LIVER DISEASE AND PREGNANCY
EARLY IDENTIFICATION OF THOSE AT GREATEST RISK

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LIVER DISEASE AND PREGNANCY: EARLY IDENTIFICATION OF THOSE AT GREATEST RISK

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Abstract

Historically, women with pre-existing liver disease were advised against pregnancy due to concerns regarding the potential for worsening of liver function, hepatic decompensation and death. The available literature detailing outcomes of pregnancy in women with liver disease is sparse, combining this with the fact that the term “liver disease” incorporates a spectrum of severity from a variety of underlying aetiologies means that generic advice regarding pregnancy risk is clearly not appropriate for all women. In addition, women with previously normal hepatic function may develop acute liver failure in pregnancy which is associated with high morbidity and mortality. Data regarding early identification of women at high risk of death from liver failure is lacking.

This body of work addresses the paucity of information regarding pregnancy risk in women with liver disease. The potential risks related to pregnancy for the mother, baby and graft in the context of different diseases and underlying severity are explored and detailed. Pre-conception parameters are identified which can predict poor pregnancy outcomes in women with different aetiologies of liver disease and severity. The King’s College Hospital poor prognostic criteria in patients with pregnancy associated acute liver failure (ALF) are shown not to be applicable to this unique cohort of patients and alternative early poor prognostic indicators are suggested.

This work should enable individualised advice regarding pregnancy risk to be given to women with liver disease who are considering pregnancy, increase our understanding of specific complications a women may encounter and aid identification of women they may benefit from liver transplantation.

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Chapter 1: Introduction

The effects of a normal pregnancy on the liver from a physiological stand point are well understood. In contrast the effects of pregnancy on the outcomes of patients with liver disease are poorly understood.

Historically, women with pre-existing liver disease were advised against pregnancy due to concerns regarding the effect of pregnancy on the underlying liver condition. These concerns related to the potential for worsening of liver function, hepatic decompensation and death. Concerns also existed regarding poor foetal outcomes and the potential risk of congenital abnormalities secondary to medication. The available literature detailing outcomes of pregnancy in women with liver disease is sparse, and for the majority of women information is limited to case reports and small case series only. The available literature is outlined in detail in this and subsequent chapters and reports variable outcomes for mother, liver and foetus in heterogeneous small cohorts of women with liver disease. This has resulted in women with liver disease being given generic advice, with little individual applicability regarding the safety of pregnancy.

This combined lack of information alongside the fact that the term “liver disease” incorporates a spectrum of severity ranging from mild abnormalities in liver enzymes to cirrhosis and its complications, or acute liver failure adds to the confusion. Moreover, given the variety of underlying diseases with their differing pathophysiologies, generic advice regarding risk is clearly not appropriate for all women. More information detailing the outcome and risk for individualised cohorts of women is therefore required so that appropriate pre-conception counselling can be undertaken along with the necessary care throughout pregnancy, delivery and the post-partum period.

In addition, women with previously normal hepatic function may develop acute liver failure in pregnancy which is associated with a high maternal morbidity and mortality. Again the published literature regarding poor prognostic outcomes and indications for consideration for liver transplantation is extremely limited.

This thesis aims to address the paucity of information regarding pregnancy risk in women with liver disease and hopes to improve preconception counselling, pregnancy management in women with liver disease and maternal and foetal outcomes.

1.1 Normal physiological changes during pregnancy

The majority of pregnant women are young and healthy and as a result have an uneventful pregnancy. When pregnant, many physiological changes and hormonal changes occur within the human body, some of which can mimic the signs and symptoms often seen in women with liver disease. These normal physiological changes associated with pregnancy need to be recognised and understood as no specific treatment or monitoring is required. Furthermore, a good understanding of what a normal pregnancy entails allows early detection and access to treatment in those who may develop liver disease and a consequence of pregnancy. (1)

A rise in maternal heart rate and cardiac output along with a fall in blood pressure all occur in a normal pregnancy. (2) A physical examination of a pregnant women may show palmer erythema and the presence of multiple spider naevi in up to 70%. (3) Spider naevi are angiomas which are found in the distribution of the superior vena cava thus commonly seen on the face, neck, upper trunk and arms. They occur due to dilatation of the cutaneous arterioles driven by increased circulating oestrogen levels. Due to their pathophysiology they are common in pregnancy women, those on hormonal contraception and women with liver disease as the liver is responsible, in part, for metabolising oestrogen. Palmer erythema is a mottled, red colouration mainly over the thenar and hypothenar eminences in the hands occurring secondary to cutaneous vasodilatation and a hyper dynamic circulation. It is a clinical sign that is

fairly non-specific and seen in heathy individuals. Indeed, any patient that may have a hyper dynamic circulation, i.e., those with hyperthyroidism and patients with liver disease. Pregnant women have a hyper-dynamic circulation with the plasma volume estimated to increase by 30% and the cardiac output by 40%, which peaks at 32 weeks gestation. (4) Despite this, blood flow to the liver remains relatively constant during pregnancy and it remains impalpable as it is displaced upwards into the thoracic cavity due to the expanding uterus.

Biochemical and haematological indices taken during pregnancy need to be interpreted in light of the normal physiological changes that occur in test results as a consequence of pregnancy. (5) The maternal alkaline phosphatase (ALP) can increase 2-4 times the upper limit of normal especially in the third trimester where ALP is produced both from the placenta and as a result of foetal bone development. The alpha fetoprotein (AFP) level increases in pregnancy as AFP is produced by the foetal liver. A marked increase however may reflect an underlying neural tube defect of the foetus. Other common biochemical and haematological tests including gamma-glytamyl transpepidase (GGY), aspartate aminotransferase (AST), alanine aminotransferase (ALT), bilirubin, total protein levels, albumin, urea, haemoglobin levels and the prothrombin time remain unchanged or slightly reduced due to haemodilution as a consequence of increased circulating plasma volume that occurs with pregnancy. (5) Therefore elevations in transaminases, bilirubin or the prothrombin time are abnormal and indicate a pathological state which requires further assessment. Pregnancy is also recognised as a pro-coagulant state and clotting factors (I, II, V, VII, X, and XII) and fibrinogen are increased.

Table 1.1 Typical ranges for biochemical and haematological indices by trimester

Laboratory Parameter	*Non Pregnant*	*1st Trimester*	*2nd Trimester*	*3rd Trimester*
ALT (IU/L)	0-40	6-32	6-32	6-32
AST(IU/L)	7-40	10-28	11-29	11-30
Bilirubin (µmol/L)	0-17	4-16	3-13	3-14
γGT (IU/L)	11-50	5-37	5-43	3-41
ALP (IU/L)	30-130	32-100	43-135	133-418
Albumin (g/L)	35-46	28-37	28-37	28-37
Bile acids (µmol/L)	0-14	0-14	0-14	0-14
Haemoglobin (g/L)		110-135	103-130	100-130

Small clinically insignificant oesophageal varices can occur in up to 50% of pregnant women in the late second and third trimester. These occur due to compression of the inferior vena cava by the enlarging uterus and a reduction in venous return.

Liver biopsy in pregnancy does not carry additional risks. Despite the hyper dynamic circulation and increased plasma volume the total blood volume to the liver remains constant, with the majority of excess blood shunted through the placenta and the bleeding risk is not thought to be increased. Liver histology is practically normal in the pregnant women, however electron microscopy shows some increase in the endoplasmic reticulum. (6)

1.2 Tolerance of the immune system in pregnancy

The human immune system has evolved to combat potential foreign pathogens and provide protection from disease. The innate immune system recognises “danger” and rapidly initiates generic immune responses. The adaptive immune system is provided by T- and B-lymphocytes and is characterised by antigen specificity and the generation of memory for a heightened specific response to subsequent antigen exposure.

Pregnancy was historically regarded as an immunological paradox where the maternal immune system tolerates the presence of a foetus expressing paternal antigens. (7) This phenomenon occurs as several specialised mechanisms have evolved which help the foetus evade attack from the maternal immune system. Firstly foetal tissue depletes tryptophan, an amino acid which is essential for rapidly dividing cells, and thereby inhibiting T-cell production. (8, 9) Secondly the foetal tissue expresses human leucocyte antigen G1, which inhibits natural killer cell activation and finally the foetal-maternal interface is a highly organised structure that provides an anatomical barrier. (10, 11)

More recently the up-regulation of regulatory T-cells has been shown to play a pivotal role in foetal-maternal tolerance. (12, 13) Regulatory T-cells are required for the maternal immune system to tolerate the foetal allograft, and there is an increase in their circulating number during pregnancy. (12, 13) The up-regulation of T-cells during pregnancy is thought to be hormonally driven. High concentrations of oestrogens are thought to inhibit immune activities whilst progesterone promotes T helper 2 cells and in itself had anti-inflammatory properties. (14, 15)

The above concept of tolerance is key to understand the phenomenon of an improvement in disease followed by a flare in the post-partum period in many autoimmune conditions including autoimmune hepatitis (AIH) and rheumatoid arthritis. (16) The mechanism for this phenomenon in autoimmune conditions is incompletely understood. It is likely, in-part,

related to the fact that pregnancy induces the temporary development of immunological tolerance in order to allow the mother to tolerate the antigens expressed from the father by the foetus. Recent advances in the understanding of the aetiopathogenesis of AIH has demonstrated that it is an impairment in regulatory T-cells that is key to the loss of immune tolerance in AIH and thus the emergence of uncontrolled effector autoimmune responses. (17, 18) Taking into account the above factors, it becomes clearer why patients with AIH, and indeed other autoimmune conditions, may induce remission during pregnancy and then flare in the post-partum period, such that when pregnancy ends, tolerance breaks down and flares in disease activity occur. Although this hypothesis has never been scientifically proven, it is attractive on many levels.

1.3 Pregnancy related liver disease

The liver diseases specific to the pregnant state are the most frequent cause of liver dysfunction in pregnancy and are reported to complicate up to 3% of all pregnancies. (19) Severe liver disease occurring in pregnancy is associated with significant morbidity and mortality for both the mother and baby. Early recognition, prompt delivery of the foetus and supportive care remain the key pertinent areas of management. The liver diseases specific to the pregnant state can be classified into those of early pregnancy (hyperemesis gravidarum) and those of late pregnancy (acute fatty liver of pregnancy (AFLP), pre-eclampsia with hepatic involvement including the haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, liver rupture/infarction and intrahepatic cholestasis of pregnancy).

1.3.1 Hyperemesis Gravidarum

Hyperemesis gravidarum is defined as intractable vomiting, resulting in dehydration, ketosis and weight loss of greater than 5%. It complicates between 0.3% and 2% of pregnancies and symptoms usually but not exclusively begin before 9 weeks gestation. (20, 21) The cause is unclear, but it is likely multi-factorial in origin contributed to by the autonomic nervous system and altered gastric motility along with high serum concentrations of human chorionic gonadotrophin (HCG) hormone and oestrogen. (20)

Biochemical abnormalities are common and include renal dysfunction secondary to dehydration, electrolyte abnormalities including hypokalaemia and hypomagnesaemia secondary to vomiting and reduced oral intake. Abnormalities in hepatic enzymes occur in approximately 50% of cases that require hospitalisation with serum aminotransferases usually 2-4 times the upper limit of normal. Jaundice can occur in those patients severely affected but is usually mild with bilirubin levels less than 4-times the upper limit of normal. Prompt treatment is essential as HG accounts for approximately one maternal death per year in the UK. This includes intravenous rehydration, correction of hyponatraemia and hypokalaemia, thiamine

supplementation, thromboprophylaxis and antiemetic treatment to enable slow reintroduction of oral fluids and diet. Hepatic biochemical abnormalities more than those outlined above or fail to resolve on resolution of the vomiting should raise the suspicion of an alternative cause for the abnormal hepatic biochemistry, including viral hepatitis, autoimmune hepatitis and Budd-Chiari syndrome.

1.3.2 Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the commonest pregnancy-specific liver disease. It is a reversible form of cholestasis characterized by pruritus in pregnancy and elevated fasting or post prandial serum bile acids with spontaneous relief of signs and symptoms within 6 weeks of delivery.(22) ICP has a high recurrence rate in subsequent pregnancies. It has a variable incidence, ranging from 3-5% of pregnant women in Chile to 0.7% in the UK; it is rarely reported in African countries. (23) ICP typically presents in the third trimester but it can present as early as 7 weeks of gestation. It occurs more commonly in multiple pregnancy and in women that have received fertility treatment. ICP has a complex aetiology with genetic, endocrine and environmental components. It is likely that elevated estrogen (24) and progesterone metabolites (25) in pregnancy unmask the disease in genetically susceptible women. The alteration in female sex hormones that occur during pregnancy are postulated to have a direct inhibitory effect on the bile salt export pump leading to impaired biliary transport across the canalicular membrane and thus induction of cholestasis. Approximately 15% of cases have genetic variation in one of the hepatocanalicular transport proteins (ABCB11 (bile salt export pump) or ABCB4 (phosphatidylcholine floppase). Smaller studies have reported genetic variation and/or heterozygous mutations in ABCC2 (conjugated organic anion transporter), (26) ATP8B1 (FIC1)) (27, 28) and the nuclear bile acid receptor. (farnesoid X receptors) (27, 29) The maternal mortality is low however it is a hepatic complication of pregnancy which carries with it a serious foetal risk and thus must be correctly identified and managed.

The initial and most characteristic symptom is pruritus which is often worse at night. Patients commonly complain of generalised pruritus, but with the palms and soles most severely affected. In its severe form, the pruritus can be intractable and intolerable leading to insomnia, excoriated skin with secondary infections, depression and in extreme cases, suicidal ideation. The only associated rash is secondary to excoriations from scratching. Some women also complain of dark urine and pale faeces.

Laboratory investigations confirm the presence of cholestasis with the key diagnostic test being a fasting serum bile acids concentration of >14umol/L. (30) The alkaline phosphatase levels are modestly elevated (3-5 times the upper limit of normal) but with a normal or minimally elevated gamma glutamyl transpeptidase (GGT) levels. The level of serum aminotransferases are often also elevated and, in severe forms can be as high as 1000IU/L, thus making the differentiation from other causes of pregnancy associated liver diseases and acute hepatitis challenging. Jaundice occurs in about 25% of cases, usually 2-4 weeks after the onset of pruritus. The hyperbilirubinemia is predominantly conjugated and levels rarely rise above 100g/dl. The prognosis is usually favourable for the mother and both the clinical and biochemical signs disappear spontaneously after delivery. A liver biopsy is not generally required unless the diagnosis is in doubt. Histological findings include dilated bile canaliculi containing bile plugs with sparing of the periportal areas. The hepatocellular architecture remains unaltered.

Serum bile acid measurement is the most useful biochemical test as the two largest prospective cohort studies of perinatal outcomes in ICP reported an association between the maternal serum bile acid concentration and the risk of adverse pregnancy outcome (spontaneous and iatrogenic preterm labour, stillbirth and admission to the neonatal unit). (30, 31) Adverse outcomes are rarely reported in pregnancies where the maternal bile acid level is

below 40μmol/L, and the risk of complications increases as the mother's serum bile acid level rises. (30, 31)

The intense cholestasis which occurs in IHCP can be associated with clinical or sub-clinical steatorrhoea. This can lead to the development of a deficiency in fat soluble vitamins, in particular vitamin K, which in turn can be associated with a prolonged prothrombin time. This cause of a prolonged prothrombin time must be identified and differentiated from the coagulopathy seen in acute liver failure.

Management for the mother is centred on symptomatic relief, close monitoring and early delivery of the foetus. The first line treatment for ICP is ursodeoxycholic acid ((UDCA, (15mg/KG/Day)) which results in improved maternal symptoms and biochemistry in approximately 75% of cases. (22, 32-35) *In vitro* and *in vivo* experiments demonstrate that UDCA enhances trans-placental transport of bile acids from the fetus to the mother and reduces placental damage.(23) A meta-analysis (34) and *in vitro* experiments (36, 37) suggest that its use may positively impact on the frequency of preterm labour, neonatal unit admission, placental damage and fetal arrhythmias. Rifampicin, is a potent pregnane X receptor (PXR) agonist. In ICP, combining rifampicin with UDCA improves the severity of cholestasis in approximately one third of women that do not respond to UDCA alone. (38)

ICP has a high recurrence rate in subsequent pregnancies, although the severity may vary from one pregnancy to the next. Affected women also have an increased risk of hepatobiliary disease later in life, most commonly gallstones (perhaps due to a common risk factor (ABCB4 gene)), hepatobiliary malignancies and immune-mediated and cardiovascular diseases.(39-41) A high prevalence of hepatitis C infection in women with ICP has been reported, (39) whether this reflects an enhanced susceptibility to Hepatitis C infection in women with ICP or visa versa remains unclear.

1.3.3 Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a medical and obstetric emergency as it can be fatal for both the mother and baby without early recognition and appropriate management. (42, 43) It is a rare complication of pregnancy, usually occurring in the third trimester, and in the UK affects approximately 1 in 20,000 pregnancies, (44) with the true incidence likely however to be higher with underreporting of subclinical / milder forms. Risk factors include nulliparity, male infants and twin pregnancies.

The presentation is similar to that of mitochondrial cytopathies (Reye's syndrome and tetracycline and sodium valproate toxicity) and an abnormality in mitochondrial Beta oxidation is a recognised cause of AFLP in a subset of cases. (43, 45). An abnormality in mitochondrial B oxidation is the recognised cause of AFLP. The enzyme long-chain 3-hydroxyacyl coenzyme A dehydrogenase is a key part of the mitochondrial trifunctional protein (MTP). (45) Neonates born to mothers with AFLP have been shown to have defects in B oxidation and to be deficient in long-chain 3-hydroxyacyl coenzyme A dehydrogenase due to mutation on one or both alleles of the α subunit of the trifunctional protein. Mothers of neonates with a long-chain 3-hydroxyacyl coenzyme A dehydrogenase deficiency have been shown to have a 79% chance of developing ALFP or HELLP. (45) Other reports have shown a 20-fold increased risk of maternal liver disease in pregnancy in foetuses with fatty acid oxidation defects. (46) The pathogenesis is that of foetal fatty acids accumulating due to the genetic defect and returning to the mother via the placenta. They are then deposited in the liver and present phenotypically as maternal liver disease.

The onset is usually between the 30^{th} and 38^{th} gestational week with a varied clinical presentation. Presenting features range from non-specific symptoms such as nausea, vomiting and abdominal pain to those of acute liver failure including hypoglycaemia, coagulopathy,

jaundice and encephalopathy. (19, 46) Pre-eclampsia is common but not invariable. (43) Risk factors include nulliparity, male infants and twin pregnancies. (47)

Biochemical changes include hyperbilirubinaemia, usually 6-8 times the upper limit of normal and a moderate transaminitis occurs usually less than 750IU/L. (5) In addition, serum ammonia, lactic acid and amino acid levels are increased reflecting mitochondrial failure. Renal dysfunction, leucocytosis and thrombocytopenia's are common. (5) The prothrombin time is prolonged and fibrinogen levels are reduced; disseminated intravascular coagulation is seen in approximately 10%. Other potential complications include ascites, pleural effusions, acute pancreatitis, respiratory and renal failure. Infections are common as is vaginal bleeding or bleeding from caesarean section wounds.

The definitive diagnosis of AFLP is made histologically. The characteristic findings are micro and macro vesicular fat droplets with ballooned hepatocytes containing dense central nuclei. The periportal areas are often spared. The microvacuoles may be clearly recognised only on fresh sections stained for fat with an oil red O stain. In severe cases hepatocytes necrosis can be seen. Recently clinical diagnostic criteria have been developed and validated for AFLP aiding rapid diagnosis without the need and associated risks of a liver biopsy. (19, 44)

Early recognition with rapid delivery of the foetus followed by maternal supportive care vastly improves prognosis for both the mother and the baby. (48) Maternal mortality rates have been reported to be as high as 92% prior to 1970, (49) but subsequently, overall mortality rates have improved, with rates of less than 10% reported in 2008. (42) The use of plasma exchange following delivery results in improved clinical outcomes including reduced maternal mortality in non-randomised clinical trials. (50-52) Successful liver transplantation in this group has been sporadically reported, however the indications for liver transplantation in this unique cohort remain so far undefined. (53, 54)

Table 1.3.3 Swansea diagnostic criteria for the diagnosis of acute fatty liver of pregnancy

Six or more of features below in the absence of other aetiology

- Vomiting
- Abdominal Pain
- Polydipsia / Polyuria
- Encephalopathy
- Bilirubin (>14 µmol/L)
- Hypoglycaemia (<4 mmol/L)
- Leucocytosis (>11x10^6/L)
- Elevated uric acid (>340 µmol/L)
- Elevated ammonia (>42IU/L)
- Ascites or bright liver on USS
- Elevated Transaminases (>42 IU/L)
- Renal impairment (Creatinine > 150 µmol/L)
- Coagulopathy (PT >14s or APTT >34s)
- Microvesicular steatosis on Biopsy

1.3.4 Hypertension related liver disease of pregnancy

Hypertension in pregnancy is defined as a blood pressure of greater than 140/90 mmHg on at least two occasions. The hypertension related complications of pregnancy include pre-eclampsia, eclampsia, hepatic infarction, hepatic rupture and the HELLP (haemolysis, elevated liver enzymes and low platelets) syndrome. Hypertension in pregnancy is associated with hepatological involvement ranging from mild abnormalities in the liver function tests to the ominous complications of hepatic haematoma and rupture.

1.3.5 Pre-eclampsia and eclampsia

Pre-eclampsia is a multisystem disorder defined as sustained hypertension after the 20th week of pregnancy (BP 140/90 or higher in a previously normotensive woman) and proteinuria (greater that 300mg in 24 hours). (55) It can present as late as 4 week's post-partum. (55) In a patient with pre-existing essential hypertension, preeclampsia is diagnosed if systolic blood pressure has increased by 30 mmHg or if diastolic blood pressure has increased by 15 mm Hg. (55) Pre-eclampsia affects between 3-5% of all pregnancies, and it occurs more commonly in women who are primiparous, those with multiple pregnancies and women at extremes of child-bearing age. (56) It also occurs more commonly in women with pre-existing hypertension, renal disease, diabetes mellitus and obesity, and in those with previously affected pregnancy or positive family history of pre-eclampsia. (55, 56) The presence of seizures differentiates pre-eclampsia from eclampsia. Pre-eclampsia and eclampsia were historically termed "toxaemia of pregnancy".

The aetiology of pre-eclampsia is incompletely understood and is thought to be multifactorial with evidence for several mechanisms including; immunological (impaired maternal tolerance against paternal and fetal antigens), abnormal trophoblastic invasion (57), genetic predisposition (58) and vascular dysfunction with a systemic imbalance between prosatcylin and thromboxane. (59-61) The trophoblast fails to invade the uterine lining, resulting in defective arterial placental perfusion which worsens as the pregnancy progresses and the demand on the placenta increases. (62) Nitric oxide, prostaglandins and endothelin from the placental tissue are released which induce platelet aggregation, endothelial dysfunction and arterial hypertension. Fibrin released from endothelial damage forms crosslinked networks in the small blood vessels resulting in a microangiopathic haemolytic anaemia. The pathogenesis of liver involvement is postulated to be secondary to fibrin deposition within the hepatic sinusoids resulting in sinusoidal obstruction and subsequent

hepatic ischaemia. It is the combination of hepatic sinusoidal obstruction and ischaemia that results in the feared complications of subcapsular haematomas, parenchymal haemorrhage and ultimately hepatic rupture. (63)

Clinical features of pre-eclampsia include right upper quadrant pain, headache, visual changes, nausea and vomiting. Many women are hyper-reflexic and oedema is common. Abnormal liver function tests are seen in about 30% of cases. Thrombocytopenia is also common. Liver biopsy is not indicated, but when performed shows characteristic periportal changes with haemorrhage, sinusoidal fibril deposition and hepatocyte necrosis. The derangement of LFT's in patients with pre-eclampsia and eclampsia should highlight the presence of severe disease and the need for emergency delivery should be considered. Delivery will result in resolution of the disease, although some cases worsen for several days postpartum. Women should be treated with glucocorticoids to enhance fetal lung maturation if the fetus is <34 weeks' gestation. If rapid hypertensive control and delivery is not achieved, women are at risk of renal dysfunction, cerebral haemorrhage, hepatic infarction, haematomas or rupture with markedly increased perinatal mortality and morbidity.

1.3.6 HELLP Syndrome

HELLP syndrome is the most common hepatic manifestation of the hypertensive related pregnancy complications. It was first describes by Weinstein in 1982 and occurs in approximately 10-20% of women with pre-eclampsia. (64-66) It carries with it a high infant mortality rate. (67) Although HELLP is recognised to complicate pre-eclampsia in up to 20% of cases, HELLP syndrome can occur in women with normal blood pressure and in the absence of proteinuria.

