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Pregnancy and sexual function in liver transplantation☆

Michael A. Heneghan[1,*], Markus Selzner[2], Eric M. Yoshida[3], Beat Mullhaupt[4]

[1]*Institute of Liver Studies, King's College Hospital NHS Foundation Trust, Denmark Hill, London SE5 9RS, United Kingdom*
[2]*Department of Surgery, Multi-Organ Transplantation Unit, Toronto General Hospital, University Health Network, University of Toronto, Toronto, Canada*
[3]*Division of Gastroenterology, Vancouver General Hospital, Diamond Health Care Centre, 5153-2775 Laurel Street, Vancouver, BC, Canada V5Z 1M9*
[4]*Swiss HPB (Hepato-Pancreato-Biliary) Center, University Hospital Zurich, Switzerland*

1. Introduction

Over the past forty years, liver transplantation (OLT) has evolved from an experimental, surgical procedure with a low likelihood of success to a universally accepted multi-disciplinary endeavor for the treatment of both acute liver failure and end-stage liver disease. In 2008, the expectation of 1-year post-transplant survival is greater than 85% for most indications, and indeed, the majority of clinical challenges have been addressed [1–3]. In that context, the expectation for most liver graft recipients is one of achieving long-term survival in conjunction with significantly improved quality of life [4–8].

For younger patients, the expectation of contributing to society means considerably more than merely returning to the workforce or achieving specific goals. For younger patients, who have undergone successful OLT, the expectation in 2008 is one of a full and normal life, including the ability to have children, and enjoyment of normal sexual relations. In this, the 11th Forum on Liver Transplantation we examine a much neglected combination of topics reflecting the full tapestry of issues pertaining to sexual health and function, contraception and pregnancy in the OLT recipient. Additionally, we examine the rare indications for transplantation in patients who develop liver failure as a consequence of pregnancy.

2. Pregnancy-related liver disease: is there ever an indication for liver transplantation? (Markus Selzner)

Alteration in aspects of liver function is normal during pregnancy. Severe liver dysfunction is rare, but when it occurs, it can do so in a catastrophic fashion for both mother and infant. Liver disease in pregnancy can be considered in three separate categories. First, liver dysfunction specific to the pregnant state, i.e. conditions occurring only in the setting of pregnancy. Second, management of the pre-existing disorders that may be provoked by the pregnant state, i.e. pre-existing liver disease that must cope with the extra physiological demands of pregnancy. Finally, liver disease coincident with pregnancy, i.e. apparent concurrent liver conditions occurring in a pregnant woman that do not typically affect the pregnancy. In the context of liver transplantation, it is this first category that is most pertinent.

Liver failure in its broadest sense, occurring in the context of the pregnant state is rare, and is most often caused by acute fatty liver of pregnancy (AFLP), eclampsia-related liver disease, or the haemolysis, elevated liver enzymes, low platelet count (HELLP) syndrome. Indeed, the distinction between eclampsia-related liver disease in pregnancy, HELLP syndrome

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* Corresponding author. Tel.: +44 207 3464952; fax: +44 207 3463167.
E-mail address: Michael.Heneghan@kch.nhs.uk (Michael A. Heneghan).

Abbreviations: orthotopic liver transplantation, OLT; acute fatty liver of pregnancy, AFLP; haemolysis, elevated liver enzymes, low platelet count, HELLP; intrauterine device, IUD; combined oral contraceptive, COC; depot medroxyprogesterone acetate, DMPA; cyclosporine A, (CyA); model for end-stage liver disease, MELD; mycophenolate mofetil, MMF; food and drug administration, FDA; National Transplant Pregnancy Registry, NTPR.

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and AFLP is blurred in many cases and it is often difficult to distinguish one from another. These specific conditions typically occur in the third trimester of pregnancy but may present at any time during pregnancy or even in the early post-partum period [9]. In considering a differential diagnosis in patients who may present with liver failure, it is important to reflect on conditions outwith those that occur only in the pregnant state. These are summarized in Table 1.

AFLP and HELLP syndromes are both infrequent with AFLP reported as occurring in 1/7000–15,000 pregnancies. First described in 1934 by Sheehan et al. as a yellow atrophy of the liver, the condition has been widely described and significant advances in the pathogenesis of the condition reported [10–13]. Histological findings are those of severe microvesicular steatosis in association with minimal necrosis.

