

Pregnancy After Liver Transplantation Following Idiopathic Subacute Liver Failure: A Multidisciplinary Approach

Nnadozie Igbokwe (MBBS, MMedSci, MRCPI, MRCOG)

ST6 Specialist Trainee Registrar in Obstetrics and Gynaecology
Royal Jubilee Maternity Hospital, Belfast, UK

Sunday P. Ugwoke (BSc, MBBS, MMedSci)

ST3 Trainee doctor, Obstetrics and Gynaecology
Royal Jubilee Maternity Hospital, UK

Meenu Sharma (MRCOG)

ST7 Trainee doctor, Obstetrics and Gynaecology
Royal Jubilee Maternity Hospital, UK

ABSTRACT

Liver transplantation (LT) is the definitive treatment for end stage liver disease. Liver cancer, viral hepatitis and alcohol related liver diseases are the common causes for transplantation. The outlook for pregnancy in post-transplant patient is generally good although they are considered higher risk than the general population. As far back as 1978, the first successful pregnancy in a liver transplant patient was reported with as many as 12 pregnancies per year occurring in liver transplant recipients in the UK. We present a 27-year old primigravida who had liver transplant when she was 9 years old due to idiopathic subacute liver failure. She conceived spontaneously and had an unremarkable multidisciplinary antenatal care with induction of labour and vaginal delivery at 38 weeks gestation with good outcomes. This case highlights the importance of multidisciplinary team (MDT) management and follow-up in liver transplant patients.

INTRODUCTION

The outcome of pregnancy following liver transplantation has improved progressively over time. Liver transplantation occurs in 8% of paediatric female age group with usually good prognosis and survival into adulthood (Horvat *et al.* 2017). About one-third of patients who undergo LT are women and of this, 8% are women of reproductive age (Alisi *et al.* 2016). Although pregnancy outcomes following LT are favourable, there are however increased maternal and foetal complication rates. Major areas of concerns to patients include the impact of immunosuppressives on the foetus and possible allograft rejection in pregnancy (Prodromidou *et al.* 2019, Kamarajah *et al.* 2019). For the clinicians, a major challenge remains lack of randomised controlled trials on major immunosuppressive drugs used, as well as lack of detailed national and international guidelines on management of pregnancy in this group of patients (Valentin *et al.* 2021). Lack of experience and information on how to manage this group of patients in pregnancy present anxiety among some clinicians especially doctors in training.

In view of the high complication rates in pregnancy including graft rejection, postpartum graft loss, prematurity, hypertensive disease in pregnancy, low birth rates and higher rates of caesarean section, MDT approach is crucial to achieve optimal outcomes (Baskiran *et al.* 2017). This explains the reason behind this presentation as the patient benefited from good preconception care, and MDT based care in pregnancy and postpartum period.

CASE PRESENTATION

A 27-years-old Primigravida, with a body mass index (BMI) of 23 kgm⁻² at booking. Her pregnancy was spontaneous and planned, 18 years after her LT which happened at the age of 9. Pregnancy was booked at 11+6 weeks gestation with a booking haemoglobin level of 138g/L (115-165) and platelets of 221 x10⁹cells/L (150-450). The serum creatinine was normal at 43 ummol/L (45-84), and slightly elevated liver function test in keeping with a post-transplant patient. The aspartate aminotransferase (AST) was 35 U/L (<32), alanine aminotransferase (ALT) was 49 U/L (33), gamma-glutamyl transferase (GGT) level of 57 (6-42), a normal total bilirubin level of 13 umol/L (<21) and normal albumin level of 45 g/L (35-50). Her blood group was ORhD positive with no antibodies. The rest of her booking investigations were unremarkable, and she had a joint care throughout her pregnancy with consultant obstetricians and hepatologists. She continued her immunosuppressive (Tacrolimus) and other medications for the course of her gestation with risks and benefits discussed. Medications were Tacrolimus 1.5mg twice daily, oral prednisolone 5mg daily, Ursodeoxycholic acid (UDCA) 500mg twice daily and bisoprolol 2.5mg daily respectively. The serum tacrolimus level was normal at booking (6.9 ng/ml) and remained within normal range throughout the pregnancy.

The fetal anomaly ultrasound scan at 20 weeks showed no obvious fetal defect, with single artery cord and anterior high placenta. She had an uneventful pregnancy and had regular normal foetal growth ultrasound scan from 28 weeks gestation. Screening for gestational diabetes (GDM) was negative. A repeat renal and liver function tests at 34 weeks gestation were all within normal limits. This was requested in part due to history of right upper quadrant abdominal pain which later settled with analgesics, and also for protocol surveillance. Her Tacrolimus dose was adjusted as necessary in keeping with the serum level. There was an MDT discussion as regards mode and timing of delivery on account of which she had induction of labour at 38 weeks gestation.

Her labour progress was uneventful, and she had an uncomplicated vaginal delivery of a live male infant who weighed 2778 grams with good Apgar scores. The birth weight was appropriate for gestational age. She was discharged home the next day in good condition. Contraceptive advice was given before discharge with different options and benefits discussed. She was followed up by the hepatologist 6 weeks postpartum with satisfactory blood tests including renal and liver function tests, and no other concerns.