The diagnosis is based mainly on clinical grounds. The presenting symptoms are varied and include right upper quadrant or epigastric pain in approximately 65% of cases, nausea and vomiting (35% of cases), headache (31% of cases) and rarer complaints including bleeding and jaundice. (68) A significant number of patients are asymptomatic. (68) On examination hypertension is evident in up to 85% and proteinuria is common. Laboratory investigations show elevated transaminases (10-20 times the upper limit of normal), evidence of haemolysis with a raised lactate dehydrogenase (LDH), decreased haptoglobin and a mild increase in unconjugated bilirubin along with thrombocytopenia (usually less than 100x 10^9/L). (5) Disseminated intravascular coagulation can occur in which case there will be evidence of elevated fibrin degradation products, a low fibrinogen and a secondary rise in the prothrombin time.

There have been two classification systems developed for HELLP syndrome, the Tennessee and the Mississippi triple classification system. The Mississippi classification was initially developed in 1999 and revised in 2006. (65, 69) It classifies HELLP syndrome into 2 subsets. Class 1 requires the presence of severe thrombocytopenia (platelets ≤50x10^9/L), evidence of hepatic dysfunction (AST and/or ALT ≥70IU/L), and evidence suggestive of haemolysis (total serum LDH ≥600IU/L); class 2 requires similar criteria except thrombocytopemia is moderate (>50-100x10^9/L); and class 3 includes patients with mild thrombocytopenia (platelets 100-150x10^9/L), mild hepatic dysfunction (AST and/or ALT >40IU/L), and haemolysis (total serum LDH ≥600IU/L). (65) The Tennessee consists of two subsets, complete and partial. (70) Complete HELLP consists of demonstration of haemolysis on a peripheral blood film with a raised LDH >600 IU/L, thrombocytopenia <100x10^9/L and elevated transaminases AST>70IU/L. Partial HELLP syndrome is characterised by 1 or 2 of the above components. (70)

Table 1.3.6 Classification systems used in HELLP Syndrome

Tennessee Classification

- Complete HELLP requires all of
  - Haemolysis on peripheral blood film
  - AST >70 IU/L
  - LDH >600 IU/L
  - Platelets <100 x 10^9/L
- Partial HELLP requires 2 of
  - Haemolysis on peripheral blood film
  - AST >70 IU/L
  - LDH >600 IU/L
  - Platelets <100 x 10^9/L

Mississippi Classification:

- AST >40 IU/L and LDH > 600 IU/L and
  - Class I: Platelets <50 x10^9/L
  - Class II: Platelets 50-100 x10^9/L
  - Class III: Platelets 100-150 x10^9/L

Imaging of the abdomen should be considered in all women with HELLP and is imperative in those with abdominal pain, shoulder tip pain or hypotension. (71) This in to investigate for the feared complications of HELLP syndrome including hepatic haemorrhage, rupture and infarction which have been reported to occur in up to 45% of women with HELLP syndrome.

Liver biopsy is rarely undertaken as the diagnosis is based on clinical criteria and due to the risks of haemorrhage in association with co-existent thrombocytopenia. In cases where liver biopsy has been performed, the microscopic findings are similar to those seen in pre-eclampsia

consisting of periportal haemorrhage and fibrin deposition with periportal hepatocyte necrosis. Macro and micro vesicular fat is present but is usually modest in comparison to AFLP. (72)

In the majority of patients the above abnormalities resolve shortly after the delivery of the foetus, which is the treatment of choice. Untreated patients however can progress to hepatic and renal failure, hepatic rupture and ultimately death. Thus women with HELLP syndrome are often monitored in a high dependency unit. The management is supportive, and the foetus should be delivered as soon as possible by the safest route, especially if the foetus is beyond 34 weeks gestation, foetal distress in evident or there is evidence of maternal deterioration. Hypertension should be treated with labetalol. Patients may require coagulation support. If gestation is less than 34 weeks, corticosteroids should be given to promote foetal lung maturity. Outcomes at the more severe end of the spectrum are difficult to predict and prognostic information is limited to small series. (73, 74)

1.3.7 Hepatic rupture, Infarction and Haematoma

Hepatic haemorrhage and rupture can complicate pre-eclampsia, eclampsia, HELLP syndrome and patients with AFLP with a 50% mortality reported. (68) Patients present with abdominal pain, pyrexia and if severe hypovolaemic shock and cardiovascular collapse. Laboratory investigations reveal transaminases in the several thousands, leucocytosis and anaemia. Imaging in the form of computed tomography or magnetic resonance is the investigation of choice. (71) Contained haematomas can be managed conservatively with aggressive coagulation support, prophylactic antibiotics and transfusion as required. (75) If there is any evidence of haemodynamic instability, then urgent angiography with hepatic artery embolization and/or surgical intervention is warranted. Surgical intervention includes packing of the liver, hepatic artery ligation and resection. (71, 76)

Necrotic infarcts can also occur as a complication of pre-eclampsia. Patients often have an unexplained rise in their transaminases to several thousand, fever, anaemia and leucocytosis. There may be associated signs of liver failure. In the majority of cases the liver recovers however with areas of extensive infarct death from multi organ failure or hepatic rupture can ensue.

1.3.8 Acute liver failure in pregnancy

In the pregnancy specific liver diseases outlined above there is a wide spectrum of disease severity ranging from minor biochemical abnormalities to severe liver disease resulting in acute liver failure (ALF).

Acute liver failure is a clinical manifestation of a sudden and severe hepatic insult that can arise from many different causes. The abrupt loss of the hepatic metabolic and immunologic function results in hepatic encephalopathy, coagulopathy and progressive multi-organ failure. Acute liver failure in the United Kingdom is classified according to the time from insult to hepatic encephalopathy. The terms hyper acute, acute and subacute describe encephalopathy within 7 days, 8-28 days and more than 28 days respectively. (77) The natural history is variable and survival without liver transplantation (LT) ranges from 10-90% mostly dependent on the underlying aetiology, grade of encephalopathy and presence of multi organ failure. (78) Survival has been transformed by the introduction of emergency LT, which now forms part of the routine care for patients with ALF.

As survival from ALF is variable, identification and selection of those patients with ALF who are likely to benefit from emergency LT is crucial. Inaccurate selection criteria will result in subjecting a patient that would have recovered with medical management to a life of

immunosuppression, its side effects and increased mortality. Furthermore, failing to identify a patient with ALF who would survive only with LT, is meaning their death is inevitable.

Different selection criteria for emergency LT have been developed based on multivariate analysis of survival factors from non-transplanted patients with ALF. The original King's College criteria for non-paracetamol acute liver failure, identify patients with ALF early in their clinical course that are at high risk of death and thus may benefit from LT. (78) The criteria state that death is likely without LT if the patient is encephalopathic (any grade) with an INR of greater than 6.5, or any three parameters from the variables of age greater than 40 years, unfavourable aetiology, INR greater than 3.5, serum bilirubin greater than 300µmol/L or interval of jaundice to development of encephalopathy of greater than 7 days. (78) The Clichy-Villejuif criteria also identify patients with ALF at risk of death without LT. The criteria state that LT should be considered if there is the presence of grade 3 encephalopathy and factor V concentrations of less than 20% in patients aged less than 30 years or the presence of grade 3 encephalopathy and factor V concentrations of less than 30% in patients aged more than 30 years. (79)

In patients with pregnancy induced ALF, the King's College criteria have never been validated, nor indeed were any patients with pregnancy associated ALF included in the original cohort when the criteria were established. (78) This raises the question as to whether "standard" King's criteria are applicable for assessing poor prognosis and need for LT in this individual cohort of patients. Furthermore it suggests that patients with pregnancy induced ALF could be receiving unnecessary LT or perhaps more concerning we may be falsely reassured by those patients not meeting poor prognostic signs which have never been assessed or validated in this cohort.

Table 1.3.8: King's College Hospital poor prognostic criteria for non-paracetamol acute liver failure.

Kings College Criteria identify patients at risk of death without early liver transplantation in non-paracetamol-induced acute liver failure

EITHER both of

- Prothombin time (PT) >100s (INR > 6.5)
- Presence of hepatic encephalopathy

OR any encephalopathy plus any three of the following five criteria

- Patient age 40 years
- Serum bilirubin >300 µmol/L
- Duration of jaundice before the onset of encephalopathy >7 days
- PT >50s (INR > 3.5)
- Aetiology: non hepatitis A/B or drug-induced

1.3.9 Liver transplantation for the pregnancy specific liver disorders

Liver transplantation for pregnancy associated ALF is uncommon and information regarding the indications for and outcomes of transplantation is limited for both the patient and the graft. (53, 73, 80)

Reported literature on transplantation for both HELLP syndrome and AFLP is sparse. The largest single experience for HELLP syndrome consists of 7 patients. (80) A review of the published literature in 2008 found 9 reported cases, (81-86) and an addition 8 cases were identified from review of the united network for organ sharing (UNOS) database. (73) Of the 17

patients, a 17% overall mortality was reported. The authors suggested that the indications for LT in HELLP syndrome were; persistent bleeding despite surgical intervention, extensive liver necrosis or liver failure, whereas contained haematoma should be managed conservatively with close haemodynamic monitoring and repeated imaging. (87)

Reports of LT for AFLP are sporadic. (53, 54) Outcomes appear largely favourable. The European Liver Transplantation registry (ELTR) database has recorded the majority of all transplant activity since 1968. During this period there have been 6 LT's performed for AFLP confirming that LT is only undertaken in exceptional circumstances.

1.4 Cirrhosis in Pregnancy

1.4.1 Abnormalities in gonadal and sex hormones in cirrhosis

End-stage liver disease alters the physiology of the hypothalamic-pituitary-gonadal axis. The majority of the work highlighting the endocrine disorders that occur in conjunction with chronic liver disease has been carried out in men. In males, cirrhosis has been shown to be associated with reduced circulating testosterone, (88-90) low levels of gonadotrophins, luteinising hormone (LH) and follicle stimulating hormone (FHS), resulting in a hypogonadal state. In addition, serum oestrogens and prolactins are elevated in cirrhotic men which may further impact sexual dysfunction. (89, 91, 92) The above disorders in sex hormones can occur in any patient with cirrhosis, however it has been suggested that alcohol consumption may have additional detrimental effects on the hypothalamic-pituitary-gonadal axis. (92) Functional studies and questionnaire based studies report that erectile dysfunction is common in males with cirrhosis. Studies also report impotence rates of between 60-90%, reduced libido/interest in sex and a decreased volume of ejaculatory fluid. (89, 93)

In women with cirrhosis, fertility is reduced. This is due to a combination of metabolic endocrine, nutritional and sexual dysfunction. (94-98) The incidence of amenorrhoea / oligo amenorrhoea has been reported to be 60% in women of child bearing age awaiting liver transplantation. (99, 100) The cause for the amenorrhoea is complex. In women with cirrhosis like men, a reduction in the gonadotrophins (FSH and LH) has been demonstrated implying dysfunction of the hypothalamic-pituitary axis. (101) In cirrhotic patients, disruption of the hypothalamic-pituitary axis in conjunction with disturbed oestrogen metabolism occurs resulting in infertility. (97) Cundy et described 2 distinct hormonal profiles in women with cirrhosis and amenorrhoea. (97) The first suggests a hypothalamically driven process with low serum gonadotrophins, oestradiol and testosterone levels in association with a low body mass index. (97) This profile mimics those seen in patients with secondary amenorrhea due to

anorexia nervosa and suggests that chronic under-nutrition in patients with cirrhosis is likely to impact on fertility. The second is a cohort of patients with normal nutritional and gonadotrophin status. (97) This group has higher oestradiol and testosterone levels mimicking profiles seen in patients with amenorrhoea due to polycystic ovarian syndrome. Amenorrhoea and infertility driven by underlying cirrhosis is largely irreversible unless liver transplantation is performed. (96)

1.4.2 Sexual functioning in patients with cirrhosis

Chronic illness is acknowledged to be associated with sexual dysfunction. The cause for this is often multifactorial contributed to by the physical effects of illness such as malaise, fatigue and in males the presence of impotence. However a wider range of social and psychological factors including altered body image, lack of self-esteem, feelings of guilt and, for women, loss of their role as the primary care giver have all been reported as causes for decreased libido in association with chronic disease. (93)

In women with cirrhosis, sexual functioning has been largely over-looked. A recent study comprising of interviews on sexual function in 71 women undergoing assessment for liver transplantation reported that 56% had no sexual activity and 13% reported a decrease in sexual activity, with the greatest decrease being in those women with more severe liver disease as assessed by the model for end stage liver disease (MELD). (93)

Sexual interaction helps to foster and maintain long term secure relationships which help patients thrive after LT. Sexual health has been poorly studied in patients with chronic liver disease and also in those after LT, despite its importance to recipients and their partners. This is likely to reflect other demands on physician's time regarding assessment for LT or maintaining good graft function. In addition, academically it is a difficult area to study with sexual practices varying widely amongst patients, and finally the subject matter still has a taboo around it.

1.4.3 Assisted Conception

In light of the above physiological changes, women with cirrhosis can often have difficulty conceiving and request advice regarding assisted conception. To-date, no published data, information or guidelines exist regarding the maternal safety and success rates of assisted conception (AC) in this unique cohort. Theoretically pregnancy is likely to carry an unacceptable high risk (hepatic decompensation and death) especially in those patients with cirrhosis of a severity to impair ovulation. Furthermore the intense hormonal ovulation induction regimens may potentially have an adverse effect in patients with non-cirrhotic autoimmune and cholestatic liver disease and those following liver transplantation

Assisted conception in patients with liver disease raises questions with regards to what cohorts of patients with liver disease can be safely offered assisted conception and which cohorts does it confer and unacceptable risk.

1.4.4 Pathophysiology of pregnancy in women with cirrhosis

Cirrhosis is typically an irreversible, progressive disease where sustained damage to the hepatocytes results in fibrosis and nodular regeneration. The fibrotic liver causes an increase in pressure in the portal venous system causing shunting of the blood and extrahepatic collateral circulation. This results in loss of hepatic filtration of toxins in the blood, the development of ascites and the potential risk of haemorrhage from tortuous collaterals through the gastro-intestinal tract.

When pregnant, many physiological and hormonal changes occur within the human body including a rise in maternal metabolism, heart rate and cardiac output. The resultant changes in hepatic blood flow through the structurally abnormal liver during pregnancy results in a further increase in portal pressure and the development or worsening of varices and ascites

along with deficiencies in metabolism and excretion of substances normally cleared by the liver. In women with underlying cirrhosis these physiological changes result in increased demands on the liver putting the patient at risk of hepatic decompensation with the development of encephalopathy and ascites. Furthermore the increased circulating volume along with the direct pressure of the gravid uterus in the inferior vena cava results in a significantly increased risk of variceal haemorrhage.

1.4.5 Historical perspective of cirrhosis and pregnancy

Pregnancy in cirrhotic women is rare. This relates to a combination of metabolic, endocrine, nutritional and sexual dysfunction as outlined above. (94-98) Historically, women with cirrhosis have therefore been considered infertile, although occasional successful pregnancies have been reported. (102) Additionally, due to the undefined risks, women with cirrhosis were routinely advised against pregnancy by their physicians.

The first case in the published literature describing pregnancy in a women with underlying cirrhosis was reported in 1954. (103) Between this initial report and 1968 a total of 64 pregnancies were reported in 47 women. (104) A significant deterioration of liver function or gastrointestinal bleeding occurred in 32 out of the 47 women (68%).

In 1968, Whelton and Sherlock reported on the clinical course and outcome in 16 pregnancies in 13 women all with biopsy proven cirrhosis either secondary to “chronic active hepatitis” or primary biliary cirrhosis. (102) Foetal outcomes included 5 abortions (4 spontaneous), 3 still births, 1 neonatal death and 7 live births. Maternal outcomes included 1 death from hepatic failure at 30 weeks gestation, 1 episode of severe variceal bleeding at 5 months gestation requiring portocaval anastomosis and one episode of decompensation with the development of ascites. (102)

More than 25-years later, a further case series reporting on the outcomes of pregnancy in 11 women with cirrhosis between 1974 and 1992 was published. (105) In this series the foetal mortality was 8%, with 6 small for dates neonates and 3 premature births. Maternal complications were common with 6/11 (55%) experiencing a variceal bleed during pregnancy, 3 (27%) developing ascites and 3 (27%) developing a significant infectious puerperal complication. (105)

Although this historic information is useful, and undeniably tells us that pregnancy in women with cirrhosis carries a significant risk both for the mother and baby, its utility in the present day to provide preconception counselling to women with cirrhosis enquiring about pregnancy is limited. With current advances in neonatal intensive care and the routine administration of corticosteroids for foetal lung maturity in premature births, infant mortality rates are therefore likely to be lower than the above reported series. Moreover, maternal outcomes are likely to have improved with the advent of endoscopic techniques and a better understanding and treatment of the complications of cirrhosis. Unfortunately however, the optimal management of pregnancy in women with cirrhosis in the current day remains undefined. What still remains unclear is why some women with cirrhosis have an uneventful pregnancy whereas others are complicated by significant hepatic decompensation and death. Identifying those women with greatest risk of complications remains challenging.

1.4.6 Variceal Haemorrhage

Variceal bleeding is the leading cause of maternal mortality in patients with underlying cirrhosis. Overall, any patient with pre-existent varices will have between a 25-75% risk of developing an episode of variceal haemorrhage during pregnancy. (48, 106) Mortality from variceal bleeding in pregnancy has been reported to be between 18% and 50%. (48) Prognosis is significantly better in those women who bleed secondary to non-cirrhotic portal hypertension with mortality rates of between 2 and 6%, likely due to the absence of underlying synthetic liver dysfunction. (107) However these figures are from over 10-years ago and with the advent of new medications, improved endoscopic technique and radiologically placed shunts mortality is likely to have decreased considerably.

The optimal management of portal hypertension during pregnancy remains challenging with the absolute need for variceal screening during the second trimester, primary prophylaxis against variceal haemorrhage and the management of a variceal haemorrhage during pregnancy largely undefined. Management is based on best guess experience extrapolated from the non-pregnant literature. Pre-conception, in a patient with “at-risk” varices, prophylactic endoscopic band ligation of varices, although not proven, appears appropriate. (108) Case reports describing this strategy in pregnancy have been published, although no randomised trials have been carried out to prove efficacy.

The American Association for the Study of Liver Disease (AASLD) recommends that once pregnant, women with cirrhosis should have a screening endoscopy in the second trimester. (109, 110) This represents the time when portal pressure increases, due to increased circulation blood volume and direct compressive effects of the gravid uterus on the inferior vena cava. Previous studies have reported the prevalence of clinically significant varices in the second trimester to be in excess of 50% with the incidence of bleeding reported to be as high as 50%. (105, 111)

Treatment of an acute variceal bleed in pregnancy is essentially the same as in the non-pregnant patient. It includes resuscitation, stabilisation, correction of coagulopathy and close monitoring ideally in a critical care unit. Endoscopic intervention includes variceal banding or sclerotherapy to try and control bleeding. (112) The administration of vasopressin or synthetic analogues is not routinely advised because of their vasoconstrictive effects and associated uterine ischaemia. Upper gastrointestinal endoscopy appears safe during pregnancy, with the main reported risks being that of foetal hypoxia from sedative drugs or positioning. (113)

Insertion of radiologically or surgically porto-systemic shunts have been used as salvage therapy when endoscopic procedures have failed to control acute bleeding in cirrhotic patients, however consideration must be given to foetal radiation exposure. (102, 114, 115)

The mode of delivery in a woman with portal hypertension needs careful consideration. It is preferable to avoid excessive straining during labour in women with documented oesophageal varices, and a shortened second stage of labour is recommended, with forceps or ventouse-assisted delivery if needed. The need for Caesarean section remains controversial with one opinion being that it should only be performed according to obstetric indications, as women with cirrhosis are at increased risk of abdominal wall varices, bleeding during labour, poor wound healing and infection, (116) whereas other data suggests that variceal haemorrhage associated with labour remains a leading cause of morbidity and mortality in such women. (117)

1.4.7 Decompensation of pre-existing cirrhosis related to pregnancy

The changes in hepatic blood flow during pregnancy can result in an increase in portal pressure and ascites can develop. Due to the presence of portosystemic shunts and an increase

in baseline metabolism, products normally metabolised by the liver can increase, in particular ammonia, leading to encephalopathy.

As in non-pregnant patients, precipitants for encephalopathy include infection, constipation, gastrointestinal bleeding, electrolyte disturbance, dehydration, and medications including opiates and sedatives. (118) Management includes identification and treatment of any precipitant, whilst admitting the patient to a place of safety until the condition resolves. (118)

1.4.8 Prognostic models in cirrhosis and their wider utilisation

Cirrhosis is the end result of repeated hepatocellular damage from any aetiology. It is defined histologically as a diffuse process evidenced by bridging fibrosis and nodular regeneration. Clinically, cirrhosis can be divided into either “compensated” or “decompensated”, Compensated cirrhosis generally describes a patient with preserved synthetic function, without ascites of encephalopathy. Decompensated cirrhosis is defined by the presence of either ascites, encephalopathy, jaundice or variceal haemorrhage. This crude clinical differentiation is important as the presence of decompensation denotes a significantly reduced survival. (119)

A scoring classification system was developed in 1964 by Child and Turcotte to predict the survival of cirrhotic patients undergoing surgery for portal hypertension. (120) The score included bilirubin and albumin along with the presence of ascites, encephalopathy and nutritional status. A modified version was developed in 1973, where nutritional status was replaced by prothrombin time. (121) Since this time further studies have shown that the “Child Pugh” (CP) score can be used to predict prognosis in a variety of clinical settings including ascites, (122) variceal haemorrhage, (123) suitability for resection of hepatocellular carcinoma, (124) non-hepatic surgery (125) and assess need for liver transplantation. Although the CP score

is used extensively in clinical practice, it does have several limitations. Firstly the presence and severity of encephalopathy and ascites is subjective. Secondly each result is grouped with an empirical cut off and thirdly all variables are equally weighted.

Various newer more sensitive and specific scoring systems now exist in clinical practice to assess the severity of cirrhosis. These include the model of end stage liver disease (MELD), Meld Sodium (MELD-Na) and the United Kingdom End Stage Liver Disease (UKELD). (126-130)

Table 1.4.8: Prognostic models used to assess risk in cirrhotic liver disease

MELD	= {(0.957 x loge creat mg/dl) + 0.378 x (loge br mg/dl) + (1.120 x loge
MELD Na	= MELD − Na − [0.025 × MELD × (140 − Na)] + 140 **(**where the Na concentration was bound between 125 and 140 mEq/L)
UKELD	= 5 x {1.5 x log(INR) + 0.3 x log(creat) + 0.6 x log(br) - 13 x ln(Na)+70} (where INR = International normalized ratio, Creat = serum creatinine (umol/l), Br = serum bilirubin (umol/l), Na = serum sodium (mmol/l)

The MELD score was initially developed to predict mortality following transjugular intrahepatic portosystemic shunt (TIPS) insertion. (126, 127) This scoring system is now widely used in clinical practice to predict prognosis in patients with cirrhosis and to help guide listing for, and in some institutions allocation of organs in liver transplantation. (128, 131) Recently, its utility has also been extended to predict outcome in other clinical scenarios including alcoholic

hepatitis, paracetamol induced liver injury, acute liver failure and survival following non liver related surgery in cirrhosis. (132-136)

The United Kingdom End Stage Liver Disease score is a validated scoring system which incorporates INR, serum creatinine, bilirubin and sodium. (130) The UKELD has been compared to MELD and MELD-Na.in a cohort of 452 UK transplant waiting list patients and was shown to be a superior predictor transplant list mortality. These finding have never been confirmed in additional or non UK cohorts. (130, 137)

1.4.9 Defining the risk of pregnancy in cirrhotic patients

As outlined above, in women with cirrhosis who are contemplating pregnancy there is a significant increased risk of complications and death. At present preconception counselling is based on historic case reports and series. The reported series do not take into account the severity of the underlying liver disease which is likely to be a significant factor in the incidence of complications. Thus women are given generic, non-specific information with regards to their individual risk.

The use of MELD or other scoring systems in predicting obstetric, foetal and maternal outcome in cirrhotic patients who become pregnant has not been assessed. In light of their widening use in other aspects of liver disease their use in predicting outcomes in cirrhotic patients who become pregnant may be of value.

