Constantinescu S, Moritz MJ, Frank AM, Ramirez CB, Maley WR, Doria C, McGrory CH, Armenti VT. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2010; **65**: 85 [PMID: 21698831]
- 5 **d'Altoche L**, Perarnau JM, Perrotin F, Bacq Y. Portal hypertension and pregnancy. *Gastroenterol Clin Biol* 2008; **32**: 541-546 [PMID: 18472375 DOI: 10.1016/j.gcb.2008.02.028]
- 6 **Britton RC**. Pregnancy and esophageal varices. *Am J Surg* 1982; **143**: 421-425 [PMID: 6978619 DOI: 10.1016/0002-9610(82)90190-8]
- 7 **Shaheen AA**, Myers RP. The outcomes of pregnancy in patients with cirrhosis: a population-based study. *Liver Int* 2010; **30**: 275-283 [PMID: 19874491 DOI: 10.1111/j.1478-3231.2009.02153.x]
- 8 **Blume C**, Sensoy A, Gross MM, Guenter HH, Haller H, Manns MP, Schwarz A, Lehner F, Klempnauer J, Pischke S, Strassburg CP. A comparison of the outcome of pregnancies after liver and kidney transplantation. *Transplantation* 2013; **95**: 222-227 [PMID: 23222883 DOI: 10.1097/TP.0b013e318277e318]
- 9 **Deshpande NA**, James NT, Kucirka LM, Boyarsky BJ, Garonzik-Wang JM, Cameron AM, Singer AL, Dagher NN, Segev DL. Pregnancy outcomes of liver transplant recipients: a systematic review and meta-analysis. *Liver Transpl* 2012; **18**: 621-629 [PMID: 22344967 DOI: 10.1002/lt.23416]
- 10 **Alvaro E**, Jimenez LC, Palomo I, Manrique A, Alegre C, Garcia M, Justo I, Abradelo M, Calvo J, Garcia-Sesma A, Cambra F, Loinaz C, Moreno E. Pregnancy and orthotopic liver transplantation. *Transplant Proc* 2013; **45**: 1966-1968 [PMID: 23769084 DOI: 10.1016/j.transproceed.2013.01.013]
- 11 **Hammoud GM**, Choudhary A, Ibdah JA. Pregnancy and liver transplantation. In: Ibdah JA: Maternal liver disease. Austin (TX): Landes Bioscience, 2012: 119-136
- 12 **Nagy S**, Bush MC, Berkowitz R, Fishbein TM, Gomez-Lobo V. Pregnancy outcome in liver transplant recipients. *Obstet Gynecol* 2003; **102**: 121-128 [PMID: 12850617 DOI: 10.1016/S0029-7844(03)00369-7]
- 13 **Jain AB**, Reyes J, Marcos A, Mazariegos G, Eghtesad B, Fontes PA, Cacciarelli TV, Marsh JW, de Vera ME, Rafail A, Starzl TE, Fung JJ. Pregnancy after liver transplantation with tacrolimus immunosuppression: a single center's experience update at 13 years. *Transplantation* 2003; **76**: 827-832 [PMID: 14501862 DOI: 10.1097/01.TP.0000084823.89528.89]
- 14 **Armenti VT**, Daller JA, Constantinescu S, Silva P, Radomski JS, Moritz MJ, Gaughan WJ, McGrory CH, Coscia LA. Report from the National Transplantation Pregnancy Registry: outcomes of pregnancy after transplantation. *Clin Transpl* 2006; **57**: 70 [PMID: 18368705]
- 15 **Christopher V**, Al-Chalabi T, Richardson PD, Muiesan P, Rela M, Heaton ND, O'Grady JG, Heneghan MA. Pregnancy outcome after liver transplantation: a single-center experience of 71 pregnancies in 45 recipients. *Liver Transpl* 2006; **12**: 1138-1143 [PMID: 16799943 DOI: 10.1002/lt.20810]
