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Clinical Course and Maternal Outcomes Following Pregnancy in Liver Transplant Recipients

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Abstract

Aims

Studies have shown largely favourable outcomes for pregnancy following liver transplantation. However, concern remains regarding maternal and foetal complications. We sought to evaluate maternal and foetal outcomes of pregnancy, post liver transplant in the Irish National Liver Transplant Unit.

Methods

We conducted a retrospective study of all self-reported pregnancies between1993 to 2016. Information was collected regarding maternal and foetal outcomes.

Results

Twenty-four pregnancies were reported in 11 patients. Median age at delivery was 31.5 years (range 18-38) and median time post-transplant was 4.5 years (1-13). There were 18 live births (78%), 6 miscarriages and no stillbirths. Delivery was by caesarean section in 14/18 cases (78%). There were no congenital anomalies, nor maternal deaths. There were five deaths remote from pregnancy, four as a result of liver graft failure and one due to lymphoma. Deaths due to graft failure occurred 6, 9, 14- and 28-years following transplantation and 4,5, 2 and 12 years following initial pregnancy. Liver tests were abnormal prior to pregnancy in three out of four patients with subsequent graft loss but normal in all 6 long term survivors.

Conclusion

Short- and medium-term maternal outcomes are good for liver transplant recipients. Although maternal life expectancy in our study is shortened this is comparable to the life expectancy for patients post liver transplantation.

Introduction

Liver transplant is a lifesaving procedure associated with excellent long-term survival rates [1]. In young females regular menstruation resumes within 12 months of transplantation in 74% of patients [2]. However, awareness of the need to consider contraception may be low. In a Polish study only one third of patients post solid-organ transplantation were using effective contraception [3]. Up to 50% of pregnancies may be unplanned [4]. In general, there is an increased incidence of hypertensive disorders, gestational diabetes and prematurity. However, in general, reported outcomes are good for both mothers and foetuses [5,6]. Nevertheless, a meta-analysis of 450 pregnancies in 308 liver transplant recipients concluded that complications rates were relatively high and that patient counselling and careful clinical decision making are important [7]. Long term maternal outcomes following pregnancy are less frequently reported. For this reason, we looked at long term maternal outcomes in liver transplant recipients attending the Irish National Liver Transplant Centre.

Methods

This is a cohort study including all self-reported pregnancies amongst women attending the Irish National Liver Transplant Unit. St Vincent's University Hospital hosts the unit, which is the only adult liver transplant unit on the island of Ireland. A total of 1004 liver transplants were performed in adult recipients in between 1993 to 2016. Of these 400 (39.84%) were female and 155 (15.44%) were considered to be of child-bearing age (< 45 years). Follow up was until the end of July 2018. The medical notes of each woman who self-reported pregnancy was reviewed. Patient demographics and clinical parameters were recorded including indication for transplant, number of pregnancies, transplant to conception interval (TCI), maternal and foetal complications during pregnancy, immunosuppression, foetal birth weight and mode of delivery. For the majority of patients, care for post-LT was co-ordinated with a specialist maternal medicine clinic in the National Maternity Hospital, Dublin.

Data is presented using median and range for numerical values. Cumulative survival rates were estimated using the Kaplan-Meier method using Graphpad Prism software version 6.0f. (GraphPad Software Inc, San Diego CA, USA).

Results

A total of 24 pregnancies were reported in 11 patients. Two patients were transplanted in the United Kingdom, one as a baby for biliary atresia and the second as an adult for primary biliary cholangitis. The patient with biliary atresia had 3 transplants. All other patients had a single liver transplant prior to pregnancy. Both patients are included as all their pregnancies occurred while attending our unit. One patient was excluded from analysis. She was transplanted in our unit but moved to the United Kingdom and had all her pregnancies occurred there. One patient had assisted conception for 4 pregnancies. The indications for transplant and the number of pregnancies per patient are summarised in Table 1**.** The median age at first pregnancy was 31.5 years (18-38) and the median time from liver transplant to conception was 4.5 years (1-13). Immunosuppression was tacrolimus alone (19 pregnancies) and cyclosporine alone (5 pregnancies).