1.5 Pregnancy in specific chronic liver disease states

1.5.1 Autoimmune Hepatitis

Autoimmune hepatitis (AIH) is a disorder that has been recognised for over 50 years. First described by Waldenstrom in the early 1950's as a chronic form of hepatitis with a classical phenotype of liver disease in a younger aged women, often in conjunction with extra-hepatic manifestations including arthralgia, endocrine abnormalities and amenorrhoea. (138) Reports regarding pregnancy in patients with AIH exist from as early as the 1970's but the reported outcomes were largely unfavourable, with a high incidence of obstetric complications noted including early foetal loss, prematurity, low birth weight and a high rate of caesarean sections. (102, 139) Moreover maternal complications included pre-eclampsia, flares in disease activity, hepatic decompensation and death. (102, 139)

Subsequent to these initial reports, there have been several recent case series indicating more favourable outcomes. (14, 140-142) Combining the largest 4 series in the published literature on AIH and pregnancy gives data on 142 conceptions. (14, 140-142) The maternal outcomes reported are largely favourable; however pregnancy is not without risk to the mother with 3 reports of hepatic decompensation, 1 liver transplant and 3 maternal deaths (1 liver related) all related to pregnancy. (14, 140-142) Foetal outcomes are favourable with a heathy infant expected in the majority of patients and live birth rates reported to be between 71% and 86%. (14, 140-142) These live birth rates are comparable to patients with other autoimmune conditions, but remain lower than the reported live birth rates for the general population. (143)

Despite our increase in knowledge surrounding the management of AIH during pregnancy, several concerns remain. Flares in disease activity have been reported to occur in 7-21% of patients within the gestational period and occur at a rate varying from 11-86% in the post-partum period. (14, 140-142) In the majority of patients a flare can be controlled by augmentation of the immunosuppression however, in rare cases, a flare can lead to hepatic decompensation with the potential need for liver transplantation (LT) or death of the patient and/or foetus. (140, 142)

Distinguishing between which patients are likely to have an uneventful pregnancy and those at risk of the above complications is currently challenging. In addition, the optimal therapeutic regimen to prevent disease flares remains undefined, with some centres discontinuing azathioprine due to a theoretical risk of birth anomalies, (141) whilst others continue it throughout pregnancy to minimise the potential risk of a flare in AIH activity. (140, 142) Finally, in those patients with underlying cirrhosis who become pregnant, there are likely to be additional maternal and foetal risks including a higher incidence of maternal decompensation, significant variceal / post-partum bleeding and foetal prematurity. (48, 144) The safety of pregnancy in patients with AIH and underlying cirrhosis remains undefined and the published literature is sparse.

1.5.2 Primary sclerosing cholangitis

Primary sclerosing cholangitis (PSC) is a chronic inflammatory condition of unknown cause, affecting all parts of the biliary tree. (145) The natural history is that of progressive obliteration of the bile ducts resulting in biliary cirrhosis, hepatic failure and potentially chalangiogcarcinoma. (145) The onset is usually between 25-45 years and although more common in men effected females are of childbearing age. (145)

The aetiology and pathogenesis of PSC is incompletely understood. A variety of causative mechanisms have been postulated including exposure of the biliary epithelium to toxins, infectious processes and ischaemia. (145) In addition genetic and autoimmune factors may play a role. The evidence for an autoimmune/immune mediated aetiology is favoured by its strong association with inflammatory bowel disease, the increased frequency of serum auto-antibodies, (146) elevated levels of circulating immune complexes (147, 148) and disordered cellular immune function. (149) Pregnancy has been shown to affect the course of autoimmune conditions including systemic lupus erythematosus, rheumatoid arthritis and AIH. (16, 140, 150) Information regarding the outcomes and risks of pregnancy for the mother and baby and the effect of pregnancy on the natural history of PSC is sparse. This renders the counselling and management of young patients wanting or reporting pregnancy difficult.

On reviewing the published literature, case reports give varied outcomes ranging from severe foetal complications including placental haemorrhage, spontaneous rupture of membranes and foetal bradycardia to healthy term infants. The effect of pregnancy on maternal disease varies from improvement in cholestasis to pruritus and evolvement of dominant strictures. (151-153) There have been two case series on pregnancy in patients with PSC published. The first by Janczewska et al described 13 pregnancies in 10 women (4 with cirrhosis). (154) The outcomes were favourable with no foetal losses reported and no significant deterioration in maternal liver function tests. Wellge et al describe 25 patients in 17 female PSC patients. (155) No serious maternal complications were reported although serum liver tests increased markedly (twice baseline) in 20% during the gestational period and 32% in the post-partum period. The foetal loss rate was 16% and there were 2 preterm deliveries. (155) Interestingly, in the two reports, pruritus was the most common complaint affecting 11/27 women and often worsened in the third trimester with difficulty distinguishing it from IHCP. (154, 155) Polymorphisms in the ABCB4 gene are common to both conditions and raise the question as to whether IHCP is more common in patients with PSC. (41, 156)

1.5.3 Primary Biliary Cirrhosis

Primary Biliary Cirrhosis (PBC) is an autoimmune liver disease that generally effects middle aged women. (157) It is characterised by a chronic inflammatory destruction of the interlobular and septal bile ducts that results in chronic cholestasis and biliary cirrhosis and portal hypertension. It is an autoimmune disorder characterised by highly specific autoantibodies, activated T cells in areas of bile duct destruction and association with autoimmune disorders. (157) The disease had predominance for women with a female to male ratio of 9:1 and a median range of onset of 50-years.

Information regarding pregnancy in women with PBC is rare, as PBC is a condition that typically has been described to effecting middle aged women and furthermore, historically women with pruritus were advised against pregnancy. Over the last decade several normal deliveries have been reported in women with PBC without an obvious effect on the underlying liver disease. (158-161) Poupon et al described 9 pregnancies in 6 patients with PBC, in which there were no foetal losses, a median gestation of 37 weeks and all infants healthy at 4 years follow-up. (160) Maternal outcomes were also favourable, with all mothers remaining asymptomatic throughout pregnancy. Interestingly, in contrast to case series reported in women with PSC, (155) in this small series cholestatic parameters and mitochondrial antibody titres fell in all women during the gestational period. (160) However in the first three months postpartum, cholestatic parameters deteriorated in all cases but subsequently returned to preconception values. (160) A recent publication has confirmed the above findings, reporting a favourable safety profile in pregnant women with PBC with a tendency to a post-partum flare in cholestatic parameters. (162)

1.5.4 Overlap syndromes

Overlap syndromes encompass variant forms of the hepatic autoimmune diseases

including AIH, PBC, and PSC. Patients with these variant syndromes usually have a mixture of hepatic and cholestatic features on biochemical, radiological and histological investigations. Generally about 10% of patients with AIH will have co-existent features suggestive of PBC and 8% features of PSC. (163)

Autoimmune sclerosing cholangitis (AISC) is an overlap syndrome between autoimmune hepatitis (AIH) and primary sclerosing cholangitis (PSC), predominantly occurring in children. (164) Fifty five percent of patients effected are female. (164) Patients present with serological and histological features of AIH, (165) but cholangiographic features of PSC, (145) usually to a less advanced degree than those observed in adult primary sclerosing cholangitis. (166) Immunosuppression (azathioprine and prednisolone) usually controls the inflammatory component but has little effect on the bile duct disease and for that reason ursodeoxycholic acid (20-30mg/kg) is usually used in conjunction. The medium term prognosis is good with survival into adulthood expected, (166) and with this many women have the desire to become pregnant. The effect of pregnancy in women with AIDC, and indeed other overlap syndromes is undefined both in relation to maternal, foetal and disease outcomes.

1.5.5 Budd Chiari Syndrome

The Budd-Chiari syndrome (BCS) results from obstruction to hepatic venous outflow, usually secondary to hepatic vein thrombosis. Several associated underlying pro-thrombotic aetiological factors have been identified with the most common being an overt myeloproliferative disorder (MPD). Pregnancy itself is a hyper-coaguable condition and BCS can present de-novo in association with pregnancy.

Historically, reports of BCS in association with pregnancy were associated with poor outcomes for the foetus and death of the mother from hepatic failure or portal hypertension being common. The standard treatment for BCS has been refined over several decades with survival

rates improving from 50% to 90% 5-year survival. These survival rates have been mirrored in the survival of pregnant women with BCS. A recent report of 7 cases of BCS in association with pregnancy reported survival in all mothers, but poor foetal outcomes remained with 3 miscarriages and 1 intrauterine death. Interestingly 6/7 women had evidence of an underlying pro-coagulant factor in addition to pregnancy when tested. This data suggests that de-novo BCS in pregnancy is unlikely to occur without the presence of an additional underlying pro-thrombotic tendency.

In light of the increasing survival of young women with BCS, the desire for pregnancy often occurs once their underlying condition has improved. Successful pregnancies have been reported following a diagnosis of BCS, however the pro-thrombotic risk pregnancy confers means there is a theoretical risk of BCS recurrence. In a recent series, 24 pregnancies were reported in 16 women previously diagnosed and treated for BCS. Maternal outcomes were good, with no reported mortality, 3 pregnancy related thrombotic episodes and an increased risk gynaecological bleeding. Foetal outcomes were less favourable were less with 7/24 foetal losses and 12/17 live births born prematurely.

1.6 Pregnancy and Liver Transplantation

1.6.1 Sexual function and fertility following LT

Liver transplantation has evolved over several decades to become a universally accepted treatment for patients with ALF and chronic end-stage liver disease which is refractory to medical treatment. Survival following LT have steadily improved over the last 2 decades, with current five-year survival rates reported to be in excess of 70% with long term survival expected in the majority. (167, 168) As survival rates following LT continue to improve, the goal of transplantation in the current day is not only to ensure survival but to also to attain a quality of life (QOL) for patients similar to their pre-morbid state. (169) Tools used to assess the success of LT are now incorporating QOL parameters such as physical, psychological, social and sexual function along with medical parameters such as graft and patient survival. Several studies have demonstrated that general QOL improves dramatically after LT. (170-172) A recent meta-analysis identified 44 longitudinal QOL studies, which incorporated 4381 patients, looking at pre and post LT outcomes. (173) General QOL ($p<0.0001$), social functioning ($p<0.0001$), physical health ($p<0.0001$) and psychological health ($p=0.014$) were all significantly improved by LT. Interestingly sexual function, which was assessed in 12 of the included studies was not found to be significantly different pre and post LT ($p=0.58$). (173)

Three studies have been published specifically addressing sexual function in women following liver transplantation. The first included 28 female LT recipients, where 71% were sexually active with 75% having weekly intercourse following LT. (174) The second by Ho et al. is less favourable with data on 62 female LT patients where problems with libido (26%), dyspareunia (40%) and inability to reach orgasm (26%) were described. (175) Patients attributed their sexual problems to side effects of medications, liver disease, and depression. A third study by Sorrell and Brown, assessed the prevalence of sexual dysfunction in 71 women presenting for LT assessment and then followed 14 of the same women post LT. (93) In women pre LT, 56%

were not sexually active at the time of assessment and 42% described decreased interest in sex. Following LT, 8/14 women had a sexual partner of whom 50% were sexually active. (93) The data from the second two studies suggest that the expectation that sexual function will recover post LT may be misplaced in certain patients and is more complex process involving general health, age, psychological, emotional and social factors.

Functionally in males, abnormalities in the hypothalamic-pituitary-gonadal axis are reversed post LT. (91, 176) In women similar studies have not been formally done, however, the majority of women of child-bearing age will recover regular menstrual bleeding within one year post-transplant, indicating that similar hormonal changes in females occur post LT. (96, 99, 177)

Transplant teams should endeavour to discuss sexual health, fertility and pregnancy as a sexual relationship and a family help promote feelings of self-worth, stability and confidence, all of which will help create a better QOL following LT.

1.6.2 Pregnancy Post Liver Transplantation

The first successful pregnancy following LT was reported 1978, with a healthy boy delivered at 40.5 weeks gestation, weighing 2,400g, with both the mother and baby in excellent health 1-year post-delivery. (178) Subsequent to this many case series have been reported, which have expanded our knowledge regarding the safety and outcomes pregnancy post LT. (179-182) Overall, the outcomes are largely favourable, with a healthy neonate and stable graft function expected in the majority. (179, 180) However, available data suggests that pregnancy in LT recipients can be associated with unpredictable graft deterioration, an increased risk of pre-eclampsia and diabetes in the mother. For the foetus prematurity, low birth weight with the potential for long term disability exists.

1.6.3 Graft Function

Pregnancy is associated with an increased risk of an episode of acute cellular rejection (ACR). In the gestational period, case series have reported the incidence of graft rejection to be between 10 and 17%. (179-183) Post-partum, the incidence is lower with reports of between 3 and 12%. (179-181) The majority appear to be easily controlled with baseline immunosuppression augmentation or intravenous methylprednisolone. Graft loss directly related to ACR in pregnancy is very rare, although reports of pregnancy termination as a consequence of deteriorating graft function exist. (179)

The timing of pregnancy appears important in relation to episodes of ACR. Published data has suggested that delaying pregnancy for at least 12 months following LT is associated with a lower risk of ACR. (179) This strategy is supported by the National Transplant Pregnancy Register (NTPR) in the USA, which gives data regarding pregnancy outcomes in 189 patients following LT. (184) The rationale is thought that by delaying pregnancy for a year post-LT allows stability of graft function and immunosuppression levels along with a reduction in the incidence of opportunistic infections and surgical complications.

The reason for increased rejection risk during the gestational period is unexplained. Pregnancy leads to a period of immunological tolerance, as previously discussed, in order for mother to tolerate the paternal antigens expressed by the foetus. Thus one may expect episodes of graft rejection to be less common during pregnancy.

1.6.4 Maternal Risk during pregnancy following Liver Transplantation

The most common maternal complications encountered during pregnancy following liver transplantation are hypertension, pre-eclampsia and eclampsia. (90, 179) The incidence of pre-eclampsia and eclampsia combined has been reported to be between 14% and 23%. (179, 181, 185) Similar levels of hypertensive related complications are seen in the renal transplant population. The reason for the increase in pregnancy related hypertension disorders is likely to be multi-factorial incorporating the direct nephrotoxic effects of calcineurin inhibitors, chronic corticosteroid usage and an increased incidence of underlying renal dysfunction. (184)

Other less common maternal risks include risk of bacterial and viral infections (27%) secondary to immunosuppression and a potential increased risk of gestational diabetes (5%) related to tacrolimus medication. (184-186)

1.6.5 Foetal Risk during pregnancy following Liver Transplantation

A live birth rate of 73%, a spontaneous abortion rate of 19% and therapeutic abortion rate of 6% has been reported by the NPTR. (187) The prevalence of prematurity and low birth weight is significantly higher than the general population. The NTPR reports a premature birth rate of 30% with low birth weight effecting 30% of neonates. (186) Although it is postulated that this is likely to reflect maternal complications explained above, this has not been conclusively demonstrated.

1.6.6 Mode of Delivery

Caesarean section rates are much higher in LT recipients than the general population, with published series suggesting rates of between 35-63%. (179, 180, 186, 188) The reason for this remains unclear but may reflect the higher incidence of hypertensive related complications and thus the need for earlier delivery. Moreover, the range in caesarean section rates varies from different institutions and relate to obstetric experience or era effect in the obstetric management of post LT pregnancies.

1.6.7 Immunosuppression Risk

Data regarding the safety of medications commonly used in patients post LT during pregnancy is scarce. Most of our information is obtained from its use in patients with other disease entities such as inflammatory bowel disease or other solid organ transplant cohorts. The United States Food and Drug Administration (FDA) categorise the safety of drugs in pregnancy based on available evidence. The categories are presented below.

Table 1.6.7: The United States Food and Drug Administration categories of the safety of drugs in pregnancy

Pregnancy Category	Description
A	Adequate and well-controlled studies have failed to demonstrate a risk to the fetus in the first trimester of pregnancy (and there is no evidence of risk in later trimesters).
B	Animal reproduction studies have failed to demonstrate a risk to the fetus and there are no adequate and well-controlled studies in pregnant women.
C	Animal reproduction studies have shown an adverse effect on the fetus and there are no adequate and well-controlled studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
D	There is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience or studies in humans, but potential benefits may warrant use of the drug in pregnant women despite potential risks.
X	Studies in animals or humans have demonstrated fetal abnormalities and/or there is positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in use of the drug in pregnant women clearly outweigh potential benefits.
N	FDA has not classified the drug.

1.6.7.1 Corticosteroids

Prednisolone can cross the placenta, thus potentially exposing the foetus to adverse effects of the drug. (189) The major foetal risks regarding steroids are cleft palate (particularly with high dose exposure in the first trimester), premature rupture of the membranes and intrauterine growth restriction. (IUGR) (190, 191) Reports of low birth weight and IUGR associated with steroid usage during pregnancy are confounded by the severity of underlying disease necessitating corticosteroid therapy. In addition, foetal adrenal hypoplasia and suppression of the foetal pituitary have also been described, although both are uncommon due to the rapid maternal metabolism and placental breakdown of corticosteroids. Prednisolone is considered a class B drug in terms of its risk for pregnancy by the FDA.

Overall, it is generally accepted amongst experts that maintenance of graft tolerance and prevention of rejection is crucial and that risks associated with steroids are outweighed by the benefit of good disease control. Thus, any maintenance prednisolone should be continued throughout pregnancy.

1.6.7.2 Cyclosporine

The teratogenic potential of cyclosporine appears low. A meta-analysis of 15 studies including 410 women on cyclosporine reported major malformations rate of 4.1%. This is not significantly different from that reported in the general population. (192) The meta-analysis concluded that cyclosporine does not appear to be teratogenic, however, increased rates of prematurity, low birth rate and neonatal hyperkalaemia were reported. Cyclosporine has been assigned to pregnancy category C by the FDA, Cyclosporine should be given during pregnancy only when benefit outweighs risk.

1.6.7.3 Tacrolimus

In the last decade, tacrolimus has been used routinely in the post-transplant setting and consequently data regarding its safety in pregnancy is emerging. The neonatal malformation rate in reported series is approximately 4%, which is similar to the risk associated with cyclosporine. (179, 188, 192) In LT recipients Jain et al. described 49 pregnancies on tacrolimus. (180) They reported a congenital abnormality rate of 2/49 (4%), consisting of a tracheoesophageal fistula and valvular heart disease in one baby and non-functioning kidney in the second. Tacrolimus is considered a class C drug in terms of its risk in pregnancy by the FDA.

1.6.7.4 Mycophenolate mofetil

Mycophenolate mofetil (MMF), an inhibitor of purine biosynthesis, has been shown to cause abnormal development of ova in animal models and therefore is potentially teratogenic. (193) A recent review of data of 119 human pregnancies with maternal exposure to MMF found outcome data for 65 and demonstrated a live birth rate of only 34% with miscarriage occurring in 31% and elective abortion in 20%. (194) The rate of congenital abnormalities, at 15%, was higher than that seen in the general population. (194) The most frequent congenital abnormalities reported included external ear and other facial malformations such as cleft lip and palate. Thus when women of child bearing age are commenced on MMF they should be counselled regarding its safety in pregnancy. If they wish to become pregnant the drug must be discontinued with at least a 6 month wash out period before conception. MMF is considered by the FDA a class D drug in terms of the risks associated with its use in pregnancy.

1.6.7.5 Azathioprine

In animal models, azathioprine has been associated with skeletal abnormalities, cleft palate, hydrops fetalis and haemopoetic abnormalities of the foetus. (195, 196) In humans, lymphopenia, hypogammaglobulinaemia and thymic hypoplasia have all been reported in children born to mothers on azathioprine. However, these latter changes seem to all be reversible after birth with no long-term effects on the child. Furthermore, azathioprine has been linked to pre-term deliveries, (197) and in light of the above reports, physicians historically recommended patients with AIH to discontinue azathioprine if they were trying to conceive.

Recently, experience with azathioprine in pregnancy has increased dramatically with information derived from other patient populations especially those with inflammatory bowel disease, rheumatoid arthritis and patients following solid organ transplantation. (140) In light of

the above studies, it is generally recommended that azathioprine therapy should be continued during pregnancy, at the same dose used to maintain stable graft function. At present no evidence exists to suggest that discontinuing the azathioprine for the gestational period is beneficial for the mother or foetal outcomes.

Azathioprine is classified as a Food and Drug administration (FDA) category as class D, which states that positive evidence of risk to the foetus exists, but it is accepted that as in many medical conditions the potential benefits of its use throughout pregnancy may outweigh the risk.

1.6.8 Breast Feeding

Most physicians advise against breastfeeding due to concerns over the safety of neonatal exposure to immunosuppressants. Corticosteroids, azathioprine and tacrolimus are all known to be excreted in breast milk. Corticosteroids, however, are excreted in extremely low concentrations and are felt to be safe during breastfeeding. (198) Meanwhile, both azathioprine and tacrolimus levels are excreted in breast milk and in some cases levels are equivalent to, or even exceed that of maternal plasma and are therefore contra-indicated. (199)

Chapter 2: Aims of Thesis

2.0 General

As highlighted in the introductory chapter of this thesis, the available literature to guide the management of patients in pregnancy is sparse and for the majority of women with liver disease information regarding pregnancy is limited to case reports and small case series only. This has resulted in generic advice being given regarding the risks / safety of pregnancy. In light of the fact that underlying "liver disease" represents a spectrum of severity generic advice regarding risk is clearly not appropriate for all women. Combining this with the fact that there are a wide variety of disease aetiologies that are likely to respond differently to pregnancy, further evaluation of these unique cohorts of women is needed.

Additionally, acute liver failure in pregnancy is rare, and again the published literature regarding poor prognostic outcomes and indications for consideration of liver transplantation is extremely limited. Further work delineating maternal risk is needed along with an assessment of whether current prognostic criteria is used to guide consideration of liver transplantation is applicable.

The overall aim of this thesis is to improve the understanding regarding the outcomes of pregnancy in patients with pre-existing liver disease and those who develop liver disease specifically related to the pregnant state. Specific attention is given to different underlying liver conditions and prediction of complications based on preconception parameters. It is postulated that this work will improve the preconception counselling that patients with liver disease receive, the management and monitoring during pregnancy and ultimately lead to an improvement in outcomes for the mother, foetus and the liver. In light of the above the overall aims of this thesis are to:

1) Develop a better understanding of the effect of pregnancy in women with liver disease with regard to maternal, foetal and hepatological risk

2) Try to identify whether there are any objective preconception factors that may indicate increased risk to mother, baby and liver

3) Assess if there are any disease specific risks associated with pregnancy with respect to the underlying hepatological pathway i.e. autoimmune disease, women with cirrhosis, women post liver transplantations and again whether these can be predicted prior to conception.

4) Identify any poor prognostic factors associated with pregnancy induced acute liver failure and whether in this setting standard liver transplant listing criteria are applicable.

To address this further, five areas have been evaluated and the specific aims are presented in the subsequent chapters.

Chapter 3: Patients and Methods

3.1 General

The Institute of Liver Studies at King's College Hospital is a tertiary referral centre for patients with liver disease of any aetiology. A variety of comprehensive databases of patient information detailing those seen or admitted at the Institute of Liver Studies have been kept dating back to as far as 1979.

These databases briefly consist of HepBase, which is a prospectively collated database of all patients seen at the institute of liver studies dating from 1980 until 2009. HepBase includes patient's clinical letters, bloods, histopathology reports and discharge summaries detailing any inpatient admissions.

MEDTRACK represents a physiological database, whereby data is entered daily on all patients who are admitted to the liver intensive care unit. This details information including organ status, and need for organ support. It also includes physiological parameters and aetiology.

An additional liver intensive care data-base detailing all patients admitted with acute or acute on chronic liver disease detailing the cause of liver disease / failure, admission parameters including bloods, lactate, encephalopathy and outcome data including survival and liver transplantation.

A dedicated autoimmune hepatitis database which includes information detailing patient's presentation, management and medication, survival and complications.

Finally a database regarding all liver transplant activity within the institute of liver studies detailing the indication for liver transplantation and survival following liver transplantation.

3.2 Selection of patients

The above databases were interrogated using search terms including “pregnancy”, “conception”, “Miscarriage”, ”abortion”, “termination”, “in vitro fertilisation”, “assisted conception”, “HELLP syndrome”, “AFLP” and “live birth”. A comprehensive master database of all women who were under the care of, or had been seen at the ILS whom had conceived or wanted to conceive was compiled. This method was thought to be the best way of identifying all patients which either chronic liver disease who had become / wanted to become pregnant and those who had developed acute liver injury as a result of pregnancy and transferred to the liver intensive care unit at King’s College Hospital. Whilst many patients were identified on repeated occasions from different databases, it was felt this was the most comprehensive method to ensure that minimal patients were missed.

