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Research Article

Keywords: Liver transplantation, Aspirin, Pre-eclampsia, Obstetric outcome

Posted Date: October 20th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-940083/v1>

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Perinatal Outcomes After Liver Transplantation – Is There a Role for Aspirin Treatment?

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Funding: This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Disclosure: The authors report no conflict of interest.

Abstract

Purpose: To describe perinatal outcomes in liver transplanted women and evaluate the effect of low-dose aspirin treatment in these women.

Methods: An observational retrospective study examining perinatal outcomes among 10 liver transplant recipients, between 2016-2020 at a single university-affiliated tertiary medical center in Israel. Demographic, obstetric and clinical data were obtained from electronic health records. Low-dose aspirin use in these women during pregnancy began in 2018 and was evaluated with regards to its effect on the risk of developing preeclampsia and hypertensive disease.

Results: Overall, 13 deliveries in 10 pregnant liver transplant recipients were identified. Primary liver disease was Wilson's in 7 pregnancies (53%), acute liver failure in 3 (23%), and a single woman with each of the following: Viral hepatitis A, Hyperoxaluria type 1 and primary sclerosing cholangitis. Median age was 23 years at transplant and 30 at conception. All recipients received tacrolimus, steroids were administered to 9 (69%), and low-dose aspirin (100mg daily) administered in 5 (38%) pregnancies. Regarding maternal outcomes, 2 women (16%) developed preeclampsia, 1 (8%) developed gestational hypertension, and 3 (24%) had postpartum infection. Of women receiving low-dose aspirin, none developed hypertensive disease or suffered excessive bleeding. Median gestational age at delivery was 37 weeks (31–39 weeks), with 6 preterm births (31-36) and a median birthweight of 3072g (1450–4100g).

Conclusions: Liver-transplanted pregnant women comprise a unique and complex patient population. Based on our single-center experience and due to its potential benefit, low-dose aspirin may be a possible preventive measure for preeclampsia. Further prospective, large studies are needed to delineate specific complications in this patient population and to evaluate treatment options, in order to improve maternal and neonatal outcomes.

Key words: Liver transplantation; Aspirin; Pre-eclampsia; Obstetric outcome.

Introduction

During the past few years, an increase in the number of pregnancies achieved following liver transplantation has been observed. These pregnancies are at increased risk for obstetric and neonatal complications (1). Maternal complications include hypertensive disorders of pregnancy, gestational diabetes, post-partum haemorrhage, blood product transfusions, graft rejection, and a higher rate of cesarean deliveries (2). Neonatal complications include preterm birth, intrauterine growth restriction and fetal distress, with no known increase in the incidence of congenital anomalies (1,3).

Since the first case of a pregnancy following a liver transplant over 40 years ago was described (8), major progress has been made in the fields of transplantation and obstetrics. This may be attributed to new surgical techniques, better anesthetic care and improved immunologic and pharmacological treatments, and yet, there is no consensus regarding optimal treatment and surveillance during pregnancy for this unique population. The obstetric field has also seen great progress in the prevention of pre-eclampsia in high-risk patients, including kidney transplant recipients, through early treatment with low-dose aspirin between 12-16 weeks of gestation (4-6).

Our tertiary university-affiliated medical center is the largest solid organ transplant center in Israel, centralizing the care of more than 300 transplant recipients each year, with performance of 70 liver transplants annually. Obstetric follow-up is performed by a multidisciplinary team comprised of a Maternal-Fetal-Medicine specialist, a hepatologist and a transplant surgeon. In our study, the first case series from Israel, we present our single-center experience managing pregnancies following liver transplantation during the past 4 years, and present maternal, fetal, neonatal and allograft outcomes. We also examined the effect of low-dose aspirin use on hypertensive disease incidence since the implementation of such treatment in pregnant liver-transplant recipients at our institution beginning 2018.