- 16 **Dei Malatesta MF**, Rossi M, Rocca B, Iappelli M, Giorno MP, Berloco P, Cortesini R. Pregnancy after liver transplantation: report of 8 new cases and review of the literature. *Transpl Immunol* 2006; **15**: 297-302 [PMID: 16635752 DOI: 10.1016/j.trim.2006.01.001]
- 17 **Sibanda N**, Briggs JD, Davison JM, Johnson RJ, Rudge CJ. Pregnancy after organ transplantation: a report from the UK Transplant pregnancy registry. *Transplantation* 2007; **83**: 1301-1307 [PMID: 17519778 DOI: 10.1097/01.tp.0000263357.44975.d0]
- 18 **Coffin CS**, Shaheen AA, Burak KW, Myers RP. Pregnancy outcomes among liver transplant recipients in the United States: a nationwide case-control analysis. *Liver Transpl* 2010; **16**: 56-63 [PMID: 20035524 DOI: 10.1002/lt.21906]
- 19 **Jabiry-Zieniewicz Z**, Szpotanska-Sikorska M, Pietrzak B, Kociszewska-Najman B, Foroniewicz B, Mucha K, Zieniewicz K, Krawczyk M, Wielgos M. Pregnancy outcomes among female recipients after liver transplantation: further experience. *Transplant Proc* 2011; **43**: 3043-3047 [PMID: 21996220 DOI: 10.1016/j.transproceed.2011.08.070]
- 20 **Mastrobattista JM**, Katz AR. Pregnancy after organ transplant. *Obstet Gynecol Clin North Am* 2004; **31**: 415-428, vii [PMID: 15200970 DOI: 10.1016/j.ogc.2004.03.005]
- 21 **Jabiry-Zieniewicz Z**, Bobrowska K, Pietrzak B, Kaminski P, Wielgos M, Durlak M, Zieniewicz K. Mode of delivery in women after liver transplantation. *Transplant Proc* 2007; **39**: 2796-2799 [PMID: 18021990 DOI: 10.1016/j.transproceed.2007.09.011]
- 22 **Armenti VT**, Constantinescu S, Moritz MJ, Davison JM. Pregnancy after transplantation. *Transplant Rev (Orlando)* 2008; **22**: 223-240 [PMID: 18693108 DOI: 10.1016/j.trre.2008.05.001]
- 23 **Jabiry-Zieniewicz Z**, Bobrowska K, Kaminski P, Wielgos M, Zieniewicz K, Krawczyk M. Low-dose hormonal contraception after liver transplantation. *Transplant Proc* 2007; **39**: 1530-1532 [PMID: 17580181 DOI: 10.1016/j.transproceed.2007.02.063]

- 24 **Coscia LA**, Constantinescu S, Moritz MJ, Frank A, Ramirez CB, Maley WL, Doria C, McGrory CH, Armenti VT. Report from the National Transplantation Pregnancy Registry (NTPR): outcomes of pregnancy after transplantation. *Clin Transpl* 2009; 103-122 [PMID: 20524279]
- 25 **Hammoud GM**, Ibdah JA. The liver in pregnancy. In: Boyer, TD, Manns MP, Sanyal AJ. Zakim and Boyer's Hepatology: A Textbook of Liver Disease. Philadelphia (PA): Elsevier Saunders, 2012: 919-940 [DOI: 10.1016/B978-1-4377-0881-3.00052-8]

P- Reviewers: Muratori L, Yamagiwa S **S- Editor:** Wen LL
L- Editor: A **E- Editor:** Wang CH





百世登

Baishideng®

Published by **Baishideng Publishing Group Co., Limited**

Flat C, 23/F., Lucky Plaza,

315-321 Lockhart Road, Wan Chai, Hong Kong, China

Fax: +852-65557188

Telephone: +852-31779906

E-mail: bpgoffice@wjgnet.com

<http://www.wjgnet.com>



ISSN 1007-9327



9 771007 932045