The master database is therefore a collection of all patients with liver disease and pregnancy who have been seen at the ILS, King’s college Hospital over the last 2 decades. The retrospective collection of data was felt to be the most suitable to address the main aims of this thesis as pregnancy in liver disease is relatively rare, and a prospective study was thought not to allow sufficient patient numbers to allow the aims of this thesis to be addressed within the time frame available. Before data collection was commenced, a sample year of all patients seen at the ILS was reviewed and it confirmed that prospective collection of data would not allow a sufficient number of patients to be identified in order to achieve the main aims of this thesis.

From the master database of patients with liver disease and pregnancy, the patients were then subdivided into specific groups in order to gather more clinical information and answer the aims of the thesis as described in chapter 2. Patients were divided into those with pregnancy induced acute liver injury, cirrhosis, autoimmune hepatitis, post liver transplantation, cholestatic liver diseases and those undergoing assisted conception. The clinical records of all patients were reviewed and relevant data pertaining to the aims of this study were extracted.

3.3 Extraction of data

To address the aims specific to women with pregnancy associated acute liver failure, information was obtained detailing maternal age, previous pregnancy details, maternal comorbidities, presentation details, diagnosis as based on Swansea / Mississippi criteria for HELLP and AFLP, delivery details, foetal outcomes (gestation, survival, complications), admission haematological and biochemical results, lactate, presence of encephalopathy, ascites, organ support, bleeding, need for surgery, listed for transplantation, survival and length of stay. In those patients listed for transplantation the indications for listing were reviewed. The above information was recorded on a database with no patient identifiable information.

To assess pregnancy risk and outcome in mothers with established cirrhosis and to answer the aims laid out for this cohort of women, all women with either histopathological evidence of cirrhosis or evidence of cirrhosis based on a combination of radiological and biochemical tests were selected from the master database. The clinical and electronic notes were reviewed and data was extracted. In particular information regarding maternal age, previous pregnancies, cause of cirrhosis, diagnosis of cirrhosis (histological vs radiological and biochemical), maternal co-morbidity, previous maternal decompensation, presence of varices, bloods at clinic appointment prior to conception, assisted conception and whether the pregnancy was planned. Foetal outcomes were collected with regards to miscarriage and gestational week, termination of pregnancy, liver birth and gestational week, mode of delivery, birth weight, admission to special care baby unit and congenital abnormalities. Maternal outcomes were collated including variceal screening, decompensation (variceal bleeding, encephalopathy, ascites) need for intensive care support, need for liver transplantation and maternal death.

To assess pregnancy risk and outcome in mothers with autoimmune hepatitis and to try and address the aims laid for this cohort of women, all women with AIH was defined by the

revised International Autoimmune Hepatitis Group were selected from the master database. Baseline characteristics were obtained from the medical notes and from investigations performed at the clinic visit immediately prior to conception being reported. Particular information gathered included maternal age at conception, duration of AIH prior to conception, frequency and severity of flares in AIH activity prior to conception, baseline biochemical and haematological data, presence of cirrhosis, assisted conception, presence of portal hypertension, details of previous hepatic decompensation (variceal bleeding, encephalopathy, ascites) and medication details including termination of pregnancy, miscarriage, gestational week, mode of delivery, gestation for live births, foetal weight, need for admission to special care baby unit and presence of any congenital abnormalities or developmental delays. Maternal outcomes were collected and included information pertaining to flare in AIH activity and timing of flare in relation to pregnancy (gestational week / post-partum), peak abnormalities in biochemical parameters during a flare, medication augmentation and details, response to augmentation, evidence of hepatic decompensation (variceal bleeding, encephalopathy, ascites), intensive are admission, need for liver transplantation and death.

To assess pregnancy risk and outcome in mothers following liver transplantation and to answer the aims laid for this cohort of women all women who had undergone liver transplantation were selected from the master database. The clinical and electronic records were reviewed and data was extracted from the medical notes and from investigations performed at the clinical visit immediately prior to conception being reported. Specific data collected included maternal age at conception, data of liver transplant, and indication for transplantation, time interval between liver transplantation and conception and presence of any maternal comorbidities. Maternal therapy was recorded detailing immunosuppressive therapy, including specific drugs, doses and any changes made prior, during or after pregnancy. Data regarding foetal outcomes was gathered to include miscarriage and gestational week, termination of pregnancy and indication, live birth and gestational week, mode of delivery,

indication for caesarean section, birth weight, need for admission to a special care baby unit, and presence of any congenital abnormalities or developmental abnormalities. Maternal data detailing outcomes was collected to include maternal complications during pregnancy (hypertension, pre-eclampsia, eclampsia, renal failure, sepsis, gestational diabetes) and death. Information regarding graft rejection was gathered to include timing of rejection, diagnosis of rejection (biopsy proven vs. clinical), treatment of rejection and graft loss.

To assess the effect of pregnancy in rarer cohorts including those women with AISC or cholestatic liver dysfunction these women were first identified form the master database. Information pertaining to their pregnancy was collected in order to address the aims laid out. Specific information collected included diagnosis, age at conception, planned conception, assisted conception, medication at the time of conception and throughout pregnancy, biochemical parameters at conception, and the presence of cirrhosis. Outcome data was collected including miscarriage, termination of pregnancy, live birth, gestation, need for special care baby unit support and maternal complications including, changes in biochemical profile in the 3rd trimester and post-partum period, medication changes, decompensation, need for ITU support and death.

To address the aim described in chapter 2 regarding the outcomes of assisted conception in women with liver disease the master database was again interrogated to identify all women who had been referred for consideration of assisted conception. The medical and electronic notes were reviewed to obtain information regarding underlying diagnosis, presence of cirrhosis, sex hormones, baseline biochemical and haematological data and maternal age. In those women accepted for assisted conception, data regarding successful conception, miscarriage, live birth, gestation and mode of delivery were recorded. Information detailing why patients were declined for assisted conception was obtained. Finally maternal outcomes were

recorded including effect of hormonal therapy on hepatic biochemistry, complications, need for ITU support and death were obtained.

3.4 Statistical analysis

Data is presented throughout the results section using median and range for numerical values. To determine whether significant differences existed between groups, the Students t test, or the Mann-Whitney-U non-parametric method as appropriate was applied. Differences in nominal data were compiled either by the Chi squared test or using a Fisher's exact test when the number was less than 5 in any given cell of a 2x2 table. A p value of <0.05 was considered to be of statistical significance.

ROC curves were generated to analyse and compare maternal outcomes related to pregnancy.

All statistical analysis was performed using SPSS statistical software package version 14 (SPSS Inc., Chicago, IL).

Chapter 4: Outcomes of severe pregnancy related liver disease; refining the use of prognostic markers and the role of liver transplantation

4.1 Introduction

Pregnancy associated liver failure is characterised by an acute onset, rapid progression and significant maternal mortality. (44, 74, 200, 201) Acute fatty liver of pregnancy, the hypertension related liver diseases including pre-eclampsia, the haemolysis, elevated liver enzymes, low platelets (HELLP) syndrome and liver rupture/infarction, are all disorders specific to the pregnant state. (144) Amongst these, there is a wide spectrum of severity ranging from minor biochemical abnormalities to acute liver failure. Outcomes at the more severe end of the spectrum are difficult to predict and prognostic information is limited to small series.(53, 74, 87) Liver transplantation (LT) for pregnancy associated liver failure is uncommon and information regarding the indications for and outcomes of transplantation is limited for both the patient and the graft.(53, 80, 87)

The natural history of acute liver failure is variable and survival without liver transplantation (LT) ranges from 10–90% mostly dependent on the underlying aetiology and grade of encephalopathy and presence of multi-organ failure. (78) Survival has been transformed by the introduction of emergency LT, which now forms part of routine care for patients with ALF. The original King's College criteria for non-paracetamol acute liver failure (Table 1.3.8), identify patients with ALF early in their clinical course that are at high risk of death and thus may benefit from LT. (78)

In patients with pregnancy induced ALF, the King's College Criteria have never been validated, nor indeed were any patients with pregnancy associated ALF included in the original cohort when the criteria were established. (78) This raises the question as to whether "standard" King's criteria are applicable for assessing poor prognosis and need for LT in this individual cohort of patients.

Without a clear understanding of poor prognostic factors in this individual cohort, identification of those patients at high risk of death from ALF may fail to be recognised and thus not have access to LT as a lifesaving treatment in a timely manner. Furthermore using criteria that have never been validated in this cohort to guide LT may lead to incorrectly subjecting a patient that would have recovered with medical management to a life of immunosuppression, its side effects and increased mortality.

Reported literature on transplantation for both HELLP syndrome and AFLP is sparse. The largest single centre experience for HELLP syndrome consists of 7 patients. (80) A review of the published literature in 2007 found 9 reported cases (81-86) and an additional 8 cases were identified from review of the united network for organ sharing (UNOS) database. (87) Of these 17 patients, a 17% overall mortality was reported. The authors suggested that the indications for LT in HELLP syndrome were; persistent bleeding despite surgical intervention, extensive liver necrosis or liver failure, whereas, contained haematoma should be managed conservatively with close hemodynamic monitoring and repeated imaging. (87)

Reports on LT for AFLP are sporadic. (53, 54) Outcomes appear largely favourable. The European Liver Transplantation Registry (ELTR) database has recorded the majority of all European LT activity since 1968. During this period there have been 6 LT performed for AFLP confirming that LT is only performed or undertaken in exceptional cases.

4.2 Aims:

In light of the paucity of literature on the outcomes, complications and the role of transplantation in this unique cohort, we undertook a review of all patients with pregnancy associated liver disease severe enough to warrant intensive care admission between 1997 and 2008. The aims were to

- To identify the aetiology of pregnancy induced acute liver failure and its effect on clinical presentation and foetal outcome
- To identify the common maternal complications encountered in women who develop pregnancy induced acute liver failure
- To identify the frequency of death and need for liver transplantation in this cohort
- To assess whether current prognostic criteria, such as the original King's College Criteria, are applicable to this unique cohort in identifying those at risk of death.
- To identify if there are any early admission parameters that are associated with death or need for liver transplantation which may improve identification of women who may benefit in the future from liver transplantation
- To examine the effect of era on outcome, highlighting significant changes as appropriate, comparing the current cohort to 46 women admitted with severe pregnancy related liver disease between 1986 and 1996. (74)

4.3 Patients and Methods:

The liver intensive care unit (LITU) at King's College Hospital is a tertiary referral centre for patients with acute liver failure (ALF). In a previous study from this unit, pregnancy related liver disease accounted for less than 5% of all admissions with ALF between 1986 to 1996. (74)

All patients admitted to the LITU with pregnancy associated liver disease between 1997 and 2008 were reviewed and included in the current study.

The diagnosis of HELLP syndrome was made using the following criteria; the presence of pre-eclampsia and a platelet count of less than $100x10^3$ cells/µl, a serum aspartate aminotransferase (AST) level of greater than 70 IU/L, a serum lactate dehydrogenase (LDH) level of greater than 600 IU/ml and/or a total bilirubin of greater than 1.2 mg/dl and the findings of a microangiopathic haemolytic anaemia with characteristic schistocytes on a blood film. (200) All patients met the Tennessee criteria for complete HELLP syndrome, with haemolysis on a peripheral blood film, a raised LDH >600IU/L, thrombocytopenia $<100x10^9$/L and elevated transaminases AST>70IU/L. (70)

The diagnosis of AFLP was made on clinical and laboratory features including presentation in the 3rd trimester, features of ALF including jaundice, coagulopathy, encephalopathy or hypoglycaemia with or without the presence of pre-eclampsia. (48) All patients with AFLP met the Swansea criteria previously proposed by Ch'ng *et al*. for establishing the diagnosis of AFLP. (19) Patients with viral or drug related ALF in pregnancy were excluded.

On admission, patients were treated with full supportive care. Inotropic support, continuous veno-venous haemofiltration (CVVHF) and ventilatory support were given when clinically indicated. All patients underwent an ultrasound examination of the liver and hepatic vasculature. When clinically indicated, computed tomography was performed. Patients who were bleeding, or at risk of bleeding, were given coagulation support to maintain international normalised ratio (INR) of less than 1.5 and platelet support to achieve a platelet count of greater than $50x10^3$ cells/µl. All patients had a full non-invasive liver screen to exclude other causes of liver disease, including autoantibodies, viral serology for hepatitis A, B, C and E viruses, cytomegalovirus and Epstein-Barr virus, ferritin, copper studies and serum immunoglobulins. Those who were deemed as having fulminant hepatic failure, were treated using a standardized

care pathway to optimize the likelihood of survival. Briefly, this consisted of sodium chloride infusions to maintain sodium levels between 145 and 150 mmol/l and ventilatory support where appropriate to keep PaCo2 levels between 4 – 4.5 Kpa. A reverse internal jugular line was inserted to provide data on cerebral perfusion, and when indicated, an intracerebral pressure monitoring device was inserted, in those patients who had deteriorated to grade 3/4 encephalopathy. N-Acetyl-Cysteine was infused at 150mg/kg/day for a maximum of 5 days and CVVHF was utilized as appropriate. Prophylactic antifungal and antibacterial cover was utilized. These protocols have been previously validated and published as standards of care in the management of ALF at King's College Hospital NHS Foundation Trust. (202, 203)

4.4 Statistical Analysis

Data is presented using median and range for numerical values. To determine whether significant differences existed between groups, we applied the Student's t test, or the Mann-Whitney-U non-parametric method as appropriate. Differences in nominal data were compared either by the Chi squared test or using Fishers exact test when the number was less than 5 in any given cell of a 2x2 table. A p value of <0.05 was considered to be of statistical significance.

4.5 Results

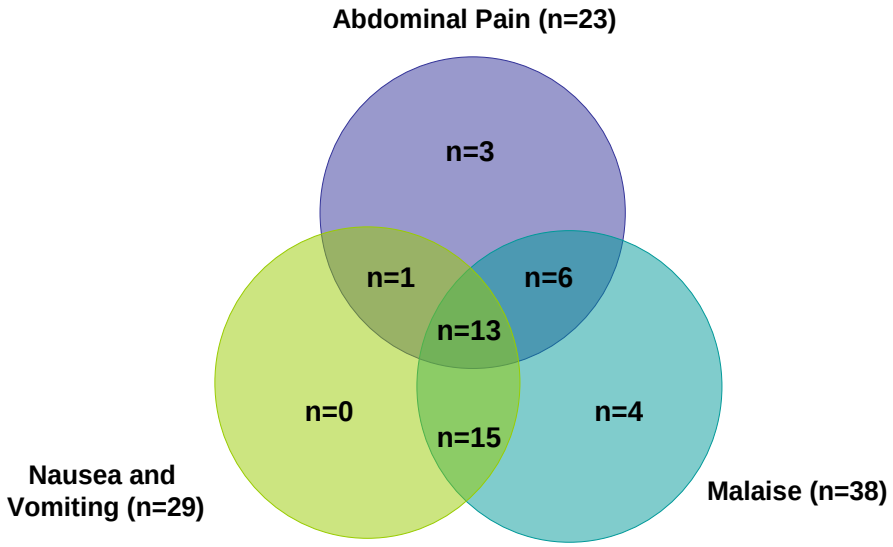
4.5.1 Presentation and delivery:

There were 54 admissions to King's College Hospital liver intensive care unit (LITU) between 1997 and 2008 with pregnancy associated liver disease. The median age at presentation was 30 years (range 21 – 40) with a median gestation of 35 weeks (range 27-40). Thirty two women (60%) were pregnant with their first child, 18 (33%) women were pregnant with their second child and 4 (8%) women were pregnant with their third child. Of those women who had previously been pregnant; 3 previous pregnancies were complicated by pre-eclampsia and 1 by HELLP syndrome. There were 6 twin pregnancies (11%).

The presentation to hospital was varied. Overall 42 patients presented with a combination of malaise (n=38), nausea and vomiting (n=29) and abdominal pain (n=38). Of the remaining 12, 7 had pre-eclampsia without the above symptoms, 1 presented with jaundice and 4 women had a normal labour with a post-partum presentation consisting of either collapse and hypoglycaemia or confusion in conjunction with deranged hepatic enzymes.

Regarding delivery, thirty-nine (72%) deliveries were performed by emergency caesarean section, whereas 15 were vaginal in nature. In those women diagnosed with AFLPD or hypertension related disease prior to delivery, 90% (45/50) delivered within 24 hours of presentation, with the remaining 5 delivering between 24 and 48 hours of presentation. Fifty-one women (94%) delivered at their local hospital with 3 women being transferred prior to delivery.

Figure 4.5.1 – Diagram demonstrating the commonest presenting complaints in women who developed severe pregnancy related liver disease



4.5.2 Aetiology of Disease and effect clinical features on arrival at King's College Hospital

Eighteen of the 54 patients admitted were diagnosed with AFLP all of which fulfilled the Swansea Criteria for diagnosis. Thirty-two patients had hypertension related disease; of these 26 had HELLP (1 of whom had small vessel veno occlusive disease (VOD)), 2 had liver rupture, 2 had subcapsular haematoma/tears and 2 with pre-eclamptic liver disease (1 associated with small vessel VOD)). The remaining 4 patients had intrahepatic cholestasis of pregnancy (n=1), ischemic hepatitis secondary to massive post-partum haemorrhage (n=1), AFLP in the context of highly active anti-retroviral therapy (HARRT) which had been prescribed throughout pregnancy (n=1), and, finally 1 patient had VOD in isolation.

All patients with HELLP syndrome had pre-eclampsia. Twenty three (82%) were nulliparous and there were 2 twin pregnancies. On arrival at King's LITU 9/26 (35%) were either intubated or encephalopathic. All patients had thrombocytopenia with a median platelet count of $48x10^3$ cells/µl (range 15-$99x10^3$cells/µl). The majority of these patients had received platelet support at their referring hospital, rendering values artificially high. Bilirubin levels were raised in 25/26 (96%) patients with a median value on admission of 48µmol/l (range 14 – 388µmol/l).

In comparison, only 11% of patients with AFLP had pre-eclampsia and 9/18 (50%) were nulliparous. On arrival at King's LITU 56% of patients with AFLP were intubated and ventilated. All AFLP patients had a raised bilirubin with a median level of 123µmol/l (range 37-194 µmol/l), and 8/16 (50%) had a platelet count of less than $100x10^3$ cells/µl (range 33-180 cells/µmol/l).

Patients with AFLP had a statistically significant higher INR level ($p=0.0015$), bilirubin ($p=0.0065$), creatinine ($p=0.04$) and platelets ($p<0.001$) and lower AST levels ($p<0.001$) when compared to those patients presenting with HELLP syndrome.

Table 4.5.2:

Aetiology of liver disease on clinical parameters and intensive care management at KCH

	AFLP (1997-2008) N=18	HELLP (1997-2008) N=26
Median age at presentation	31 (21-38)	34 (23-40)
Week of gestation	36 (33-38)	35 (27-40)
Pre-eclampsia (%)	11%*	100%*
Number encephalopathic/ventilated	10 (56%)	9 (35%)
Platelet count (150-450 cells/µL)	100 (33-180)*	48 (15-99)*
Creatinine (45-120 mg/dL)	210 (100–396)	160 (52–309)
CVVH	8 (47%)	13 (46%)
AST (10-50 IU/L)	78 (16-3003)*	2270 (58-7755)*
Bilirubin (3-20 µmol/L)	123 (37-194)*	48 (14-388)*
Lactate (<2 mg/dl)	2 (1-6.5)	1.9 (0.7-7.3)
INR (0.9-1.2)	1.8 (1.09–4.3)*	1.2 (0.84–3)*

* Statistical significant value for AFLP versus HELLP ($p<0.05$).

4.5.3 Foetal Outcomes.

The overall foetal mortality rate was 7% (4/60). This comprised of 4 deaths; 2 deaths occurred in foetuses from patients with HELLP syndrome, whereas 2 occurred in patients with AFLP. Three of the four foetal deaths occurred in women with twin pregnancies.

The first foetal death was in a 35 year old woman who was pregnant with twins, and presented at 30 weeks gestation with HELLP syndrome complicated by a sub-capsular haematoma. An emergency caesarean section was preformed but the second twin was still born. The subsequent two foetal deaths occurred in a 30 year old woman who presented with abdominal pain at 34 weeks gestation, was diagnosed with AFLP and went into spontaneous labour 36 hours after presentation. Unfortunately both her twins were still born. She subsequently developed grade IV encephalopathy, required intubation for airway protection, but recovered with supportive medical care. The final foetal death occurred in a 28 year old women who presented with nausea, vomiting and abdominal pain at 31 weeks gestation. She was diagnosed with HELLP syndrome, which was complicated by ischaemic hepatitis secondary to placental abruption. The baby was delivered vaginally, but was still born. The women developed ascites and renal failure but recovered with supportive medical care.

Interestingly foetal death was not associated with the severity of the maternal liver disease, as guided by maternal platelet count, INR, bilirubin, AST, creatinine or the presence of encephalopathy. (Table 4.5.3) This is likely due to the rapid delivery of the fetus. (90% within 24 hours)

Table 4.5.3: Severity of maternal liver disease at presentation and impact on foetal survival

	Foetal Death (n=4)	Foetal Survival (n=56)
Median age at presentation	30 (28-35)	30 (21-40)
Week of gestation	31 (30-34)	35 (27-40)
Number encephalopathic	1	6
Platelet count (150-450 cells/µL)	99 (58-116)	55 (15-225)
Creatinine (45-120 mg/dL)	247 (67-262)	152 (52-396)
AST (10-50 IU/L)	975 (78-5041)	307 (16-775)
Bilirubin (3-20 µmol/L)	53 (30-87)	63 (9-388)
Lactate (<2 mg/dl)	2.0 (0.7-2.9)	2.0 (0.8-18.0)
INR (0.9-1.2)	1.06 (1.03 – 1.58)	1.40 (0.84-4.3)

***** Statistical significant value for Foetal death vs. Foetal survival ($p<0.05$).

Thirteen neonates required admission to the special care baby unit for supportive care and all were subsequently discharged, with no ongoing medical sequelae. Admission to the SCBU was associated with earlier maternal gestation (34 (27-36) vs. 36 (35-42)).

4.5.4 Maternal Outcomes

The overall maternal survival rate was 87% (47/54). Four deaths occurred in patients with AFLP, 2 patients had severe necrotising pancreatitis and died of sepsis and multi-organ failure. The third patient died from a hypovolaemic cardiac arrest secondary to a bi-lobar liver rupture following an emergency cesarean section. The final patient with AFLP who died had been on long term anti-retroviral therapy and died from sepsis and MOF, with the sepsis severity precluding LT in that case. Three patients with hypertension/eclampsia related disease died. The first underwent LT for acute liver failure but had delayed graft function and was re-listed for LT. Following re-transplantation she died of MOF and sepsis. The second death in this category was in a patient with pre-eclampsia, who had progressive encephalopathy and liver failure. She died from MOF whilst awaiting a liver graft. The final patient died secondary to hypovolaemia with bi-lobar liver rupture and failure to achieve haemostasis. (Table 4.5.4)

Patients that died were more likely on admission to have encephalopathy (6/7(86%) versus 18/47(38%) p=0.04), have a higher lactate (5.0, (1.05-18) versus 1.62, (0.7-12) p=0.03) and to be commenced on CVVHF (7/7 versus 10/47 p=0.01). There was no statistical difference in platelet count, INR, bilirubin, AST, serum creatinine or the rate of bleeding complications. None of the patients that died met the non-acetaminophen King's College criteria for poor prognosis in acute liver failure.

Closer examination of the patients with ALFP who died revealed a 31 year old woman who presented with foetal distress, deranged LFT's and acute pancreatitis. She developed pancreatic ascites, a laparotomy demonstrated necrotic pancreatitis and a cholestatic liver. Liver biopsy was compatible with ALFP. She died of sepsis and multi-organ failure (MOF) on day 16 following admission. The second death occurred in a 33 year old patient who presented with jaundice, abdominal pain, hypoglycaemia and a raised INR. Following emergency caesarean

section, she was admitted to ITU with grade 2 encephalopathy. She also had CT evidence of severe necrotising pancreatitis. Laparotomy findings demonstrated turbid ascites and liver biopsy was consistent with AFLP. She died of sepsis and multi organ failure on day 10 following admission. In light of the severity of the pancreatitis neither of these patients were listed for LT. The third death in this category was in a 24 year old woman who had a caesarean section for foetal distress. She developed abdominal distension with deranged hepatic enzymes and laparotomy revealed bi-lobar liver rupture. Such was the degree of bleeding that she was rendered anhepatic. She died of a cardiac arrest on the operating table. Finally one patient died with AFLP who had been on long term to anti-retroviral therapy from sepsis and MOF, with the sepsis severity precluding LT in that case

For patients with HELLP syndrome, the first death occurred in a 23 year old woman who presented with pre-eclampsia at 31 weeks gestation. Following caesarean section she was admitted to ITU with transaminitis and renal failure. CT scan showed necrotic infarction of the right lobe. She subsequently underwent LT but had delayed graft function and in conjunction with progressive clinical deterioration she was re-listed for LT. She underwent re-transplantation, but later died of MOF and sepsis. The second death was in a 37 year old woman who presented with pre-eclampsia and underwent an emergency caesarean section. She had progressive encephalopathy, rising lactate levels and was listed for transplant. She died from MOF whilst awaiting an organ. The final patient died secondary to hypovolaemia with bi-lobar liver rupture and failure to achieve haemostasis.