Maternal outcomes

There were no maternal deaths during pregnancy or in the puerperium. Maternal complications are summarised in Table 2. Three patients developed respiratory infections requiring antibiotics. One patient had rupture of a splenic artery aneurysm requiring splenectomy two weeks post-partum and one patient had bleeding from oesophageal varices requiring band ligation. Four patients developed abnormal liver tests. Two were treated by an increase in tacrolimus dose at 6 and 32 weeks. In one patient labour was induced and the baby delivered by caesarean section. The fourth patient was initially transplanted for primary biliary cholangitis and had chronic active hepatitis diagnosed by liver biopsy prior to her 3rd pregnancy. At 12 weeks gestation she developed worsening liver tests and variceal bleeding requiring band ligation. She remained in hospital from 21 weeks gestation and her course was complicated by hospital acquired pneumonia. The baby was delivered by caesarean section at 33 weeks.

There were five deaths remote from pregnancy. Post-transplant, post pregnancy maternal survival and post pregnancy graft survival are shown in Figure 1. Mean twenty-year patient survival post liver transplant was in excess of 50%. For comparison purposes, current survival rates in our unit for elective first liver transplants are 93% at 1 year, 79% at 5 years and 68% at 10 years[8]. Twenty-year survival for first transplants, elective and emergency is 38.8%. One patient developed a B cell lymphoma and died 8 years following first pregnancy and 20 years following liver transplant. Four patients developed graft failure and died 6, 9, 14- and 28-years following transplantation and 4,5, 2 and 12 years following initial pregnancy. The patient with variceal bleeding in pregnancy developed hepatic encephalopathy 5 days post-partum and further variceal bleeding 2 months post-partum. Re-transplantation was attempted 9 months post-partum, but the patient died of massive intra-operative haemorrhage. The second patient was initially transplanted for Bylers disease (PFIC1) and was re-transplanted 2 years' post-partum for chronic rejection. She developed early post-operative hepatic artery thrombosis, had an emergency re-transplant but died intra-operatively. The third patient was initially transplanted for fulminant hepatic failure due to a paracetamol overdose. She had a re-transplant five years' post-partum for chronic rejection but died as a result of an intra-operative haemorrhage. The fourth patient developed graft failure and was listed for re-transplantation. She suffered recurrent severe variceal bleeding and was treated with emergency trans jugular intrahepatic portosystemic shunt but died as a result of intestinal ischaemia. Three of the five patients who died had abnormal liver function tests prior to pregnancy. One was known to have graft cirrhosis, one had steatohepatitis and the third chronic hepatitis on liver biopsy prior to pregnancy. An additional patient had a successful re-transplantation 2 years following pregnancy for late hepatic artery thrombosis.

Foetal outcomes

There were 18 live births (78%), 6 miscarriages and no stillbirths. Delivery was by caesarean section in 14/18 cases (78%). Seven caesarean sections were described as urgent or emergency. There were 7 pre-term births at 29,31,31,32,35 and 35 weeks' gestation. All were delivered by caesarean sections. Birth weights were available for 16 infants; median 3.02 Kg (1.67 -4.25 Kg). There were no congenital anomalies reported.

	Number of patients	***Live births***
1 pregnancy	*5*	*4*
2 pregnancies	*3*	*6*
3 pregnancies	*1*	*3*
4 pregnancies	*1*	*3*
6 pregnancies	*1*	*2*
Aetiology of liver disease	*Hepatitis B*	*1*
	Cryptogenic cirrhosis	*1*
	Paracetamol overdose	*3*
	Hereditary Haemorrhagic Telangiectasia	*1*
	Primary Biliary Cholangitis	*1*
	Biliary atresia	*1*
	Byler's disease	*1*
	Primary sclerosing cholangitis	*1*
	Alpha 1 antitrypsin deficiency	*1*

Table 1. *Numbers of pregnancies and aetiology of liver disease.*

Maternal complications	
Hypertension	*3*
Pre-eclampsia	*1*
Venous thrombosis	*1*
Respiratory infection	*3*
Deranged liver function	*4*
Liver decompensation	*1*