Materials and Methods

We performed an observational study examining 13 deliveries among 10 liver-transplant recipients, delivering between 2016 and 2020 at our medical center. Complete data for retrospective analysis were obtained from the Maternal-Fetal Medicine and Hepatology clinic hospital records. The following maternal and obstetric parameters before and during pregnancy were assessed: primary liver disease, age at liver transplantation, age at conception, time interval between transplantation and delivery, immunosuppressive regimen received, pre-pregnancy co-morbidities (diabetes mellitus and hypertension), gravidity, parity and aspirin use.

Obstetric complications were evaluated and included: Mode of delivery, preterm birth (defined as delivery before 37 weeks of gestation), gestational hypertension, pre-eclampsia, gestational diabetes mellitus, cholestasis, anemia, urinary tract infections and other infections, graft rejection, postpartum fever, postpartum hemorrhage, and blood transfusion.

Neonatal outcomes were assessed and included: gestational age at delivery, birthweight, Apgar score<7, PH<7.15, neonatal death, jaundice requiring phototherapy, NICU admission, respiratory composite (respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN) or need for mechanical ventilation), and sepsis.

Results

We identified 13 deliveries in 10 pregnant liver transplant recipients. The indications for liver transplantation included: acute liver failure (3 recipients), Wilson's disease (4 recipients), liver failure caused by Hepatitis A virus (1 recipient), primary sclerosing cholangitis (1 recipient) and heperxaluria type 1 (1 recipient) (Table 1). Median maternal age at liver transplant was 23 (range 4-33), median age at conception was 30 (range 25-35), and median time between organ transplantation and delivery was 4.5 years (range 0-26 years). 6 women were nulliparous, 2 had pre-gestational diabetes and 1 suffered from depression (Table 2).

All recipients were treated with tacrolimus in all pregnancies, and steroids were administered to 9 recipients (69%). Low-dose aspirin (100 mg daily) was administered at our institution to pregnant liver-transplant recipients beginning 2018 and was given in 5 (38%) of the pregnancies described here (Table 2).

Obstetric and neonatal outcomes

Regarding maternal outcomes (Table 3), 2 women (16%) suffered from pre-eclampsia, 4 (32%) from diabetes of any kind (pre-gestational diabetes mellitus or gestational diabetes), and 6 (46%) delivered by cesarean section for various indications (3 due to abnormal lie, 1 due to non-reassuring fetal heart rate, 1 due to liver transplantation during pregnancy and one due to previous CS). There were no cases of maternal death. Elevated liver enzymes were observed in 3 patients and resolved after delivery, with no cases of acute rejection identified.

Cholestasis occurred in 4 cases (32%), thrombocytopenia in 4 (32%) and infection (UTI, bacteremia, sepsis, endometritis) in 3 (24%). Post-partum hemorrhage occurred in 2 cases (16%), with one woman requiring blood products transfusion. There were no cases of placental abruption or admissions to the ICU during or after pregnancy.

Regarding neonatal outcomes (Table 4), median gestational age at delivery was 37 weeks (range, 31–39), with 6 (48%) women experiencing preterm birth (range 31-36 weeks), with a median birthweight of 3072 g (range, 1450–4100 g). 5-min-apgar scores were all >8, PH was >7.15, and 2 neonates (16%) were admitted to the NICU. No cases of sepsis, asphyxia or intrauterine fetal death were observed.

None of the five women receiving low-dose aspirin beginning 12 weeks of gestation until 35 weeks, developed hypertensive disease or preeclampsia, while 2 of the 8 women not receiving aspirin (25%) developed mild preeclampsia, and one (12.5%) developed gestational hypertension. (Table 5). None of the aspirin treated patients suffered excessive bleeding during pregnancy.

Two unusual pregnancies:

Of note, one woman in our cohort underwent a liver transplantation in her 29th week of gestation because of acute liver failure attributed to propylthiouracil (PTU) use. She delivered by cesarean section at 31 weeks due to elevated liver enzymes and suspected intra-uterine growth restriction.

Another patient, a liver transplant recipient subsequent to Wilson's disease with pre-gestational diabetes and depression, presented at 32 weeks of gestation with sepsis and fever, and was delivered by cesarean section due to non-reassuring fetal heart rate and an abnormal biophysical profile.