Table 4.5.4: Clinical features of patients who died with pregnancy related liver disease

Patient	Age (years)	Gestation at presentation	Delivery mode	Baby Survival	Diagnosis	Listed for LT	Liver Transplant
Patient 1	23	31	Caesarean	Yes	HELLP	Yes	Yes x2
Patient 2	31	34	Vaginal	Yes	AFLP	No	No
Patient 3	29	32	Vaginal	Yes	Liver rupture	No	No
Patient 4	37	33	Caesarean	Yes	HELLP	Yes	No
Patient 5	33	33	Caesarean	Yes	AFLP	No	No
Patient 6	31	32	Caesarean	Yes	AFLP / Drug related	No	No
Patient 7	24	35	Caesarean	Yes	AFLP	No	No

4.5.5: Liver Transplantation and outcomes

Six patients were listed for LT, 3 with HELLP, 1 with AFLP, 1 with ischaemic hepatitis secondary to severe post-partum haemorrhage and 1 with pre-eclamptic liver disease. Three patients were listed due to acute liver failure all with encephalopathy, coagulopathy and hyperbilirubinaemia and two patients were listed on the basis of having functional Budd-Chiari syndromes, secondary to haematoma causing compression on the hepatic veins. The final patient was listed because of failure to control hepatic blood loss in conjunction with worsening

hepatic function. None of the listed patients fulfilled the non-acetaminophen King's College criteria. Two of the six listed patients died, 3 patients underwent successful LT and one patient recovered with medical management alone.

Of the 3 patients that underwent successful LT, all are maintained on tacrolimus based immunosuppression, and graft function remains excellent over a median follow-up period of 8 years**.**

Table 4.5.5.1: Diagnosis, clinical features and outcomes of patients with pregnancy associated acute liver failure that were listed for liver transplantation.

	Age	Diagnosis	Transplant	Length of hospital stay (days)	Survival	Graft function	Follow up period
Patient 1	37	HELLP	No	3	No	NA	NA
Patient 2	23	HELLP	Yes x 2	43	No	NA	NA
Patient 3	33	AFLP	NA	38	Yes	NA	Discharged Jan 2002
Patient 4	40	HELLP/VOD	Yes	31	Yes	Good	4.5 years
Patient 5	30	Ischemic hepatitis	Yes	25	Yes	Good	8 years (then emigrated)
Patient 6	24	Pre-eclamptic liver disease	Yes		Yes	Good	10 years

Patients who were listed for liver transplantation had a higher AST (3040 IU/L, (3000-3739 IU/L) versus 307 IU/L, (16-775 IU/L), p<0.01), a higher lactate after a period of resuscitation (6.0 mg/dl, (2.6-12.0 mg/dl) versus 2.0mg/dl, (0.7-18.0 mg/dl), p<0.01) and lower platelets (40 cells/µl, (21-54 cells/µl) versus 70 cells/µl, (15 – 225 cells/µl), p=0.01) on admission to out LITU. Additionally listed patients and were more likely to require CVVH (6/6 versus 22/48, p=0.02) and to have encephalopathy (6/6 (100%) versus 7/48 (15%) p<0.01), when compared to non-listed patients. There was no statistical difference in levels of bilirubin, creatinine and INR on admission. These data are summarized in table 4.5.5.2.

Table 4.5.5.2: Differences in clinical, biochemical and haematological parameters between patients listed and not listed for liver transplantation on admission to intensive care.

	Patients listed for liver transplantation (n=6)	Patients not listed for liver transplantation (n=48)	p value
AST (10-50 IU/L)	3040 (3000 - 3739)	307 (16 - 775)	<0.01
Lactate (<2 mg/dl)	6.0 (2.6 – 12.0)	2.0 (0.7 – 18.0)	<0.01
Platelet count (150-450 cells/µL)	40 (21 – 54)	70 (15 – 225)	0.01
Creatinine (45-120 mg/dL)	200 (143 – 224)	156 (52 – 396)	0.34
CVVH	6/6 (100%)	22/48 (46%)	0.02
Bilirubin (3-20 µmol/L)	89 (66 – 208)	63 (9 - 338)	0.17
INR (0.9-1.2)	1.39 (1.09 - 3)	1.4 (0.84 – 4.3)	0.48
Encephalopathy	6/6 (100%)	7/48 (15%)	<0.01
Length of ITU stay (days)	31 (3 – 43)	5 (1 – 33)	<0.01

4.5.6 Analysis of differences between medical survivors and those that died / received liver transplantation

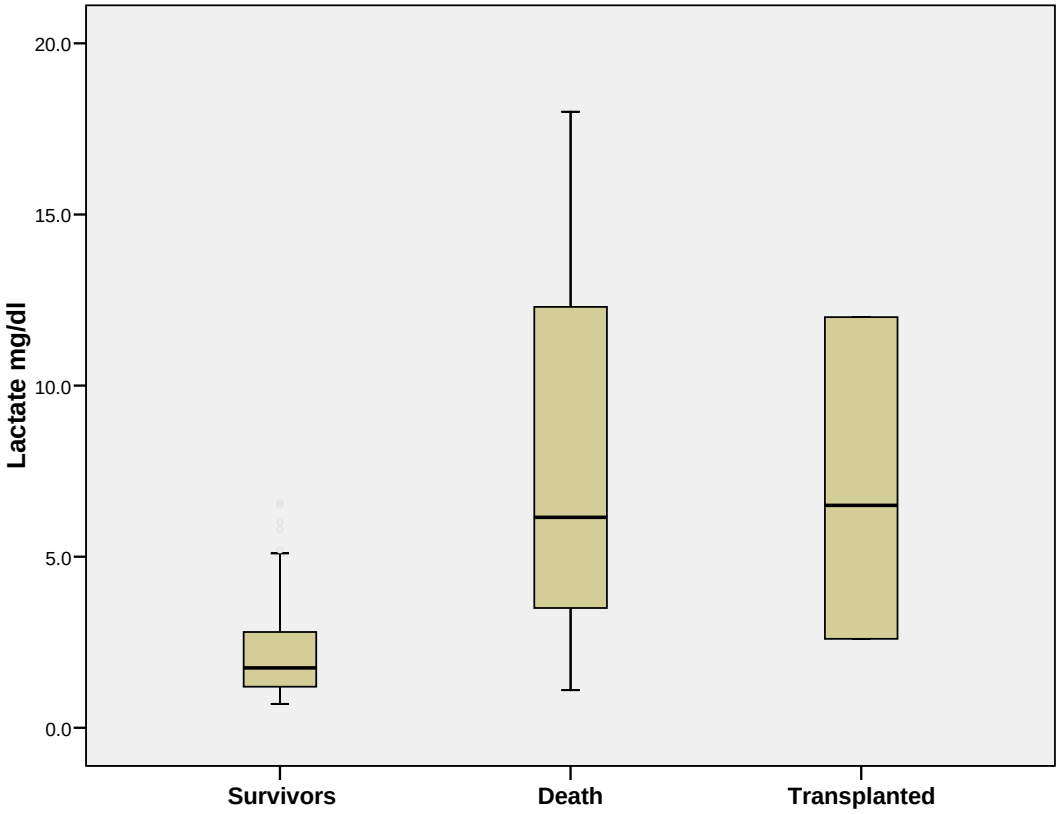
Analysis of differences in admission characteristics to intensive care between medical survivors and those patients that were either transplanted or died revealed that lactate (p=0.03) (following a period of resuscitation) and the presence of any grade of encephalopathy (p=0.04) were the only statistical significant parameters separating survival from both death and LT (Table 4.5.6.1).

Table 4.5.6.1: Differences in clinical, biochemical and haematological parameters on admission to intensive care between medical survivors and those who died or underwent transplantation.

	Medical survivors N=44	Death (without transplant) N=6	Transplanted N=4	Death or Transplanted N=10
AST (IU/L)	1551 (16 – 7755)	627 (48 – 3040)	3345 (3000 – 3739)*	1714 (48 – 3739)
Lactate (mg/dl)	2.5 (0.8 – 6.6)	7.8 (3.5 – 18.0)*	7.3 (2.6 – 12.0)*	7.6 (2.6 – 18)*
Platelet count (cells/µL)	81 (19 – 255)	73 (25 - 153)	34 (21 – 54)*	57 (21 – 153)
Creatinine (mg/dl)	1.99 (0.58 – 4.47)	1.94 (0.83 – 3.73)	2.04 (1.61 – 2.5)	1.98 (0.83 – 3.73)
Bilirubin (mg/dl)	5.26 (0.81 – 22.69)	5.61 (0.52 – 12.16)	4.85 (3.85 – 5.49)	4.23 (0.5 – 12.2)
INR	1.5 (0.8 – 3.9)	2.2 (1.1 – 4.3)	2.0 (1.24 – 2.7)	2.1 (1.1 – 4.3)
Encephalopathy (%)	43	83	100*	90*

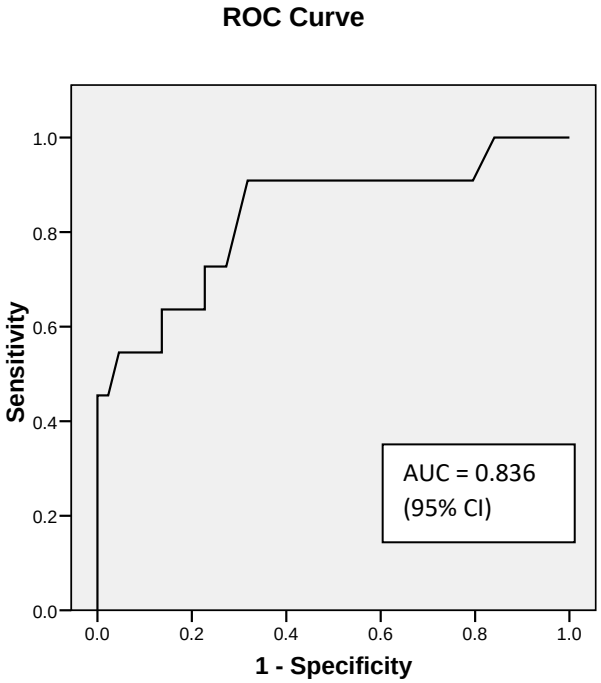
*p<0.05 when compared to medical survivors

Figure 4.5.6.1: Box and Whisker plot comparing admission lactate levels in patients who survived, died and were transplanted.



The differences in lactate levels between the three groups are demonstrated above. The receiver operator characteristic (ROC) curve for lactate (figure 4.3.6.2) demonstrates an area under the curve (AUC) of 0.84 at a 95% confidence interval (0.64 - 0.98). Furthermore an admission lactate greater than 2.8mg/dl, following a period of volume resuscitation had a 73% sensitivity and a 75% specificity for predicting which patients with ALF in pregnancy are likely to die or require transplantation. The AUC was not predictive of death or transplantation in other admission parameters. (Table 4.5.6.2)

Figure 4.5.6.2: ROC curves for lactate (and other admission parameters) as a predictive marker for either death/transplantation.



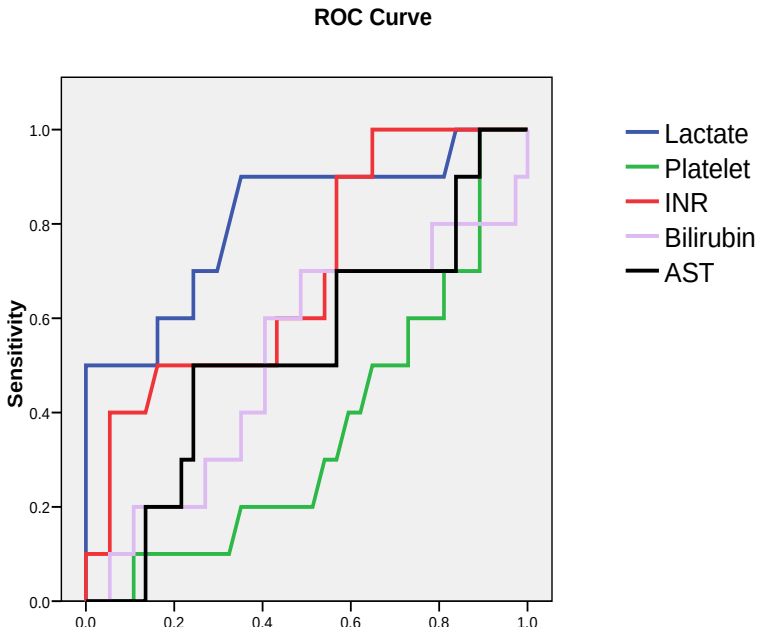


Table 4.5.6.2: Table showing the area under the curve for admission haematological and biochemical parameters with 95% confidence intervals.

Test Result Variable(s)	Area under curve	Asymptotic 95% Confidence Interval	
		Upper Bound	Lower Bound
Lactate	.836	.646	.979
Platelet	.359	.174	.545
INR	.693	.512	.875
Bilirubin	.516	.300	.733
Creatinine	.510	.325	.695
AST	.532	.325	.740

A lactate level of greater than 2.8mg/dl, after appropriate volume resuscitation, has been shown above to have a 73% sensitivity and a 75% specificity for predicting which patients are likely to die or require LT. The only other parameter we identified as being statistically significant in predicting death or need for LT is the presence of any grade of encephalopathy. Combining a serum lactate of greater than 2.8mg/dl with the presence of encephalopathy correctly identified 9/10 patients that either died or were transplanted (sensitivity 90%). The one patient who died without meeting the above criteria had AFLP in conjunction with acute pancreatitis and subsequent MOF. Of the 44 patients who survived 6 (14%) had a combination of a lactate greater than 2.8mg/dl and encephalopathy (specificity 86%). The negative predictive value of the test was 97% with a positive predictive value of 60%.

4.5.7: Maternal complications

The main complications, other than death and need for LT discussed above were renal failure, haemorrhage, sepsis, encephalopathy and cerebral oedema.

Haemorrhage, defined as the presence of frank blood either in abdominal drains or suspected on radiological imaging in conjunction with haemodynamic instability and the need for red blood cell transfusion occurred in 59% (32/54). Twenty one out of thirty two (66%) cases were gynaecological, 15/32 (47%) were hepatobiliary and 4/32 (13%) patients bled from both sites. Surgical intervention to manage the bleeding was needed in 23/32 (72%) patients. There was no association between the mode of delivery (vaginal versus caesarean) and the incidence of bleeding complications from a gynaecological source (p=0.22) or a hepato-biliary source (p=0.51). Length of stay was significantly longer in patients that bled (10 days, (1-43) versus 4 days, (1-14) p=0.004).

Sepsis was more common in those with bleeding complications (21/32 (66%) versus 8/22 (36%) p=0.02). The overall prevalence of culture positive sepsis was 29/55 (52%) and was associated with a significantly prolonged LITU stay (10 days, (2-43) versus 3 days, (1-23) p=0.005).

The prevalence of renal failure was 63%, as classified using the 'RIFLE' criteria (Risk of renal dysfunction, Injury to the kidney, Failure of kidney function, Loss of kidney function and End stage kidney disease).(204) The median creatinine level on admission was 1.72 mg/dl (range 0.59-4.5mg/dl). CVVH was required in 27/54 (50%) patients, however none required ongoing renal replacement therapy after discharge from hospital.

Liver specific complications included encephalopathy of any grade in 56% (26/54), ascites in 26% (14/54) and cerebral oedema as defined by arterial ammonia greater than 150,

encephalopathy and or raised pressure on an intra-cerebral pressure monitoring device in 15% (8/54).

4.3.8: Effect of era on outcome.

Finally to assess the effect of era on outcome of women transferred and admitted to King's College Hospital Liver Intensive Care Unit the current data set was compared to a previous collected cohort of patients. In this cohort, patients were collected over a 10-year period from 1986 – 1996. In total 46 patients with severe hepatic dysfunction in late pregnancy were transferred indicating that the number of admissions with pregnancy associated liver disease has remained constant over the two era's.

Between the two eras 1986-1996, and 1997–2008, there appears to be a change in the aetiology of liver disease presenting. During the first era, 32/46 (70%) of the patients were admitted with AFLP whereas 7/46 (15%) were admitted with HELLP. This compares to a prevalence of 18/53 (33%) with AFLP and 26/54 (48%) with HELLP syndrome in the subsequent 11 years. Yet, despite this apparent change in case-mix, baseline haematological and biochemical parameters on admission have remained similar over the two time periods. Similarly, mortality rates have not changed significantly between the two eras (9% versus 13%). Between 1986 and 1996, 2 patients were listed for LT, one with AFLP and liver rupture who died before a liver became available, and the second patient 1 with pre-eclamptic liver rupture who underwent successful LT and continues to survive. Although the number of patients listed for liver transplantation has increased over the 2 time periods this did not reach statistical significance (p=0.2), and perhaps this increase represents institutional experience in determining which patients are most likely to benefit from LT.

Table 4.5.8.1: Aetiology of liver disease and effect of era on clinical parameters and intensive care management at KCH

	AFLP (1997-2008) N=18	HELLP (1997-2008) N=26	AFLP (1986-96) N=32	HELLP (1986-96) N=7
Median age at presentation	31 (21-38)	34 (23-40)	30 (17-40)	31 (23-41)
Week of gestation	36 (33-38)	35 (27-40)	36 (28-40)	34 (27-38)
Pre-eclampsia (%)	11%*	100%*	50%*	100%*
Number encephalopathic/ventilated	10 (56%)	9 (35%)	20 (63%)*	1 (14%)*
Platelet count (150-450 cells/µL)	100 (33-180)*	48 (15-99)*	123 (26-262)*	39 (19-89)*
Creatinine (45-120 mg/dL)	210 (100–396)	160 (52–309)	245 (99-758)	102 (63-526)
CVVH	8 (47%)	13 (46%)	-	-
AST (10-50 IU/L)	78 (16-3003)*	2270 (58-7755)*	99 (25-911)	342 (60-328)
Bilirubin (3-20 µmol/L)	123 (37-194)*	48 (14-388)*	142 (63-646)*	34 (19-124)*
Lactate (<2 mg/dl)	2 (1-6.5)	1.9 (0.7-7.3)	-	-
INR (0.9-1.2)	1.8 (1.09–4.3)*	1.2 (0.84–3)*	-	-

* Statistical significant value for AFLP versus HELLP ($p<0.05$).

4.6 Discussion

In this chapter we have demonstrated that there are key clinical and biochemical parameters on admission to intensive care that allow early detection of patients at significant risk of death and/or in need of LT in severe pregnancy associated liver disease. Patients that died or were transplanted were more likely on admission, to have a higher lactate level, and have encephalopathy. In addition, we have identified that current prognostic models of poor survival in ALF, including the original King's College Criteria may not correctly identify patients at risk of death without LT in this clinical setting.

The Original King's college criteria for non-acetaminophen aetiology, identify patients with ALF early on their admission that are at high risk of death and thus may benefit from LT. (78) None of the patients in this cohort that were listed for transplantation fulfilled these criteria. Although all patients were encephalopathic, none met the requirement of either an INR greater then 6.5, or any three parameters from the variables of age greater than 40 years, unfavourable aetiology, INR greater than 3.5, serum bilirubin greater than 300µmol/L or interval of jaundice to development of encephalopathy of greater than 7 days. This is likely in-part, related to the high incidence of bleeding complications in pregnancy associated ALF (59% in this study) and the consequence of correction of coagulopathy through the use of blood products resulting in artificially low INR values. In addition to this virtually all our patients (96%) were under the age of 40, a key parameter in the original criteria. Finally, in our series, only 2 patients had a bilirubin of greater than 300µmol/L and all had progression from development of jaundice to development of encephalopathy duration of less than 7 days. Consequently, a patient with pregnancy induced ALF, could be denied the benefit of listing if strict adherence to these criteria is enforced.

In patients with pregnancy induced ALF, the King's criteria have never been validated, nor indeed were any patients with pregnancy associated ALF included in the original cohort

when the criteria were established. (78) This raises the question as to whether “standard” King’s criteria should be used in this individual cohort of patients. In 2002, Bernal *et al.* increased the sensitivity of the acetaminophen Kings College criteria by adding the parameter of serum lactate, following a period of resuscitation. (205) Serum lactate is often elevated in patients with ALF due to increased systemic production secondary to a combination of tissue hypoperfusion with subsequent tissue hypoxia and decreased hepatic clearance secondary to injured hepatocytes. In addition to this, patients with AFLP have an abnormality in mitochondrial beta oxidation of fatty acids associated with 3-hydroxyacyl-CoA dehydrogenase deficiency which results in excess fatty acids within the liver causing direct hepatoxicity, elevating the lactate further. Patients at the severe end of the HELLP spectrum have extensive hepatocyte injury as reflected by the elevated AST due to complications of infarction, haemorrhage and rupture further compounding hyperlactatemia in this group. In light of the pathophysiology in pregnancy induced liver failure it is unsurprising that lactate has been identified in this cohort as a discriminating factor when considering LT or predicting poor outcomes.

Additional prognostic scoring systems have been published and validated, albeit never in pregnancy associated liver failure. These include the Clichy criteria and the BiLE score (bilrubin, lactate and aetiology score). (79, 206, 207) The Clichy criteria define that the presence of grade 3 or 4 encephalopathy with suppressed factor V levels (defined according to age) identifies patients who would benefit from transplantation in acute liver failure. (79, 207) In pregnancy associated liver failure, this prognostic system is likely to be unhelpful due to the correction of clotting disturbance. The BiLE score in contrast, which incorporates serum bilirubin, lactate and aetiology may be of greater use in pregnancy induced liver failure since it does not define an age restraint or specific coagulation parameter. Moreover, it includes serum lactate. (206)

Reported literature on transplantation for both HELLP syndrome and AFLP is sparse. The largest single centre experience for HELLP syndrome consists of 7 patients. (80) A review of the published literature in 2007 found 9 reported cases (81-86) and an additional 8 cases were identified from review of the United network for organ sharing (UNOS) database.(87) Of these 17 patients, a 17% overall mortality was reported. The authors suggested that the indications for LT in HELLP syndrome were; persistent bleeding despite surgical intervention, extensive liver necrosis or liver failure, whereas, contained hematoma should be managed conservatively with close haemodynamic monitoring and repeated imaging. (87) Our experience supports this paradigm of management. In this series, 2 patients with HELLP syndrome died, one awaiting liver transplant and second from MOF and sepsis, following re-transplantation. One further patient underwent successful transplantation with the indication being extensive haemorrhagic liver necrosis in association with poor hepatic function.

Reports on LT for AFLP are sporadic. (53, 54) Outcomes appear largely favourable. In this study, only one patient with AFLP was listed for LT but recovered with medical management and was subsequently taken off the waiting list. The European Liver Transplantation Registry (ELTR) database has recorded the majority of all European LT activity since 1968. During this period there have been 6 LT performed for AFLP confirming that LT is only performed or undertaken in exceptional cases.

Pancreatitis is a recognized complication of AFLP which is associated with poor maternal outcomes. (208) The largest reported series in the literature described 12 patients with AFLP and co-existing pancreatitis. (208) Of these, 2 patients died, 3 patients developed pancreatic pseudocysts and 1 developed haemorrhagic pancreatitis. In all cases, the radiological and biochemical findings of pancreatitis occurred after the onset of hepatic abnormalities. In our current series 2/18 (11%) patients with AFLP had associated pancreatitis. Interestingly, both patients died, confirming that the development of associated pancreatitis is a poor prognostic

sign. Consequently, it is our belief that since associated pancreatitis is associated with more adverse outcomes, that all patients with AFLP should also undergo screening for pancreatitis.