Acute fatty liver of pregnancy is regarded as one of the family of diseases characterised by a mitochondrial cytopathy, which also includes conditions such as Reye's Syndrome, drug-related liver disease and other genetic defects in mitochondrial function. Ultimately, these conditions are characterised by vomiting, hypoglycaemia, lactic acidosis, hyperammonaemia and microvesicular fat in organs. Acidosis occurs as a result in defective energy supply within the mitochondria during oxidative phosphorylation. Hypoglycaemia in these disorders may relate to failure of mitochondrial tricarboxylic acid cycle enzymes [11–13].

The understanding of the pathogenesis of the condition has been greatly enhanced by the description of full term infants born to mothers with AFLP in whom hypoglycaemia, hepatic encephalopathy and steatosis developed. The infants were found to have a defect in fatty acid oxidation, and specifically were deficient in long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD)[13]. In a seminal investigation, this pattern was noted in 11 women whose pregnancies were complicated by acute fatty liver with features of HELLP syndrome. Six babies from this series were found to have LCHAD deficiency[13]. Heterozygosity for LCHAD in the mother appears to be responsible at least in part for the development of disease in the infant. The molecular basis has been identified as the substitution of guanosine to cytosine in the alpha-subunit that catalyses the last three steps of beta oxidation. Consistent with these findings is the fact that in murine models, pregnancy decreases fatty oxidation with the effect mediated by estrogens and progesterones.

Patients with AFLP present in the third trimester at a mean gestational age 34 weeks with non-specific symptoms, such as vomiting, malaise, fever, and abdominal pain [13]. In later stages, patients develop jaundice, coagulopathy, hypoglycaemia, and encephalopathy. Serum transaminases rarely exceed 1000 IU/L, and usually ranges from 300 to 500 IU/L [14]. Disseminated intravascular coagulation (DIC) may occur in up to 70% of cases. In severe cases, the clinical course may be complicated by hepatic necrosis and liver rupture. The differential diagnosis includes acute viral hepatitis and HELLP syndrome. Ultrasound imaging and viral serological assessment are required in all cases. Liver biopsy is not mandatory but may be necessary if the diagnosis is clinically unclear, the liver function tests do not normalise after delivery or, the diagnosis of ALFP is required as an indication for delivery [15]. The therapy of choice is rapid delivery, usually by caesarian section.

In the past, AFLP was considered to be universally fatal, but aggressive optimization in the peri-delivery period, has improved the prognosis with both maternal and foetal mortality rates ranging from 0% to 20% reported in the literature [16]. Although AFLP may progress to acute liver failure (ALF), liver transplantation is rarely indicated/required since the condition is typically reversible following delivery. Liver transplantation should be considered in cases with severe disseminated intravascular coagulation (DIC), rupture of the liver, or severe encephalopathy. Where present, the cardinal management paradigm is emergency delivery by caesarian section, with aggressive supportive care. OLT is performed only in the context of failure to recover liver function.

In the European Liver Transplantation Registry (ELTR) database (www.eltr.org) 75,530 liver transplantations have been recorded since 1968. OLT has been performed in only six instances for AFLP during this time, (René Adam, personal communication) demonstrating that transplantation is rarely required, and is only indicated in exceptional cases of advanced disease.

Table 1
Liver dysfunction in pregnancy in patients without pre-existing liver disease

Liver disease specific to pregnancy	
Acute fatty liver of pregnancy	
Hypertension-associated liver disease of pregnancy	
Pre-eclampsia and eclampsia	
Hepatic infarction, hematoma and rupture	
HELLP syndrome	
Liver disease coincident with pregnancy	
Acute viral hepatitis	Hepatitis A–E
	Herpes simplex hepatitis
Drug toxicity	
Acetaminophen toxicity	
Budd-Chiari syndrome	
Liver transplant recipients	

Consideration should be given in differential diagnosis to each of these conditions. For patients with liver disease specific to pregnancy, it is pertinent to consider that it is frequently clinically difficult to differentiate between HELLP syndrome AFLP and eclampsia-related liver disease. In all such instances, early delivery and intensive supportive care may abrogate the need for liver transplant.