Discussion

In this summary of our single-center institutional experience, we demonstrated that pregnancy after liver transplantation holds good results for the mother, neonate and allograft. No maternal or fetal deaths occurred and there was no acute allograft rejection.

Despite the limited number of cases described in the literature, our results match larger case series outcomes, such as that depicted by Kubo et al (3), with the incidence of pre-term birth being 48%, cesarean section rate 46%, pre-eclampsia 16%, and low birth weight 24%. The immunosuppressive medication regimen in our cohort is in accordance with the treatment recommended in such cases in previous publications, with all patients receiving tacrolimus and most receiving steroids (1,2,8).

Low-dose aspirin treatment for pregnant liver transplant recipients, with the aim of reducing the risk for preterm preeclampsia, began in 2018 at our institution after the results of the ASPRE study (5), and owing to the subsequent favourable results and effects we saw at our institution with such treatment in pregnant kidney transplant recipients (4,5,7).

The incidence of preeclampsia in pregnant liver transplant recipients in our study was 16.6%. No case of pre-eclampsia was seen in the aspirin-treated women, compared to a rate of 28% in the no-aspirin group (Table 5). Whilst previous studies have reported rates ranging between 21%-26% for pre-eclampsia in liver-transplanted pregnant women, more recent studies reported a lower incidence for pre-eclampsia ranging between 7%-12%. (1,3,6).

Preeclampsia is a form of hypertension unique to human pregnancy, and is considered a complex, multisystem heterogenous condition, that may originate from multiple causes. It is believed to evolve from changes in placental development that result in placental ischemia, thereby producing inflammation and oxidative stress. This stress may be a result of pathological placental development and placental ischemia, an overactive inflammatory response to normal placentation or due to a pre-existing inflammatory condition. Organ transplant recipients hold at least two of these risk factors – a higher risk for pathological placental development and a pre-existing inflammatory state (4).

The use of drugs with anti-inflammatory, anti-angiogenic, and antiplatelet properties, such as low-dose aspirin, holds a preventive effect on the risk for preeclampsia development. A recent

review by Rahim et al (6) linked this preventive effect to increased management of immunosuppression and risk factors associated with pre-eclampsia. Rahim's team also recommended daily aspirin treatment starting before 16 weeks of gestation in order to improve placental hemodynamics and reduce the risk for preterm pre-eclampsia in women at risk.

Post-partum infection in liver transplant recipients is another pregnancy-related complication obstetricians need to be aware of. In our study, 2 women were diagnosed with sepsis due to urinary tract infection, and another patient was diagnosed with endometritis. This is higher than the rate in the general obstetric population, where 3% suffer from UTI post-partum and 2% from endometritis (9), most probably secondary to immunosuppression. Expedient diagnosis and treatment can be lifesaving for these immunosuppressed women.

Our study has several limitations. First, the small number of cases included precludes reaching statistically significant conclusions regarding outcomes and management in this patient population, although due to the rarity of the entity of pregnant liver transplanted women, reaching a proper sample size for adequate power is challenging, especially at a single-center. Future studies combining multi-center experiences may shed light on this important and complex group of pregnant women. Secondly, another inherent limitation lies in the observational and retrospective nature of our study, requiring future validation in prospective studies, especially with regards to the use of low-dose aspirin in this patient population.

Conclusion

Liver transplanted pregnant women comprise a unique and complex patient group, requiring close surveillance by a multidisciplinary team. Relying on our single-center experience, we recommend considering low-dose aspirin treatment starting 12-16 weeks of pregnancy in liver transplant recipients, with the aim of preventing pre-eclampsia and its complications. There is need for further prospective studies regarding low-dose aspirin use in liver transplant recipients during pregnancy, in order to reduce complications and improve maternal and neonatal outcomes.

Declarations:

All methods were carried out in accordance with relevant guidelines and regulations.

Informed consent: The study was approved by Rabin Medical Center's local Institutional Review Board (Study code 0339-19-RMC). All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. Informed consent was waived by Rabin Medical Center's local Institutional Review Board who approved the study, due to the study's retrospective design.

Consent to publication: Not applicable.

Data availability: All data generated or analysed during this study are included in this published article.