This study does have several limitations. Firstly, there is unquestionable selection bias given the referral patterns to our institution. Admission criteria to the institution are difficult to define and the decision to transfer a patient was based on review of the case and discussion with the referring centre. Thus, the bias in our series is towards more severe hepatic dysfunction and patients with bleeding complications who might need surgical intervention in the course of management. Other limitations include the retrospective nature of the cohort, although, it is apparent that no single centre could generate a prospective study with adequate recruitment numbers and comparable data does not generally exist, even in multi-centre series.

In summary, severe pregnancy associated liver disease is a condition with a high morbidity and mortality. We have reported the complications encountered in clinical practice, identified predictors of poor outcome and shown that standard listing criteria for transplantation may be inappropriate in this unique cohort. We have identified that the serum lactate on admission is a predictor of both death and listing for transplantation, but his needs to be validated in further prospective analysis. This study may therefore aid management of patients in the intensive care and allow accurate discussions about outcomes to occur with patients and their families.

Chapter 5: Utilisation of prognostic scoring systems to predict outcomes in pregnant women with cirrhosis

5.1 Introduction

Pregnancy in cirrhotic women is rare relating to a combination of metabolic, endocrine, nutritional and sexual dysfunction as discussed in chapter 1. (94-98) Disruption of the hypothalamic-pituitary axis in conjunction with disturbed oestrogen metabolism leads to anovulation, amenorrhoea and infertility.(96, 97) Historically, women with cirrhosis have therefore been considered infertile although, occasional successful pregnancies have been reported in women with well compensated cirrhosis. (102) The current literature regarding maternal and foetal outcomes is limited to case reports and small historic series which have limited value in advising women today regarding the safety of pregnancy. (102, 105)

It is recognized that women with cirrhosis who become pregnant are at risk of worsening liver synthetic function and hepatic decompensation including the development of ascites, variceal haemorrhage and encephalopathy.(48, 95) Overall, maternal mortality for pregnant women with cirrhosis has been reported to be as high as 10.5% in the early 1980's, however, (98) with advances in the management of liver disease and variceal haemorrhage, mortality is likely to have improved.

In chapter one it is detailed how various scoring systems exist in clinical practice to assess the severity of cirrhosis and guide management of such patients. These include the model for end stage liver disease (MELD), MELD Sodium (MELD-Na), the United Kingdom end stage liver disease (UKELD) and Child-Pugh (CP) scores. (120, 126-130) Although the MELD score

was initially developed to predict mortality following trans-jugular intrahepatic portosystemic shunt (TIPS) insertion, (126, 127) this scoring system is now widely used in clinical practice to predict prognosis in patients with cirrhosis and to help guide listing for, and allocation of organs in liver transplantation. (128, 131)

Recently its utility has been extended to predict outcome in other clinical scenarios including alcoholic hepatitis, paracetamol induced liver injury, acute liver failure and survival following non liver related surgery in cirrhosis. (132-136) The use of MELD score or other scoring systems in predicting outcome and complications in cirrhotic patients who become pregnant has not been assessed. In light of their widening use in other aspects of liver disease, our hypothesis is that these scoring systems may have utility in risk stratifying cirrhotic patients wishing to become pregnant.

5.2 Aims

In light of the paucity of literature on the outcomes, complications and the role of prognostic scoring systems in predicting outcomes of pregnancy in cirrhotic women a review of all patients at our centre between 1984 and 2009 with cirrhosis and pregnancy was undertaken. The aims were:

- To identify the foetal outcomes in women with cirrhosis with regard to miscarriage, still birth, gestation, need for special care support, congenital and developmental abnormalities.
- To identify maternal complications in women with cirrhosis including mortality and liver and non-liver related morbidity. Particular attention was given to hepatic decompensation (ascites, encephalopathy, variceal bleeding).
- To assess the use of prognostic scoring systems (calculated pre conception) at predicting maternal or foetal adverse outcomes.
- To assess whether prognostic scoring systems or other markers of portal hypertension (platelet count, known varices, imaging) pre-conception might predict presence of varices on screening endoscopy in the second trimester.
- To establish evidence based guidance that quantifies risk for women with cirrhosis wishing to conceive.

5.3 Patients and Methods

All cirrhotic patients who reported pregnancy at our institution between 1984 and 2009 were reviewed. The clinical records were reviewed in all patients and data extracted in a standard fashion. The diagnosis of cirrhosis was made on histological grounds on the basis of

liver biopsy or using a combination of radiological and laboratory investigations in cases where a biopsy wasn't deemed necessary on clinical grounds.

MELD, MELD Na, UKELD and CP scores were calculated where appropriate information was available, according to published formulae. (120, 127, 130) Scores were calculated from information gathered at the clinic visit immediately prior to pregnancy being reported. Maternal complications during pregnancy were recorded including hypertension, pre-eclampsia, gestational diabetes and renal failure along with specific hepatological complications including encephalopathy, ascites, development of jaundice and variceal haemorrhage. Data on abortions, including spontaneous and elective terminations of pregnancy were obtained in addition to the gestational duration, live birth rate and foetal outcomes. Upper gastrointestinal endoscopy results were reviewed to assess the prevalence of varices, and the impact of screening on delivery and bleeding rates. MELD, MELD Na, UKELD and CP scores at the time of conception were correlated with outcomes to assess if complications can be predicted more accurately in this group.

5.4 Statistical analysis

Data is presented using median and range for numerical values. To determine whether significant differences existed between groups, we applied the Student's t test, or the Mann-Whitney-U non-parametric method as appropriate. Differences in nominal data were compared either by the Chi squared test or using Fisher's exact test when the number was less than 5 in any given cell of a 2x2 table. A p value of <0.05 was considered to be of statistical significance. ROC curves were generated to analyse and compare the accuracy of the MELD and UKELD scores in predicting adverse maternal outcomes related to pregnancy. All statistical analysis was performed using the SPSS statistical software package version 14 (SPSS Inc., Chicago, IL)

5.5 Results

There were 62 pregnancies in 29 cirrhotic women. Cirrhosis was diagnosed on liver biopsy in 41/62 (66%) and by radiological and laboratory parameters in 21/62 (34%). For the pregnancies, the underlying aetiology of cirrhosis was autoimmune (n=27), alcohol related (n=10), viral (n=6), biliary atresia (n=6), genetic (n=4), vascular (n=2) and other (n=7). The median age at conception was 29 years (range 16-40 years). Three patients conceived using in-vitro fertilization and 21/62 (34%) of pregnancies were unplanned. There were 2 twin pregnancies, these occurred in women who had not undergone IVF.

Median MELD score at conception was 7 (range 6-17), median Meld-Na was 9 (6-17), median UKELD at conception was 44 (range 36-53) and median CP score was 5(5-8). Thirty seven pregnancies occurred in patients who were Child's class A and 16 were Childs class B. Scores could not be calculated in 7 patients due to absence of occasional pieces of laboratory data at the time of conception. Eleven pregnancies occurred in 8 women who had a previous episode of decompensation, (3 encephalopathy, 5 ascites). Three women had a previous variceal bleed prior to becoming pregnant.

5.5.1 Foetal Outcomes

The live birth rate was 58% (36/62). There were 9/62 (15%) elective terminations of pregnancy and 13/62 (21%) spontaneous miscarriages (spontaneous loss of pregnancy prior to 20 weeks gestation). Four of the 62 (6%) pregnancies were still births (spontaneous loss of pregnancy after 20 weeks gestation). Three pregnancies were conceived using IVF, 2 of which resulted in spontaneous miscarriage and 1 neonate was born at 27 weeks with cerebral palsy. Regarding terminations, 5 were medically advised due to concerns regarding maternal safety with respect to the severity of the underlying cirrhosis or portal hypertension. The median

MELD score in the medically advised terminations was 8 (range 6-15) and median UKELD was 45 (range 37 – 51); the remaining were related to patient preference. Neither MELD score (p=0.64), MELD-Na (p=0.45), UKELD score (p=0.46) nor CP score (p=0.24) at conception were predictive of a termination of pregnancy, when compared with scores in mothers who had a live birth. This is likely due to the impact of patient wishes regarding termination as well as medical advice based on the severity of the underlying liver disease. Spontaneous foetal loss occurred in 27% of pregnancies, including miscarriage and still birth. Interestingly, this was not associated with higher MELD (p=0.88), MELD-Na (p=0.28), UKELD (p=0.45) or CP (p=0.29) scores at conception when compared to mothers who had a live birth.

The median gestational week was 36 weeks (range, 24-38 weeks). Prematurity, defined as a birth prior to 37 weeks gestation, occurred in 64% of the live births and 18% delivered prior to 30 weeks gestation. A higher MELD score (8(6-15) v 6(6-15), p=0.01), MELD-Na score (11(6-15) v 9 (6-13), p=0.01), UKELD score (47 (41-50) v 42(39-47), p=0.01), and CP score (5(5-7) v 7(5-8), p=0.03) at conception was associated with a birth prior to 37 weeks gestation. Aetiology of the underlying liver disease had no impact on the gestational week. Eighteen deliveries were by caesarean section and 18 were vaginal. Neither MELD score (p=0.31), MELD Na (p=0.91), UKELD score (p=0.29) nor CP score (p=0.32) at conception defined the mode of delivery. Neonatal intensive care was required for 17% (6/36). The need for admission of a neonate to intensive care was associated with higher maternal MELD score (11(7-15) v 6(6-15), (p=0.04), UKELD score (48(42-49) v 42(41-48), p=0.04) but not CP score (7(5-8) v 6(5-7), p= 0.35) or MELD Na (7(6-14) v 9(6-15), p=0.28) at conception.

Eleven pregnancies occurred in 8 women who had previously had an episode of decompensation. These resulted in 4 live births, 3 miscarriages, 2 still births and 2 terminations of pregnancy. An episode of maternal hepatic decompensation prior to pregnancy was not associated with spontaneous pregnancy loss (p=0.31).

There were no infant peri-natal deaths. Two children however have cerebral palsy and one child had learning difficulties but in other regards reached developmental milestones normally.

Figure 5.5.1: Algorithm demonstrating the outcomes of 62 conceptions in women with cirrhosis

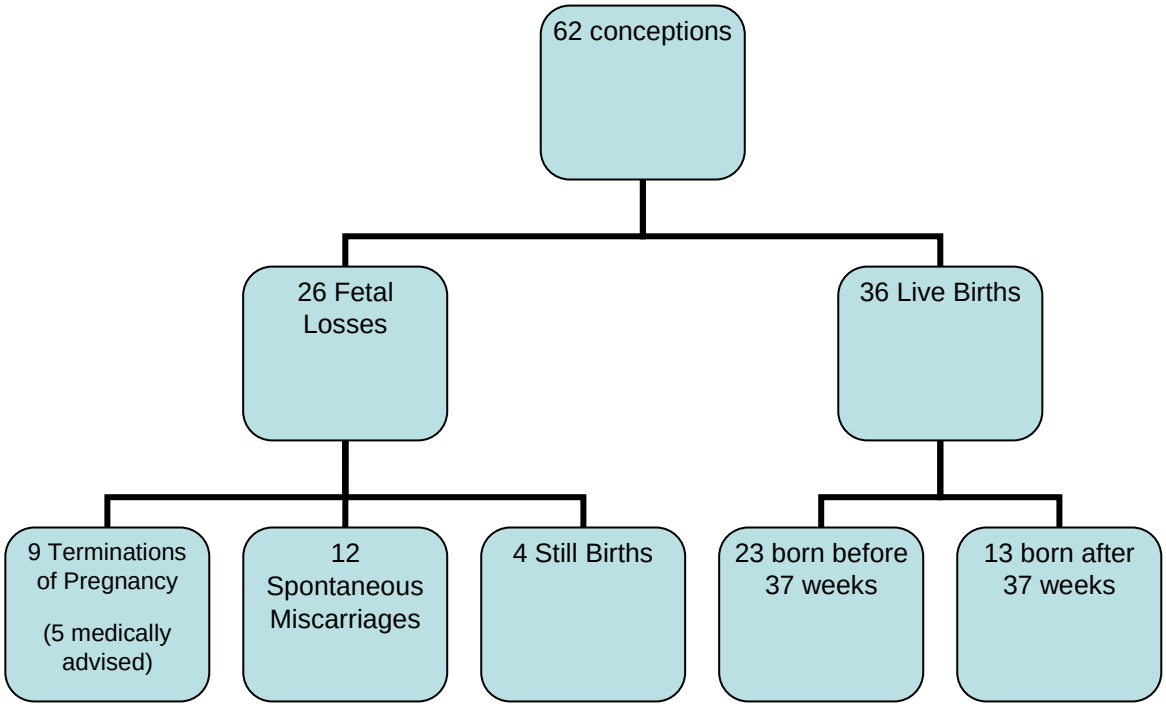


Table 5.5.1: Utility of the prognostic scoring systems in predicting foetal outcome.

	MELD	MELD-Na	UKELD	CP
Live birth v miscarriage or still birth	7(6-15) v 7(6-16) P=0.88	8(6-15) v 9(8-17) p=0.45	43(36-50) v 44(40-51) P=0.45	5(5-8) v 6(5-8) p=0.29
Live birth v termination	7(6-15) v 8(6-15) p=0.64	9(6-14) v 9(7-17) p=0.28	43(36-50) v 45(37-51) p=0.46	6(5-8) v 6(5-8) p=0.24
Gestational week <37 v > 37	8(6-15) v 6(6-15) **p=0.01**	11(6-15) v 9(6-13) **p=0.01**	47 (41-50) v 42(39-47) **P=0.01**	7(5-7) v 7(5-8) **p=0.02**
Caesarean v vaginal delivery	7(6-15) v 6(6-15) p=0.31	9(7-15) v 8(6-13) p=0.91	43 (36-50) v 42 (20-48) P=0.29	6(5-8) v 6(5-7) p=0.86
Neonatal ICU v ward	10(7-15) v 6(6-15) **p=0.02**	7(6-14) vs. 9(6-15) p= 0.28	48(42-50) v 42(36-48) **P=0.02**	7(5-8) v 6(5-7) p=0.08

5.5.2 Maternal Complications

Maternal mortality directly associated with pregnancy occurred in 1/62 (1.6%) pregnancies, although this represents 1/29 mothers in total (3.4%). A significant maternal complication, occurred in 6/62 (10%) of the pregnancies (6/29 (21%) of mothers) and included variceal bleeding (n=3), decompensation with development of significant ascites (n=2) and hepatic encephalopathy (n=1).

Review of these cases in more detail demonstrated that the first variceal bleed occurred at 31 weeks gestation following an emergency caesarean section for foetal distress. The patient became haemodynamically unstable, underwent emergency laparotomy which revealed ruptured splenic varices. A splenectomy was undertaken but haemostasis could not be achieved and she died following a hypovolemic arrest. The second patient had a variceal bleed in the second trimester which was controlled using endoscopic band ligation. A healthy baby was delivered by caesarean section at 34 weeks gestation, but she died 6 months later following a further variceal bleed. The third case of variceal bleeding again occurred again in the second trimester and was controlled using endoscopic therapy. A healthy baby was delivered at 34 weeks gestation by caesarean section. The mother remains clinically stable at 3-years post-delivery.

Two patients developed new onset ascites associated with pregnancy. The first had spontaneous rupture of membranes and cord prolapse at 25-weeks. She underwent emergency caesarean section at 27 weeks, required admission to critical care and was hospitalised for a total of 6-weeks following delivery. She remains clinically well at 5-years follow-up. The baby also required intensive care, was ventilated for 48 hours and has mild cerebral palsy. The second patient who developed ascites underwent an emergency caesarean section at 34 weeks gestation for foetal distress. Although the baby required intensive care support the mother remains well at 3-years follow-up. The final patient has autoimmune hepatitis and developed

significant deterioration of her liver function tests post-partum. She developed encephalopathy, and underwent transplantation. She died 14 months later from graft failure secondary to recurrent rejection on a background of poor adherence.

In addition to the aforementioned cases, there was one further maternal death 28 months following the delivery of her second child. Despite priority listing for liver transplantation she died awaiting a graft. Two further patients required transplantation, with one patient transplanted for chronic liver disease 4-months following a termination of pregnancy and the second transplanted 24 months post-delivery.

Table 5.5.2: Maternal Deaths in women with cirrhosis who became pregnant

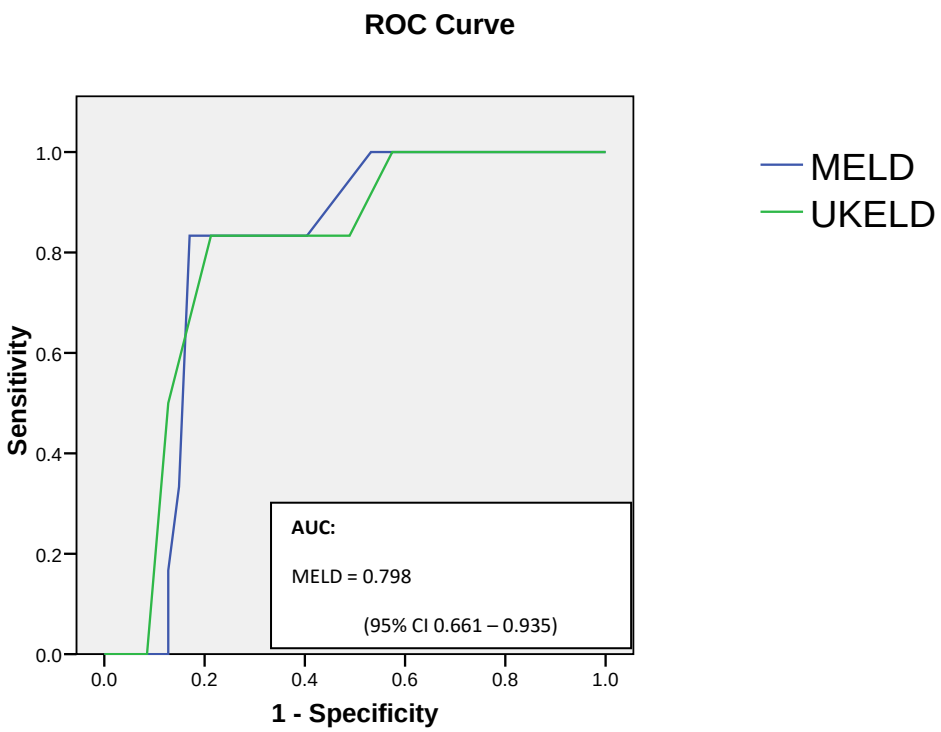
Age at conception	MELD	UKELD	Live birth	Significant pregnancy related complication	Interval from birth to death (months)	Transplanted
16	7	43	Yes	Yes	16	Yes – 2 months post-partum
34	15	47	Yes	No	28	No
33	14	47	Yes	Yes	6	No
25	10	48	Yes	Yes	At delivery	No

5.5.3 Use of prognostic scores to predict maternal outcomes

A higher median MELD score (10, (7-14) v 7, (6-17), p=0.01) and UKELD score (48, (43-48) v 43, (36-51), p=0.02) at conception was associated with an increased risk of the mother developing a significant liver related adverse event. Interestingly, neither MELD-Na (p=0.16) nor Child Pugh (p=0.2) score at conception were associated with an increased risk of the mother developing a significant liver related adverse event.

Evaluation of the receiver operator characteristic (ROC) curves for MELD and UKELD scores at conception and the development of a significant liver related complication for the mother both demonstrated an area under the ROC curve (AUC) of 0.80 at a 95% confidence interval (figure 5.5.2). Furthermore, a MELD score of greater than 10 points demonstrated 83% sensitivity and 83% specificity for predicting which patients with cirrhosis were likely to experience a significant liver related complication during pregnancy. Regarding UKELD, a score of greater than 47 demonstrated an 83% sensitivity and a 79% specificity for predicting which patients with cirrhosis are likely to experience a significant liver related complication. Interestingly no patient who had a MELD score of 6 or a UKELD score of less than 42 developed any significant hepatological complications related to their pregnancy.

Figure 5.5.2: Receiver Operator Curve for MELD and UKELD as a predictor for maternal complications related to pregnancy



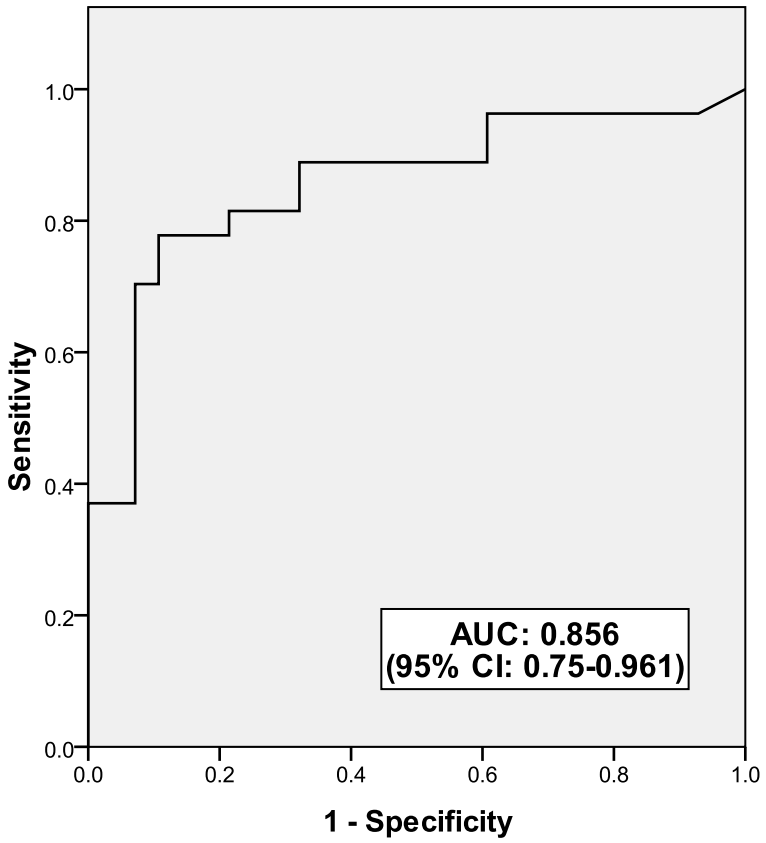
Over a mean maternal follow-up period of 7 years, in addition to the aforementioned cases, there was one further maternal death 28 months following the delivery of a second child. Despite priority listing for liver transplantation she died awaiting a graft. Two further patients required transplantation, with one patient transplanted for chronic liver disease 4-months following a termination of pregnancy and the second transplanted 24 months post-delivery.

5.5.4 Variceal Screening and Bleeding

Forty-one women carried pregnancies into the second trimester. Of these, 93% (38/41) underwent endoscopic screening for varices. One patient went into spontaneous labour following endoscopic screening at 24 weeks gestation. Her MELD and UKELD scores at conception were 8 and 45 respectively. The baby required neonatal intensive care and has learning difficulties on follow-up. No other complications related to endoscopy were noted.

Oesophageal varices were present in 50% (19/38) of those screened. No gastric varices were reported. The MELD, MELD-Na, UKELD and CP scores at conception were not associated with the presence of varices on screening endoscopy in the second trimester. The platelet count however at conception was predictive of the presence on varices on screening endoscopy (84 (28-225) vs. 184 (62-308), $p<0.001$). ROC curve analysis of platelet count at conception (as a predictor for varices on screening endoscopy in the second trimester) demonstrated an AUC of 0.856 (Fig 5.5.4). Furthermore a platelet cut off of 110 x10^9cells/l gives a 78% sensitivity and 89% specificity for predicting the presence of varices on screening endoscopy in the 2nd trimester.

Figure 5.5.4: Receiver operator curve for platelet count as a predictor of oesophageal varices on screening endoscopy in the second trimester of pregnancy



Three patients had a variceal bleed associated with pregnancy, as discussed above. All three women were known to have varices prior to conception, one of whom had had a prior episode of variceal bleeding. MELD (p=0.06) and UKELD (p=0.08) scores at conception were associated with a trend towards variceal bleeding but this did not reach statistical significance.

Women who had varices detected on screening endoscopy were more likely to deliver by caesarean when compared with women without (13/18 vs. 4/15, p=0.02). Neither MELD

(p=0.31) nor MELD-Na score (p=0.91), UKELD score (p=0.29) nor CP score (p=0.32) at conception were associated with the mode of delivery. No patient with confirmed varices had significant bleeding following caesarean section from the presence of abdominal wall varices.