Table 2. *Maternal complications.*

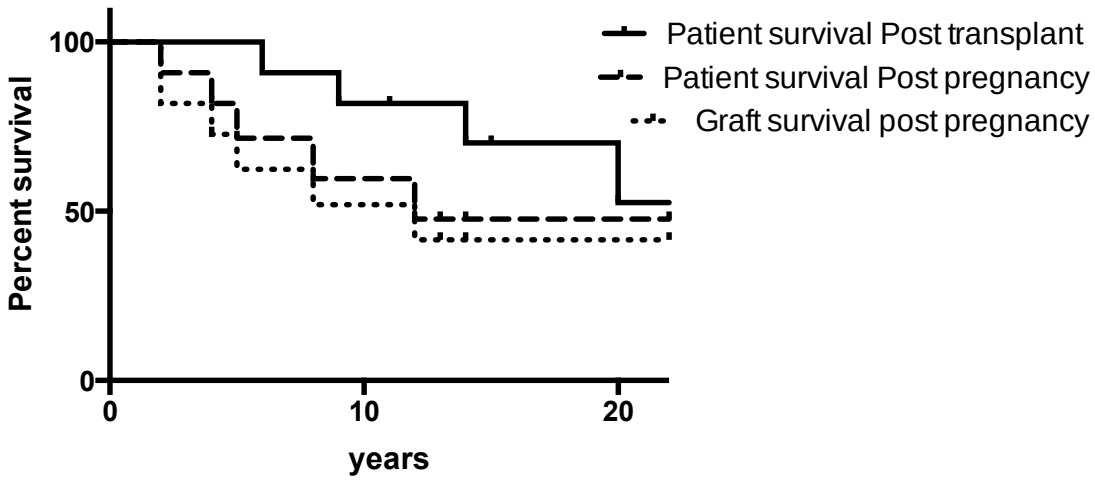

Figure 1: *Actuarial patient survival post liver transplant was greater than 50% at 20 years.*

Discussion

In this study we report on 24 pregnancies in 11 patients following liver transplantation. Foetal outcomes were good with a live birth rate of 78%. There were no maternal deaths. Maternal and foetal mortality rates in Ireland are comparatively low with a maternal mortality rate of 9.8 and a foetal mortality rate of 4.8 per 100,000 in 2018[9].

However long-term follow-up of this post-transplant cohort of patients revealed significant liver graft loss and late mortality. Whether these rates of graft loss and mortality were accelerated by the preceding pregnancies is not clear.

There is relatively little data in the literature on remote deaths following pregnancy in women post liver transplant. A large study from the UK reported that 11/93 mothers died during follow-up and another 8 underwent re-transplantation [6]. In another study of 28 mothers followed for a median of 7.2 years at 2 centres there were no late maternal deaths or re-transplantations [5]. In a separate study from Kings College of 79 mothers followed for 52 months there were 3 maternal deaths[10].

Three quarters of infants were delivered by caesarean section and half of these were urgent or emergency procedures. The caesarean section rate is higher than the normal population (28%) and also higher than internationally reported figures of 45-50% [7,11]. Many of these caesarean births were related to preterm delivery associated with maternal pregnancy complications. Pregnancy related complication were as expected and in line with international experience.

Late deaths following pregnancy was significant in this cohort. One patient died as a result of late lymphoma and four because of graft loss. An additional patient had re-transplantation for late hepatic artery thrombosis. Despite this over all post-transplant survival was in excess of 50% at 20 years which is comparable with published results [1]. Acute cellular rejection has been reported in approximately 15% of pregnancies and appears to be more common if the pregnancy occurs within a year of liver transplantation[10]. However, it is unclear whether pregnancy itself contributes to rejection or graft loss [7]. Jain et al found in a large study of over 4000 patients 18-year mortality post liver transplant was 48% [12]. Therefore, it is unclear whether pregnancy itself contributes to rejection or graft loss [7].

The major limitation of this study is its small size and the number of late maternal deaths may be a chance finding and un-representative of the true risk. Our results indicate that pregnancy outcomes for mother and baby are generally good following liver transplantation. Although maternal life expectancy in our study is shortened this is comparable to the life expectancy for patients following liver transplantation.

Declaration of Conflicts of Interest:
The authors have no conflicts of interest

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