Disclosure of potential conflicts of interest: The authors have no relevant financial or non-financial interests to disclose.

Funding: None.

Authors' contributions:

- Gil Zeevi, MD – Substantial contributions to conception and design; acquisition of data; analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- Marius Braun, MD – drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- [Eviatar Nesher](#), MD – drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- Arnon Wiznitzer, MD – drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- Eran Hadar, MD – drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- Alyssa Hochberg, MD MPH – Substantial contributions to conception and design; analysis and interpretation of data; drafting the article and revising it critically for important intellectual content; final approval of the version to be published.
- **Acknowledgements:** Not applicable.

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Tables

Table 1 - Primary Liver Diseases		
Primary Liver Disease	Number of Women n=10	Number of Pregnancies n=13
Wilson	4 (40%)	7 (53%)
Acute liver failure NOS ^a	3 (30%)	3 (23%)
HAV ^b	1 (10%)	1 (8%)
Hyperoxaluria type 1	1 (10%)	1 (8%)
PSC ^c	1(110%)	1 (8%)

Continuous variables are presented as median (range) and categorical numbers as n (%).

^aNOS = Not otherwise specified

^bHAV = Hepatitis A virus

^cPSC = Primary sclerosing cholangitis

Table 2 - Characteristics of the 13 Pregnancies

	Values
Age at liver transplant (years)	23 (4-33)
Age at birth (years)	30 (25-35)
Transplant-to-delivery interval	
Less than 2 years	2 (1 during pregnancy)
More than 2 years	11
Gravidity	1-5
Parity	
0	5 (38.5)
1	5 (38.5)
2	3 (23)
DM ^a	2 (17)
HTN ^b	0 (0)
BMI^c	
Normal (18-25)	10 (77)
>25	3 (23)
>30	0 ^d (0)
Immunosuppressive Medications	
Prograf	13 (100)
Prednisone	9 (69%)
Aspirin	5 (38%)

Continuous variables are presented as median (range) and categorical numbers as n (%).

^aDM = Diabetes Mellitus

^bHTN = Hypertension

^cBMI = Body mass index (kg/m²)

^d Number of cases out of the 10 pregnant cases

<u>Table 3 - Obstetric outcomes</u>		
n=13 (%)		
Mode of delivery		
Normal vaginal delivery	6 (46)	
Vacuum extraction delivery	1 (8)	
Cesarean section	6 (46)	
Preterm birth (<37weeks)	6 (46)	
Gestational hypertension	1 (8)	
Preeclampsia	2 (16)	
Gestational diabetes	2 (16)	
Thrombocytopenia	4 (32)	
Cholestasis	3 (24)	
Elevated liver enzymes	3 (24)	
Postpartum infection	3 (24)	
Postpartum hemorrhage	2 (16)	
Postpartum infection	3 (24)	
Severe anemia	0	
Blood transfusion	1 (8)	
Graft rejection	0	

Continuous variables are presented as median (range) and categorical numbers as n (%).

Table 4 - Neonatal outcomes

5-minute Apgar score		
Less than 7	0	
More than 7	13	
Gestational age at delivery		
Less than 32 weeks	1 (8%)	
32-37 weeks	5 (38%)	
More than 37 weeks	7 (54%)	
Birthweight		
1000-1500 grams	1 (8%)	
1500-2500 grams	2 (16%)	
More 2500 grams	10 (72%)	
Congenital anomalies	0	
Neonatal intensive care unit (NICU) admission	2 (18%)	
PH<7.15	0	
Neonatal death	0	
Jaundice requiring phototherapy	1 (8%)	
Respiratory composite ^a	1 (8%)	
Blood transfusion	1 (8%)	
sepsis	0	

Continuous variables are presented as median (range) and categorical numbers as n (%).

^a Respiratory composite = respiratory distress syndrome (RDS), transient tachypnea of the newborn (TTN) or need for mechanical ventilation.

Table 5 – Aspirin treatment

	Number of pregnancies	Pre-eclampsia	%
No aspirin	8	2	25%
Aspirin	5	0	0