5.6 Discussion

In this chapter we have identified that pregnancy in patients with cirrhosis carries a high incidence of maternal morbidity, occurring in 10% of pregnancies. A live birth rate of 58% is reported with 75% of neonates born prematurely and 17% of live births requiring neonatal intensive care support. We have also demonstrated that the prognostic scoring systems of MELD, MELD-Na, UKELD and CP score at the time of conception can be used to predict certain outcomes and complications that may be encountered during pregnancy. Moreover we have found that a MELD score of 10 or above prior to conception has an 83% sensitivity and specificity for predicting a serious liver related complication during pregnancy or after delivery. This information therefore allows tailored advice to be given to the individual regarding their specific risks associated with pregnancy in relation to the severity of their underlying cirrhosis.

Discussions regarding pregnancy and its associated risks are rarely undertaken in women with cirrhosis due to the high incidence of infertility. Failure to discuss contraception in cirrhotic women of child bearing age can therefore lead to a number of unplanned and/or unwanted pregnancies (38% in this cohort). Furthermore the safety of undergoing planed termination of pregnancy in patients with cirrhosis is unknown, with publications limited to isolated case reports. In our cohort of 9 patients who underwent medical termination, one patient had a deterioration of hepatic function and needed transplantation. We suggest therefore, that all women of child bearing age with cirrhosis should be advised regarding the importance of contraception to avoid unwanted and unplanned pregnancies along with the potential risks associated with a termination.

Spontaneous pregnancy loss in this study was 27%, when both miscarriage and still births were combined. By comparison a relatively recent prospective population study in 2003 stated a self-reported clinical abortion rate of 7.9% in the general population. (209) Interestingly, this study has shown that although the foetal loss rate is increased significantly in women with cirrhosis, this specific occurrence does not appear to correlate with the severity of the underlying cirrhosis. This may be related to several factors, the first being that cirrhotic women have irregular menstruation as cirrhosis advances and that consequently, an early pregnancy loss in patients with more advanced cirrhosis could be missed. Secondly, due to the limitations of the retrospective nature this study, many early losses may not have been reported to us. Indeed, previous published reports have estimated the spontaneous abortion rate to be higher, reported between 30% and 40% of pregnancies in women with cirrhosis. (210)

Previous case series of foetal outcomes in cirrhotic patients reported a foetal mortality rate of 8%, (105). This is considerably greater than in our report where no peri-partum foetal deaths occurred. This original study however was published in 1994 and included patients from an era dating to back to 1970's. It can be postulated therefore that mortality rates have fallen as a consequence of improved standards of medical care over the last two decades. (211) Although our cohort does include patients from as early as 1984, the majority of patients 57/62 (92%) date from 1990, making advances in medical care likely to be a significant contributing factor in foetal survival. Additionally, although the earlier study offered minimal information regarding the severity of the mothers underlying liver disease, 6/11 were reported as having developed an episode of decompensation prior to conception and 6/11 had a variceal bleed during pregnancy. This suggests that the underlying maternal liver disease was more severe in the earlier published cohort. Finally the numbers are much smaller thus one death may be over represented.

The optimal management of portal hypertension during pregnancy remains challenging with the absolute need for variceal screening during the second trimester, primary prophylaxis against variceal haemorrhage and the management of a variceal haemorrhage during pregnancy largely undefined. Management is based on best guess experience extrapolated from the non-pregnant literature. In a patient with 'at-risk' for bleeding oesophageal varices, endoscopic band ligation of varices, although not proven, is appropriate. Case reports describing this strategy in pregnancy have been published,(108) although no randomized trials have been carried out to prove efficacy. Currently, the American Association for the Study of Liver Disease (AASLD) recommends that once pregnant, women with cirrhosis should have a screening endoscopy in the second trimester,(110) since this represents the time when portal pressure increases, due to increased circulating blood volume and direct compressive effects of the gravid uterus on the inferior vena cava. Previous studies have reported the prevalence of varices in the second trimester to be in excess of 50%. (212) This current study reports a similar prevalence with varices reported in 50% of those screened. In this study, variceal haemorrhage occurred in 3 cases, which is much lower than previous reports where the incidence of bleeding has been reported to be as high as 50%. (105, 111) The lower incidence of haemorrhage, in this study is likely in-part to reflect screening in the second trimester and subsequent delivery by caesarean section if large or 'at risk' varices were present. Additionally, the use of non-selective beta blockers in patients who were deemed 'at-risk' or who had undergone a previous variceal bleed may have modified this outcome. We have demonstrated that a cut-off platelet count of 110x10^9cells/L has an 78% sensitivity and 89% specificity for predicting the presence of varices at screening endoscopy in the second trimester. Based on this finding, it may be possible if confirmed in other cohorts to use this cut-off platelet count as an arbiter for categorizing patients into those that require screening for varices in pregnancy. However, it must be acknowledged that current AASLD guidelines recommend screening everyone with cirrhosis for varices regardless of the platelet count.(110)

Caesarean section, although not proven, is thought to avoid the theoretical increased bleeding risk associated with an increase in portal pressure in the context of the Valsalva manoeuvre during labour. It must be appreciated that these women may also have abdominal wall varices and a caesarean section should not be regarded as entirely safe, although no significant bleeding was reported in this cohort. The optimal timing of when to book patients in for a caesarean section remains challenging and the risks between electively delivering a premature baby and the avoidance of a spontaneous labour must be balanced.

Liver related maternal complications including variceal bleeding, development of ascites and encephalopathy occurred in 10% of pregnancies. One patient died directly as a result of the complication and a further 2 patients that had a significant complication during pregnancy died at 6 and 16 months following delivery. This raises the question as to whether patients that decompensate during pregnancy should be considered for transplantation post-delivery even if their synthetic function recovers. Similarly, it suggests that although the prognostic scores such as MELD or UKELD are significantly lower than those at which transplantation would ordinarily be considered, patients that decompensate during pregnancy are a group that lack functional hepatic reserve and therefore may benefit from earlier transplantation.

This study has also demonstrated that a MELD score of greater than 10 points has an 83% sensitivity and specificity for identifying which patients during pregnancy are likely to have a significant liver related complication. This highlights the fact that physicians cannot be reassured by “low” MELD scores in pregnant patients with cirrhosis and suggests women with a MELD score of 10 or above should be advised against pregnancy. This is interesting since data from non-pregnant cohorts with cirrhosis has shown that in patients with a MELD score of less than 14 prior to transplant, transplantation is associated with a higher mortality than in patients with similar MELD score who are not transplanted. (213)

In conclusion we have demonstrated that the MELD and UKELD scores at conception can be used to predict likely outcomes of pregnancy in cirrhotic patients. Higher scores are associated with foetal prematurity and neonatal intensive care admission. Additionally a MELD score of greater than 10 or a UKELD of greater than 47, have a greater than 80% sensitivity and specificity for predicting which patients with cirrhosis are likely to experience a significant liver related complication and it may be safest to advise these patients against becoming pregnant. Conversely, patients with a MELD score of 6 or less can reassured that the risk of encountering a significant complication is minimal.

CHAPTER 6: Predicting outcomes of pregnancy in women with Autoimmune Hepatitis

6.1 Introduction:

Autoimmune hepatitis (AIH) is a disorder that has been recognised for over 50 years. First described by Waldenström in the early 1950's as a chronic form of hepatitis with a classical phenotype of liver disease in a younger aged women, often in conjunction with extra-hepatic manifestations including arthralgia, endocrine abnormalities and amenorrhoea.(138) Reports regarding pregnancy in patients with AIH exist from as early as the 1970's but the reported outcomes were largely unfavourable, with a high incidence of obstetric complications noted including early foetal loss, prematurity, low birth weight and a high rate of caesarean sections.(102, 139) Moreover maternal complications included pre-eclampsia, flares in disease activity, hepatic decompensation and death.(102, 139)

Subsequent to these initial reports there have been several recent case series indicating more favourable outcomes.(14, 140-142) Combining the 4 largest series in the published literature on AIH and pregnancy gives data on 142 conceptions. (14, 140-142) The maternal outcomes reported are largely favourable; however pregnancy is not without risk to the mother with 3 reports of hepatic decompensation, 1 liver transplant and 3 maternal deaths (1 liver related) all related to pregnancy.(14, 140-142) Foetal outcomes are favourable with a healthy infant expected in the majority of patients and live birth rates reported to be between 71% and 86%. (14, 140-142) These live birth rates are comparable to patients with other autoimmune conditions, but remain lower than the reported live birth rates for the general population. (143)

Despite our increase in knowledge surrounding the management of AIH during pregnancy, several concerns remain. Flares in disease activity have been reported to occur in 7-

21% of patients within the gestational period and occur at a rate varying from 11-86% in the post-partum period. (14, 140-142) In the majority of patients a flare can be controlled by augmentation of the immunosuppression however, in rare cases, a flare can lead to hepatic decompensation with the potential need for liver transplantation (LT) or death of the patient and/or foetus. (140, 142)

Distinguishing which patients are likely to have an uneventful pregnancy and those at risk of the above complications is currently challenging. In addition the optimal therapeutic regimen to prevent disease flares remains undefined, with some centres discontinuing azathioprine due to a theoretical risk of birth anomalies, (141) whilst others continue it throughout pregnancy to minimise the potential risk of a flare in AIH activity.(140) Finally, in those patients with underlying cirrhosis who become pregnant, there are likely to be additional maternal and foetal risks including a higher incidence of maternal decompensation, significant variceal / post-partum bleeding and foetal prematurity. (48) The safety of pregnancy in patients with AIH and underlying cirrhosis remains undefined and the published literature is sparse.

6.2 Aims

The data discussed above and in the introductory chapter indicate that pregnancy in this cohort of women is not without risk with reports of disease flares, hepatic decompensation, need for liver transplantation and death. Despite the above detailing potential complications in this cohort of women, identifying those women which women are likely to have an uneventful pregnancy and those at risk of the above complications is yet to be defined.

The aims of this chapter were therefore:

- To assess the incidence and severity of maternal complications in women with autoimmune hepatitis who become pregnant
- To assess the incidence and severity of foetal complications in women with autoimmune hepatitis who become pregnant
- To identify if there are any pre conception parameters that would enable physicians to predict / identify those women with AIH who are at greatest risk of developing complications in association with pregnancy.
- To assess the safety and usage of immunosuppressive regimes with regards to foetal and maternal safety.
- To allow individualised rather than generic advice to be given to individual patients with AIH who wish to become pregnant.

6.3 Methods

The master database, as described in the methods chapter was interrogated to identify all women with AIH who had reported pregnancy or whom were trying to conceive (1982-2009). In total, 81 pregnancies had been self-reported by 53 women. All women included fulfilled the criteria for definite AIH as defined by the revised International Autoimmune Hepatitis Group criteria. (214) Baseline characteristics were obtained from the medical notes and from investigations performed at the clinic visit immediately prior to conception being reported.

Information was gathered on disease duration, activity of disease, number and frequency of disease flares and medication regimen prior to pregnancy. In addition, the presence of cirrhosis was recorded if there was histological evidence on biopsy or it was deemed likely based on a combination of radiological and laboratory parameters. Maternal complications during pregnancy and in the post-partum period were recorded including flares in AIH activity, hepatic decompensation and any other adverse events. Data on abortions, including spontaneous and elective terminations of pregnancy were obtained in addition to the gestational duration, live birth rate and foetal outcomes.

For the purpose of this study, a flare of AIH was defined as a two-fold increase in serum aspartate aminotransferase (AST) activity above the upper limit of normal or a lesser increase in AST in conjunction with increased serum globulin concentration and the re-emergence of symptoms. Disease remission was defined as the disappearance of symptoms, improvement of serum AST levels to less than twice normal, normal gamma globulin levels and if biopsy done the presence of normal hepatic tissue or minimal inflammation and no interface hepatitis. (215)

6.4 Statistical Analysis

Data is presented using median and range for numerical values. To determine whether significant differences existed between groups, we applied the Student's t test, or the Mann-Whitney-U non-parametric method as appropriate. Differences in nominal data were compared either by the Chi squared test or using Fishers exact test when the number was less than 5 in any given cell of a 2x2 table. A p value of <0.05 was considered to be of statistical significance. All statistical analysis was performed using the SPSS statistical software package version 14 (SPSS Inc., Chicago, IL).

6.5 Results

A total of 81 pregnancies in 53 women with AIH were reported between 1982 and 2009 at the Institute of Liver Studies, King's College Hospital. The median age at diagnosis of AIH was 20 years (range 5-42 years) and the median age at conception was 26 years (range 16-42 years). The median duration of disease prior to conception was 7 years (range 0-25 years). Sixty three percent (51/81) of patients were in biochemical remission for over a year prior to conception. Thirty three conceptions occurred in 21 women who had underlying cirrhosis. Six pregnancies were conceived with the help of in vitro fertilisation (IVF).

6.5.1 Assisted conception

There were 7 conceptions with IVF occurring in 5 women. Overall these resulted in 4 live births (one chid had cerebral palsy), 1 still birth and 2 miscarriages. The median age at conception was 35-years (range 29-42 years).

There were three conceptions in 2 women with cirrhosis (Childs Pugh A). The first women had 2 miscarriages at 8 and 10-weeks with no adverse maternal effects noted. The second women with cirrhosis delivered a healthy baby at 36-weeks following an uneventful pregnancy, however she had a significant deterioration in hepatic function 12-months post-partum and died whilst undergoing a liver transplant assessment.

There were 4 conceptions with IVF in 3 non-cirrhotic women. Two women delivered healthy babies at 38-weeks' gestation. The first had a mild post-partum flare in AIH activity which settled spontaneously; the second developed de-novo AIH 3 month's post-partum which was successfully treated with a combination of prednisolone and azathioprine. The final non cirrhotic patient had 2 conceptions with IVF. In the first pregnancy she developed severe AIH activity at 24-weeks, with the development of ascites. A caesarean section was performed at 28

weeks and the child has cerebral palsy. Her second pregnancy was complicated by a spontaneous rupture of membranes at 20 weeks resulting in foetal loss. There was no change in the AIH activity.

Table 6.5.1: Outcomes of 7 conceptions with IVF in 5 women with AIH

Patient	Age at conception	Cirrhosis	Foetal outcome	Maternal Outcome	Comments
1	35	YES	Miscarriage 8 weeks	No Change	No adverse maternal effect
	36	YES	Miscarriage 10-weeks	No Change	No adverse maternal effect
2	29	YES	Live Birth 36-weeks	No effect	Significant deterioration 12 months post-partum, and mother died awaiting transplant assessment
3	40	NO	Live Birth 38-weeks	Post-partum flare – settled spontaneously	Overlap with PBC
4	40	NO	Live Birth 38-weeks	De Novo AOH at 3 months post-partum	Good resolution with prednisolone
5	30	NO	C. Section 28-weeks, baby has cerebral palsy	Severe AIH at 24-weeks	Recovered post-delivery with prednisolone and azathioprine
	33	NO	SROM at 20-weeks with foetal loss	Severe PV bleeding	No flare in AIH activity

6.5.2 Therapeutic Regimens

At conception, 61 patients (75%) were receiving therapy for control of their AIH. Of these, 27 patients were on prednisolone monotherapy (mean dose 10mg/day, range 2.5mg - 40mg), 7 were on azathioprine monotherapy (range, 1mg/kg/day-2mg/kg/day) and 25 patients were on combination therapy of azathioprine (1mg/kg/day - 2mg/kg/day) and prednisolone (mean dose 5mg (range 2.5-20mg)). In addition, one patient was taking tacrolimus (2mg/day) in conjunction with prednisolone. Amongst those patients on medication, 46 (74%) had been stable on their medication regimen for over 1-year prior to conception.

Twenty patients were on no treatment prior to conception, 2 were de novo presentations of AIH in association with pregnancy, 5 were cirrhotic with burnt out disease, 6 were in biochemical and histological remission and had subsequently had treatment discontinued at a median time of 32-months prior to conception. The remaining 7 had their medication stopped either due to personal wishes or on medical advice with regards to their wish to become pregnant.

In total, 32 conceptions occurred in women on azathioprine. Of these, there were 21 live births, 6 elective terminations, 4 spontaneous abortions and 1 maternal (and subsequent foetal) death. Of the live births, there were no reported foetal anomalies. In the 20 conceptions that occurred in women on no treatment, there were 17 live births, 2 elective terminations and one still birth at 21 weeks gestation. Of the live births abnormalities have occurred in 2 children. The first has cerebral palsy as described above and the second developed Perthes' disease of the hip.

A comparison between those pregnancies that occurred on therapy (prednisolone, azathioprine or tacrolimus) with pregnancies that occurred in women not on immunosuppression revealed no significant differences in the live birth rate (42/61 vs. 17/20,

p=0.24), termination rates (10/61 vs. 2/20, p=0.72), miscarriage rates (8/61 vs. 0/20, p=0.19) or gestational period (39 (28-40) vs. 39 (27-30), p=0.8).

However, the incidence of a flare occurring in AIH activity at any time in the gestational period or and time in the post-partum period was significantly higher in those women that were not on therapy when compared to those on therapy (10/20 vs. 16/61, p=0.048). Data pertaining to pregnancy outcome and disease flares in relation to therapy is summarised in table 6.5.2.

Table 6.5.2: Effect of therapy on maternal and foetal pregnancy outcomes

	Live birth rate	Termination	Miscarriage	Gestation <37 weeks	Gestational flare	Post-partum flare	Any Flare
Prednisolone monotherapy	20/27 (74%)	3/27 (11%)	4/27 (15%)	37 (28-40)	2/20 (10%)	7/20 (35%)	8/20 (40%)
Azathioprine +/- prednisolone	21/32 (65%)	6/32 (19%)	4/32 (13%)	38 (32-39)	0/32 (0%)	7/32 (21%)	7/32 (21%)
Any therapy (prednisolone, tacrolimus, azathioprine)	42/61 (68%)	10/61 (16%)	8/61 (13%)	38 (28-40)	2/61 (3%)	15/61 (24%)	16/61 * (26%)
No Therapy	17/20 (85%)	2/20 (10%)	0/20 (0%)	38 (27-39)	3/20 (15%)	8/20 (40%)	10/20 * (50%)

* $p<0.05$

6.5.3 Foetal Outcomes

The live birth rate was 73% (59/81). Of the remaining 22 conceptions, there were 8 spontaneous miscarriages (10%), 12 terminations of pregnancy (5 of which were medically advised), 1 still birth and 1 foetal death related to unexpected maternal death as a result of severe pulmonary hypertension due to pulmonary emboli. The median gestation was 38-weeks (range 27-40 weeks) and the median birth weight was 2750 grams. Prematurity, defined by a live birth prior to 37-weeks' gestation occurred in 12/59 (20%) of pregnancies.

Six neonates (11%) required admission to a SCBU immediately after birth. All survived to hospital discharge however one neonate born at 28 weeks gestation by caesarean section has cerebral palsy (as discussed above). One neonate died 10 weeks following delivery (mortality rate 1/59, (0.2%)) due to overwhelming sepsis. In that instance the mother was not taking azathioprine.

Importantly, the live birth rate was lower in individuals who were cirrhotic at the time of conception (14/33 vs. 4/48, p=0.02). In addition, a neonate was statistically more likely to need admission to the special care baby unit (SCBU) if the mother had pre-existing cirrhosis (4/19 vs. 2/40, p=0.07) or had a flare in disease activity during pregnancy (2/4 vs. 4/55, p=0.047). Prematurity, as defined by a birth prior to 37 weeks gestation was not statistically associated with the absence of maternal therapy (p=0.07), nor associated with a flare in AIH activity during the gestational period (p=0.18).

All children have been followed up for a median of 7-years. Two significant abnormalities have been identified (both in mothers not on azathioprine). The first is the child born at 28 weeks with cerebral palsy, the other child has Perthes disease of the hip.

Table 6.5.3: Foetal outcomes in women with AIH

	Live Birth rate	Prematurity <37 weeks	SCBU
Cirrhosis vs. no Cirrhosis (n=33) (n=48)	19/33 vs. 40/48 p=0.02	5/19 vs. 7/40 p=0.43	4/19 vs. 2/40 p=0.07
Maternal disease remission > 1year (n=52) vs. no remission (n=29)	38/52 vs. 21/29 p=0.95	8/38 vs. 4/21 p=0.99	3/38 vs. 3/21 p=0.65
Therapy (n=61) vs. no therapy (n=20)	42/61 vs. 17/20 p=0.25	6/42 vs. 6/17 p=0.07	5/42 vs. 1/17 p=0.66
AIH gestational flare (n=5) vs. no gestational flare (n=76)	4/5 vs. 55/76 p=0.99	2/4 vs. 10/55 p=0.18	2/4 vs. 4/55 p=0.047

6.5.4 Maternal Outcomes

The overall maternal complication rate was 31/81 (38%) conceptions. These consisted of 1 maternal death (whilst pregnant), 3 maternal deaths within 12 months of delivery. Two patients required liver transplantation (LT) within 12 months of delivery and 1 patient decompensated during pregnancy but subsequently re-compensated post-delivery. In addition to the above a flare in disease activity occurred in association with 26 pregnancies (32%) and 2 women had a severe post-partum haemorrhage requiring blood transfusion.

A flare in disease activity was the most common complication occurring in 26/81 (33%) pregnancies (median AST 200, range 80-1025 IU/L). Twenty occurred post-partum (within the first 3 months following delivery), and 6 during the gestational period. Medication

augmentation was required in 20 cases and consisted of increased doing of prednisolone (20/26), azathioprine (4/26) and tacrolimus (2/26). In 5 cases, a flare in disease activity precipitated an episode of hepatic decompensation. A flare in AIH was more likely in patients who had not achieved disease remission for greater than 1-year prior to conception (14/29 vs. 12/52, p=0.03) or were older at conception (26 vs. 29 years, p=0.047). Additionally, patients who had a flare in association with pregnancy were more likely to decompensate from a liver standpoint (5/26 vs. 1/55, p=0.01).

A serious maternal adverse event (death or LT during or within 12 months of delivery or hepatic decompensation during or within 3 months of delivery) occurred in association with 9 pregnancies (11%). The maternal death which occurred in pregnancy underwent post-mortem examination and the cause of death was a result of severe pulmonary hypertension due to pulmonary thrombi (discussed above). Six conceptions were associated with hepatic decompensation. The first women who decompensated was cirrhotic at conception, and she developed a significant deterioration of her liver function tests peri-partum. Post-partum she developed encephalopathy, and subsequently underwent liver transplantation (LT). She died 14-months later from graft failure secondary to recurrent rejection on a background of poor adherence. The second woman was also cirrhotic at conception. At 10 weeks gestation she developed ascites which was resistant to diuretics. She underwent a termination of pregnancy at 12-weeks' gestation and re-compensated. The same women had a second pregnancy 1-year later she developed a gestational flare at 26-weeks she delivered at 28-weeks but decompensated with ascites post-partum. She underwent LT 12-months later and remains well over the subsequent 10-year follow-up period. The third women had a variceal bleed at 31-weeks' gestation. The bleeding was controlled endoscopically and she delivered a healthy baby at 34-weeks by caesarean section. She died 7-months later from a further variceal bleed. The fourth women who decompensated (discussed above) developed severe AIH activity at 24 weeks and her baby delivered at 27-weeks has cerebral palsy. Her disease remains stable on

immunosuppression 11-years post-delivery. The final woman who decompensated, had a post-partum flare and developed significant jaundice and small volume ascites. She was transplanted 3-yers post-partum. In addition to the above cases, 2 further women died within 1 year of delivery; the first developed severe worsening of her liver function 12-months post-partum and died whilst undergoing a LT assessment. The second was poorly compliant with AIH treatment, had a variceal bleed 12-months post-partum, refused blood transfusion and died.

Table 6.5.4: Summary of 9 conceptions with severe adverse maternal outcomes in association with pregnancy

Patient	Cirrhosis	Maternal complication	Peak AST	Foetal Outcome	Maternal Outcome
1	No	Died 28 weeks gestation	24	Died	Death: sudden death at 25 weeks for pulmonary hypertension secondary to thromboembolism
2	Yes	Post-partum flare with encephalopathy – transplanted	217	Alive / healthy	Death: 14-months post-partum, from poor compliance on chronic rejection
3	Yes	Post-partum flare – very difficult to control. Significant jaundice mild ascites.	643	Alive / healthy	Transplanted: 3 years post –partum
4 a 4 b	Yes Yes	Post-partum flare with decompensation (ascites) Ascites at 10 weeks, unable to control therefore Termination of pregnancy	647 151	Born 28 weeks – SCBU, Alive healthy NA	Transplanted: 3 years post-partum of second child
5	No	Severe flare at 24 weeks, decompensated with ascites	200	Baby delivered at 28 weeks – cerebral palsy	Alive Remains stable on immunosuppression
6	Yes	Variceal bleed at 31 weeks, controlled endoscopically	30	Alive healthy, 34 weeks	Death: 7 months post-partum secondary to uncontrollable variceal bleed.
7	Yes	Severe PPH		Born 32 weeks needed SCBU	Death: Variceal bleed 1 year post-partum, refused blood transfusion
8	Yes	Uneventful pregnancy	28	Healthy	Deterioration 12 months post-partum, died whilst having LT assessment

6.5.5 Impact of cirrhosis

Thirty three conceptions occurred in 21 women with cirrhosis. The presence of maternal cirrhosis impacted on foetal outcome with the live birth rate being lower in mothers who were cirrhotic at the time of conception (14/33 vs. 4/48, p=0.02). Furthermore maternal cirrhosis was also associated with prematurity and the need for a neonatal admission to a special care baby (4/19 vs. 2/40, p=0.07) post-delivery, although this did not reach statistical significance.