TRANSPLANT HISTORY AND PRECONCEPTION CARE

She developed jaundice at the age of 9, and progressively had subacute liver failure which necessitated a successful liver transplant in a specialist children hospital. No definite cause of the liver failure could be found following multiple investigations. Her protocol liver biopsy 5 years after the LT showed mild chronic hepatitis. She developed post-transplant hepatitis 7 years after her LT and was consequently started on Ursodeoxycholic acid (UDCA) and azathioprine.

One year prior to her conception, her LFT showed a worsening picture of obstructive jaundice. She consequently had a magnetic resonance cholangiopancreatography (MRCP) which revealed mild biliary stricture but otherwise stable. The jaundice settled with UDCA before pregnancy. Her lipid profile and HbA1c were normal, with a normal serum Tacrolimus level also. She had no gastrointestinal symptoms and maintained a good diet. Her menstrual period was regular, and she did not smoke.

DISCUSSION

Pregnancy after LT is generally safe with no increased maternal mortality, however the adverse outcomes in pregnancy are increased comparatively (Wiles *et al.* 2016). The rates of preterm birth, preeclampsia and caesarean section are 32.1%, 12.5%, and 42.2% respectively which are higher than the background rates (Valentin *et al.* 2021). The high caesarean delivery rate could be due to the high-risk nature of the pregnancy coupled with prematurity and maternal anxiety (Prodromidou *et al.* 2019). Hypertensive disease has been attributed to the use of calcineurin inhibitors (e.g., Tacrolimus) and steroids (prednisolone) both of which could cause post-transplant hypertension. The higher incidence of GDM at 28.6% has been linked to the alteration of glucose metabolism with the use of immunosuppressants and steroid. Other complications include fetal growth restriction, and obstetric cholestasis (Coscia *et al.* 2009). In general, the use of immunosuppressive medications is associated with high risk of miscarriage, prematurity, low birth weight (Prodromidou *et al.* 2019). None of these complications was seen in our case. According to the 2017 Transplant Pregnancy registry International (TPRI), pregnant patients with LT because of hepatitis B, should be considered very high-risk. This is due to unusual higher risk of graft rejection, postpartum graft loss and increased prematurity (Coscia *et al.* 2017).

It has been recommended that pregnancy should be delayed at least one year after LT (Deshpande *et al.* 2012). This is due to the higher risk of acute graft rejection or failure within the first year (Valentin *et al.* 2021). Furthermore, patients are often on very high doses of immunosuppressants within the first year, and this can increase this risk of foetal exposure (Sibanda *et al.* 2007). The patient in our case conceived after 18 years of LT with no pregnancy-related graft rejection. Preconception care is an important modality of care in this group of patients. This provides the opportunity to discuss the effect of pregnancy on liver transplant graft, ensure therapeutic level of immunosuppressant, review drugs that are teratogenic in pregnancy such as Mecophenolate, and ensure patients are registered in a centre with the capacity to provide an adequate antenatal care (Valentin *et al.* 2021). In pregnancy, the key management principle involves regular monitoring of graft function and serum level of immunosuppressants (Lim *et al.* 2018, Sohail *et al.* 2020). This is best achieved using MDT comprising of liver transplant hepatologists, experienced obstetricians and fetal medicine specialists. Patients on calcineurin inhibitors should also have their renal function monitored as exemplified in our case (Lim *et al.* 2018).

There are some concerns regarding the effect of pregnancy on the liver graft. The risk of postpartum graft loss has been suggested to be as high 10.55, with 2-17% risk of acute cellular rejection in pregnancy (Wiles *et al.* 2016). Factors attributed to graft loss include age below 18 years at the time of transplant, history of graft rejection in pregnancy, viral hepatitis as the cause of hepatic failure, and being of Caucasian race (Gwiasda *et al.* 2017). Patients should be aware of the possible effects of immunosuppressive medications on the foetus, as they all cross

the placenta and gain access into the fetal circulatory system (Westbrook *et al.* 2015, Parolin *et al.* 2009). This necessitated the need for serial monitoring of immunosuppressive used in pregnancy to avoid fetal toxicity while also achieving therapeutic level to ensure graft function. Although some birth defects have been recorded with calcineurim inhibitors, Tacrolimus is generally considered safe in pregnancy (Prodromidou *et al.* 2019).

While there is a high caesarean section rates in these group of patients, vaginal delivery is not contraindicated (Wiles *et al.* 2016). The decision as to the timing of delivery is individualised and should be MDT based as seen in our case. Our patient had an uneventful vaginal delivery. Contraceptive advice is paramount and barrier contraception presents minimal risks (Parolin *et al.* 2009). Oral contraceptives may be used in patients with stable graft function, with no other general contraindications (Klein and Josephson 2021). With regards to intra-uterine contraceptive devices, there is a potential increase in infection with reduced efficacy while on immunosuppressives. In patients who have completed their family sizes, surgical sterilisation is recommended as it avoids drug interaction (Alisi *et al.* 2016).

CONCLUSION

Although pregnancy after LT is considered high-risk, the outcome is generally good. Preconception care and the use of MDT management approach in pregnancy ensure optimal outcomes.

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