Maternal outcomes were also affected by the presence of cirrhosis. Conception in a women with AIH and underlying cirrhosis was more likely to be complicated by the mother

developing a serious maternal adverse event (defined above) when compared to conceptions in women with AIH without cirrhosis (7/33 vs. 2/48, p=0.028). This remained significant when an individual women's outcomes were analysed rather than individual conceptions (p=0.041).

The model for end stage liver disease (MELD) score was calculated in all cirrhotic patients where data available (n=19) from the clinic visit immediately prior to conception. Both a birth prior to 37 weeks (p=0.07) and the need for admission to a special care baby unit (p=0.06) were non-significantly associated with a higher MELD score at conception. Moreover a higher MELD score at conception was non-significantly associated with the development of a serious maternal adverse event (p=0.07).

6.5 Discussion

In this chapter we have identified that pregnancy in AIH can be associated with a high incidence of disease flares (33%) and serious maternal adverse events (11%). We have shown that disease flares are associated with poor disease control in the year preceding pregnancy (p=0.03) and the absence of therapy whilst pregnant (p=0.047). Disease flares are clinically important as they were associated with a significantly increased risk of hepatic decompensation (p=0.01) and an increased need for neonatal admission to special care baby units (p=0.047). Furthermore we have shown that continuing immunosuppression throughout pregnancy in women with AIH is relatively safe with no apparent increased risk of adverse effects on either live birth rate or congenital anomalies. Finally we have demonstrated that in women with underlying cirrhosis the live birth rate is reduced and mothers with cirrhosis are more likely to develop a significant adverse event.

Pregnancy is widely accepted to impact on AIH activity. In this study a flare in AIH activity occurred in 33%, with the majority (78%) occurring in the post-partum period. Previous studies on AIH during pregnancy report similar findings, with a stable course of AIH activity in the gestational period with the majority of flares occurring in the post-partum period. (14) The mechanism for this phenomenon is incompletely understood. However, evidence published regarding the aetiopathogenisis of AIH has demonstrated that an impairment in regulatory T-cell number and function is key to the loss of immune tolerance and thus the emergence of an uncontrolled effector autoimmune response. (17, 18) Pregnancy induces the temporary development of immunological tolerance in order to allow the mother to tolerate the paternally derived antigens expressed by the foetus. Regulatory T-cells are therefore required for the maternal immune system to tolerate the foetal allograft, and there is an increase in their circulating number during pregnancy. (12, 13) Taking into account the above factors, it becomes clearer why patients with AIH, and indeed other autoimmune conditions frequently undergo

remission during pregnancy and then flare in the post-partum period, such that when pregnancy ends, tolerance breaks down and flares in disease activity occur.

The delivery of a healthy baby is a prime consideration of any woman who wishes to become pregnant. Concerns regarding continuing immunosuppression whilst pregnant, and in particular azathioprine remain. In animal models, azathioprine has been associated with skeletal abnormalities, cleft palate, hydrops foetalis and haemopoetic abnormalities of the foetus. (195, 196) In humans, lymphopenia, hypogammaglobulinaemia and thymic hypoplasia have all been reported in children born to mothers on azathioprine. (216) Furthermore, azathioprine has been linked to pre-term deliveries. (197) Experience with azathioprine in pregnancy has increased dramatically in recent times with accumulated data derived from other patient populations especially those with inflammatory bowel disease, rheumatoid arthritis or patients following solid organ transplantation. (179, 217, 218) The conclusions from these studies corroborate our findings, that azathioprine is safe and should ideally be continued during pregnancy to maintain maternal disease remission.

In this current study, little has been found to suggest that azathioprine or its metabolites are toxic in pregnancy with its use having no adverse impact on the live birth rate, gestational age or rate of congenital abnormalities. Moreover, immunosuppressive therapy was associated with a significantly reduced maternal AIH flare rate ($p=0.047$) when compared to women with AIH not on therapy and foetal prematurity was more common in mothers not immunosuppressive on therapy, however this did not reach statistical significance ($p=0.07$). This study therefore adds growing support to the theory that the greatest chance of a healthy baby in patients with AIH is attained by continuing therapy with the aim of achieving a healthy mother throughout pregnancy via good disease control.

The incidence of a serious maternal adverse event occurred in 9 conceptions (11%). This is significantly higher than that of the general population. (219) The increased incidence of a

serious maternal adverse event in association with pregnancy in women with AIH has been reported in other series; Schramm et al. and Terrabuio et al. both describe a serious maternal complication rate of 9% and 7.8% respectively. (141, 142) To-date, identifying which women with AIH are likely to have a risk free pregnancy and who are at an increased risk of developing serious complications has been challenging. This study has identified that sub-optimal disease control in the year prior to conception (p=0.03), the absence of therapy (p=0.047), cirrhosis (p=0.02) and increasing maternal age (p=0.047) are all pre-conception parameters that confer increased pregnancy risk. This study therefore will hopefully help to optimise pre-conception counselling allowing potential mothers to make informed decisions regarding pregnancy.

We have demonstrated in the previous chapter that prognostic scoring systems such as MELD score can help identify pre conception which cirrhotic women are likely to develop liver related decompensation during pregnancy. (220) In this study we have identified that women with cirrhosis are more at risk of developing a serious maternal adverse event (p=0.028) and are more likely to have premature babies (0.07) with an increased need for admission to a special care baby unit (0.07) when compared to those mothers without cirrhosis. Moreover we have shown that in those women with cirrhosis a higher MELD score at conception is associated with a further increased chance of the above adverse outcomes. Whilst we appreciate that not all of the above findings reach statistical significance and therefore must be interpreted with caution, we feel the findings have clinical significance and have thus been included in the manuscript.

This study has several limitations. Firstly the retrospective nature means that all women were not monitored in the same way throughout their pregnancy. Pregnancy was self-reported and thus early miscarriage may not have been noted and thus the reported incidence may be falsely low. Secondly as experience and treatment of AIH has evolved the treatment at out centre of AIH and pregnancy has changed. This means that all women were not treated with the same protocol during pregnancy, in that in the earlier pregnancies azathioprine was

discontinued due to concerns regarding its safety whereas our current practice is to maintain immunosuppression throughout pregnancy. Finally although we have identified several preconception parameters which are associated with adverse outcome, these have been evaluated by univariate analysis due to the relatively small numbers and may not be individually associated on multivariate analysis.

In conclusion, we have shown for the first time that poor AIH control in the year prior to pregnancy and the absence of therapy are associated with an increased risk of a flare in AIH activity whilst pregnant. This is important as we found that AIH flares were significantly more likely to lead to hepatic decompensation, and an increased risk neonatal admission to SCBU. Furthermore we report no adverse effects of azathioprine and have demonstrated better foetal and maternal outcomes in patients on therapy. We hope that this study will help optimise pre-conception counselling and pregnancy management in women with AIH.

Chapter 7: Pregnancy following Liver Transplantation – predicting outcomes

7.1 Introduction:

Liver transplantation (LT) has evolved to be a universally accepted treatment for patients with acute liver failure and end-stage chronic liver disease. Survival rates following LT have improved steadily over the last 2 decades, with current five-year survival rates reported to be in excess of 70% and long-term survival is now expected in the majority of recipients.(167, 168) As survival rates following LT improve, focus of medical care has broadened to incorporate factors that impact on quality of life. (173) For female transplant recipients of child bearing age, the desire for a family often arises and carries with it with questions regarding fertility and the safety of pregnancy for the mother, graft and foetus.

The first successful pregnancy following LT was reported 1978, with a healthy boy delivered at 40.5 weeks gestation, weighing 2,400g, with both the mother and baby in excellent health 1-year post delivery. (178) Subsequent to this, many case series have been reported, (179-182) which have expanded our knowledge regarding the safety and outcomes pregnancy following LT. Overall, the outcomes are largely favourable. (179, 180) However, data suggests that pregnancy in LT recipients can be associated with unpredictable graft deterioration, an increased risk of pre-eclampsia, infections and diabetes in the mother. For the foetus, prematurity, low birth weight with the potential for long term disability exists.

Acute cellular rejection (ACR) has been reported to complicate between 10 and 17% of patients in the gestational period, (179-183) and 3-12% of patients in the post-partum period.(179-181) Graft loss directly related to ACR in pregnancy appears rare with the majority of episodes controlled with immunosuppression augmentation or intravenous steroids.

Although ACR during pregnancy is unpredictable, there is evidence that delaying pregnancy for at least 12 months following LT is associated with a lower risk. (179, 184) Regarding non graft related maternal complications the incidence of pre-eclampsia and eclampsia are increased with rates of between 14 and 23%. (179, 181, 184) Other maternal risks include bacterial and viral infections (27%) and gestational diabetes (5%). (184) Foetal outcomes are largely acceptable with a live birth rate of 73% reported by the national transplant pregnancy register (NTPR) but with 30% of neonates born prematurely and 30% with low birth weight. (184)

Distinguishing the minority of LT recipients who are at risk of the above serious adverse outcomes during pregnancy and those who are likely to have an uneventful pregnancy remains challenging. This makes tailoring pre-conception counselling to the individual difficult and results in each patient being given generic outcome data from a largely heterogeneous cohort of women. Combining this with the fact that much uncertainty remains regarding the effect of immunosuppression on foetal outcomes and the optimal timing of pregnancy following LT, makes it is clear that more data in this unique cohort of patients is needed.

7.2 Aims

The data discussed above and in chapter 1 indicates that pregnancy following liver transplantation is a realistic prospect for the majority of healthy female LT recipients with good outcomes for the mother, graft and foetus. Despite this, there remains a subset of patients in which pregnancy can precipitate rejection and can result in adverse outcomes. Detailing the potential complications in this cohort of women and trying to identify those who are at risk of adverse outcomes pre-conception is the focus of this chapter. The work detailed in this chapter aims:

- To assess the effect of pregnancy on graft function post liver transplant
- To assess the effect of liver transplantation on maternal complications during pregnancy
- To assess the incidence and severity of foetal complications in women post LT who become pregnant
- To identify if there are any pre conception parameters that would enable physicians to predict / identify those women post LT who are at greatest risk of developing complications in association with pregnancy.
- To assess the safety and usage of immunosuppressive regimes with regards to foetal and maternal safety.
- To allow individualised rather than generic advice to be given to post LT patients who wish to become pregnant.

7.3 Patients and Methods

We reviewed and audited all LT patients who reported pregnancy at our institution between 1988 and 2011. Patients were identified from a prospectively collated liver database using the search terms pregnancy, LT, miscarriage, termination and live birth. The clinical records were reviewed in all patients and data extracted in a standard fashion. Details regarding maternal age, indication for LT, interval between LT and conception, and baseline immunosuppression were recorded. Maternal complications during pregnancy including hypertension, pre-eclampsia, gestational diabetes, sepsis and renal failure along with specific hepatological complications including acute cellular rejection and graft loss were recorded. Data on pregnancy losses, including spontaneous and elective terminations of pregnancy were obtained in addition to the gestational duration, birth weight, live birth rate and congenital abnormalities. Longer term outcomes were assessed regarding child development and graft and maternal survival.

7.4 Statistical analysis

Data is presented using median and range for numerical values. To determine whether significant differences existed between groups, we applied the Student's t test, or the Mann-Whitney-U non-parametric method as appropriate. Differences in nominal data were compared either by the Chi squared test or using Fisher's exact test when the number was less than 5 in any given cell of a 2x2 table. A p value of <0.05 was considered to be of statistical significance. All statistical analysis was performed using the SPSS statistical software package version 14 (SPSS Inc., Chicago, IL)

7.5 Results:

A total of 117 conceptions occurred in 79 LT recipients between 1988 and 2011. The indications for LT are summarised in table 7.4.1. The majority of conceptions occurred in patients maintained on either cyclosporine (n=34) or tacrolimus (n=81) as their primary immunosuppression. In addition 1 patient was taking sirolimus and 1 was maintained on azathioprine and prednisolone. The median age at conception was 29-years (range 19-47 years) and the median interval between LT and conception was 48-months (range 1 – 240 months). Overall 49 women had one conception, 19 women had 2 conceptions, 7 women had 3 conceptions, 1 woman had 4 conceptions and 1 woman had 5 conceptions.

Table 7.5.1: Indications for Liver Transplantation among 79 patients who reported pregnancy at King's College hospital

Aetiology	**N (%)**
Drug Toxicity	15 (19%)
Seronegative hepatitis	12 (15%)
Autoimmune hepatitis	10 (13%)
Budd Chiari Syndrome	6 (8%)
Wilsons Disease	6 (8%)
Primary Sclerosing Cholangitis	5 (6%)
Primary Biliary Cirrhosis	5 (6%)
Secondary Biliary Cirrhosis	5 (6%)
Viral	3 (4%)
Miscellaneous *	12 (15%)

***** Alpha 1 antitrypsin deficiency, familial ductopenia, intrahepatic cholestasis, glycogen storage disease, Fibrolamellar liver tumour, Epitheloid haemangioendothelioma, congenital hepatic fibrosis, Crigler Najjar

7.5.1 Maternal Outcomes

No patient died as a direct result of pregnancy. Four women (5%) had a complication associated with pregnancy that necessitated admission to the liver intensive care unit (LITU). The first patient developed a hepatic artery thrombosis (HAT) following a spontaneous miscarriage at 12 weeks, she required re-transplantation. The second patent underwent a termination of pregnancy (TOP) due to patient choice, following which she developed septicaemia secondary to a liver abscess in her auxiliary graft. The auxiliary graft was removed as her native graft function had recovered. The third patient developed infected ascites and streptococcal sepsis at 20-weeks' gestation on a background of chronic ductopaenic rejection. She delivered at 28-weeks following spontaneous rupture of membranes and the neonate required a prolonged stay in the special care baby unit (SCBU). The final patient admitted to the LITU developed gram negative sepsis following intravenous methylprednisolone for treatment of acute cellular rejection (ACR) following a caesarean section at 36 weeks gestation. No common features existed in these women prior to conception that would have identified the 4 women at increased risk of requiring admission to LITU.

Additional maternal complications encountered during pregnancy included hypertension (n=22), pre-eclampsia (n=16), eclampsia (n=3) and gestational diabetes (n=8). Hypertension, pre-eclampsia or eclampsia were no more common with cyclosporine based immunosuppression when compared to those pregnancies in women on tacrolimus. Furthermore, the incidence of gestational diabetes was not higher in those women taking tacrolimus when compared to those on cyclosporine based immunosuppression (Table 7.5.2).

Table 7.5.2: Maternal complications related to pregnancy in relation to primary immunosuppression (2 patients excluded from analysis (patient on sirolimus / patient on prednisolone and azathioprine)

Maternal Complication	All n=115(%)	Cyclosporine n=34 (%)	Tacrolimus n=81 (%)	P value
Pregnancy induced Hypertension	22 (19%)	4 (12%)	18 (22%)	0.29
Preeclampsia	16 (14%)	5 (15%)	11 (13%)	0.35
Eclampsia	3 (3%)	1 (3%)	2 (2%)	0.99
Gestational diabetes	8 (7%)	1 (3%)	7 (7%)	0.43
Bacterial sepsis	6 (5%)	1 (3%)	5 (6%)	0.67
Viral infections	5 (4%)	2 (6%)	3 (4%)	0.63
Rejection	17 (15%)	8 (24%)	9 (11%)	0.08

7.5.2 Acute cellular rejection

Eighteen cases of acute cellular rejection (ACR) were identified on clinical and biochemical parameters during pregnancy or in the immediate post-partum period (within 8 weeks of delivery). Sixteen were confirmed histologically. In all cases the liver biopsy was done under ultrasound guidance and no complications were noted. No episode of rejection resulted in graft loss. Five cases were deemed to be of a severity to require intravenous methyl-prednisolone, followed by a reducing course of prednisolone. The remaining 13 were controlled with augmentation of baseline immunosuppression and oral prednisolone.

Rejection was significantly more common in those women who conceived within 12 months of LT (p=0.001) and was associated, non-significantly with cyclosporine based immunosuppression (p=0.08). An episode on rejection during the pregnancy did not impact on the gestation at delivery (p=0.67), the need for a neonate to be admitted to SCBU (p=0.26) or the live birth weight (p=0.13). Women that had an episode of rejection were more likely to be delivered by caesarean section (p=0.07) although this did not reach statistical significance.

7.5.3 Long term maternal outcomes

Over a median follow-up period of 52-months post-delivery, there were 3 maternal deaths. The first death was related to post-transplant lymphoproliferative disease, 18 months post-delivery of a healthy neonate. The second died of graft failure following a redo LT for chronic rejection, 7 years following a molar pregnancy. The final patient that died had autoimmune hepatitis and had been transplanted 4 times for chronic rejection. Her pregnancy miscarried at 10 weeks. No death was considered to be pregnancy related.

Eight patients underwent re-transplantation at a median time of 60 months post LT (range 18 – 120 months). Indications for re-transplantation included chronic rejection (n=4), recurrent disease (n=3) and late hepatic artery thrombosis (n=1). In all cases, graft loss was thought to be unrelated to pregnancy. Interestingly, women that had an episode of ACR during pregnancy were more likely undergo re-transplantation over long term follow-up than those women that did not. (5/18 vs. 3/99, p=0.001).

7.5.4 Immunosuppression

Eighty one patients were maintained on tacrolimus based immunosuppression and 34 on cyclosporine throughout pregnancy. In addition 1 patient was taking sirolimus and 1 was maintained on azathioprine and prednisolone. Two conceptions occurred in women on mycophenolate moefetil and tacrolimus; 1 of these women had an elective termination, the second delivered at 28 weeks following hepatic decompensation on a background of chronic rejection. The neonate required admission to the SCBU for 7 weeks but has no congenital abnormalities and normal developmental milestones on follow-up. Patients who were on cyclosporine as their primary immunosuppressive agent were more likely to be on dual therapy with prednisolone (84% vs 31%, p=0.0002) and/or azathioprine (57% vs. 1%, p=0.0001) and had a trend towards an increased rate of pregnancy associated graft rejection (p=0.08). The choice of immunosuppression did not impact on other maternal complications or foetal outcomes. (Tables 7.5.3)

Table 7.5.3: Foetal outcomes in relation to pregnancy and maternal immunosuppression (2 patients excluded from analysis (patient on sirolimus / patient on prednisolone and azathioprine)

Foetal Outcome / Complication	**All n=115 (%)**	**Cyclosporine n=34 (%)**	**Tacrolimus n=81 (%)**	**P value**
Miscarriage	20 (17%)	5 (15%)	15 (19%)	0.62
Termination of pregnancy	12 (10%)	1 (3%)	11 (14%)	0.10
Live Birth rate	83 (72%)	27 (79%)	54 (67%)	0.17
Foetal Outcomes for live births	**All n=83**	**Cyclosporine n=28**	**Tacrolimus n=55**	
Caesarean section	34 (41%)	10 (35%)	24 (44%)	0.45
Normal birth weight	59 (71%)	18 (65%)	41 (75%)	0.30
Low / very low birth weight	24 (29%)	10 (35%)	14 (25%)	0.30
Gestation <37 weeks	26 (31%)	10 (35%)	16 (29%)	0.50
SCBU admission	7 (8%)	3 (11%)	4 (7%)	0.68

7.5.5 Foetal outcomes

The live birth rate was 73% (85/117) including 2 twin births. Of the remaining conceptions, 20 (17%) miscarried (spontaneous loss of pregnancy prior to 24 weeks), 12 (10%) underwent an elective termination of pregnancy (TOP), there was 1 molar pregnancy and 1 still birth (spontaneous loss of pregnancy after 24 weeks gestation). The indications for patients having a TOP were medical advice secondary to deterioration in graft function / persistent severe chronic rejection (n=3), warfarin therapy in the 1st trimester (n=2), uncontrolled psychiatric illness (n=1) and patient choice (n=4). In 4 of the above cases, a TOP was associated with a significant maternal complication including precipitation of an episode of ACR in one

patient. Two patients had severe vaginal bleeding necessitating blood transfusion post TOP and finally one patient developed septicaemia secondary to development of a liver abscess in her auxiliary graft. Of the 20 patients that had a spontaneous miscarriage the median gestational week of pregnancy loss was 12 (range 6-18 weeks). There was no significant difference in pre-conception IS regime, time from transplant, or maternal age that would have allowed an increased risk of miscarriage to be predicted.

Overall, median gestation for the 85 live births was 38 weeks, with 26/85 (31%) of neonates born before 37 weeks gestation and 5/85 (6%) born at less than 30 weeks gestation. Of the 26 neonates born before 37 weeks gestation 9 were secondary to medically induced prematurity for maternal pre-eclampsia/eclampsia (n=6), maternal hepatic decompensation (n=1) and intra uterine growth retardation (n=2). The median birth weight was 2745 grams (range 554 – 4256 grams), 71% of new-borns were of normal birth weight (>2500 grams), 19% were of low birth weight (1500-2500grams) and 10% were of very low birth weight (<1500grams). Seven neonates needed admission to the special care baby unit (SCBU) and all survived to hospital discharge. The need for admission to SCBU was associated with an earlier gestational week ($p<0.0001$) and a lower birth weight ($p=0.0003$). Both prematurity ($p=0.001$) and a low or very low birth weight ($p=0.001$) were associated with the development of maternal pre-eclampsia. No other adverse maternal events including ACR ($p=0.67$), diabetes ($p=0.76$), or sepsis ($p=0.58$) were significantly associated with prematurity.

Thirty four (40%) women delivered by caesarean section and 51 (60%) had a vaginal delivery. There were no congenital abnormalities and only one child who was born at 24 weeks gestation has delayed developmental milestones. Maternal baseline immunosuppression had no significant effect on any of the above foetal outcomes. The above data are summarized in table 7.5.3.

7.5.6 Timing of pregnancy:

Out of the 117 conceptions, 13 (11%) occurred within 12 months of LT and 105 occurred beyond 12 months of LT. Delaying conception for at least 1 year post liver transplantation had no differences in foetal outcomes with respect to the live birth rate (p=75), the need for a caesarean section (p=0.58), the incidence of prematurity (p=0.2) or the need for neonatal admission to the SCBU (p=0.99). The incidence of rejection was significantly higher in those women conceiving within 1 year of LT (p=0.001). This data is summarised in table 7.5.4.

Table 7.5.4: Comparison of the rates of maternal complications and foetal outcomes classified according to conception within 12 months of transplant or conception beyond 12 months from transplant.

	All Pregnancies N=117	**LT → conception <12 months**	**LT → conception > 12 months**	**p value**
All conceptions	117	13	104	
Live Birth Rate	85/117 (73%)	10/13 (77%)	75/104 (72)	0.75
Rejection	17/117 (15%)	6/13 (46%)	11/104 (11%)	**0.001**
Pre-eclampsia / eclampsia	19/117 (16%)	3/13 (23%)	16/104 (15%)	0.39
Caesarean section	36/85 (44%)	5/10 (50%)	31/75 (41%)	0.58
Prematurity	28/85 (32%)	5/10 (50%)	23/75 (31%)	0.20
Admission to SCBU	7/85 (8%)	1/10 (10%)	6/75 (8%)	0.99

7.6 Discussion:

In this large single centre outcome study of pregnancy post LT, we have demonstrated that a successful and safe pregnancy can be achieved for the majority of women. However, 5% needed admission to intensive care, 3% of women developed graft loss in association with pregnancy and 15% of conceptions were complicated by an episode of ACR, indicating that pregnancy following liver transplantation still caries significant maternal risk. A live birth rate of 73% is reported with no congenital abnormalities. Prematurity is common occurring in 31% and 7% of neonates needed SCBU support immediately post-delivery.

Women of reproductive age who have undergone LT require extensive counselling regarding contraception and pregnancy. Ideally this should form part of pre-transplantation work-up. Women with chronic liver disease are often infertile secondary to a combination of metabolic, endocrine, nutritional and sexual dysfunction.(94-97, 221) Disruption of the hypothalamic-pituitary axis in conjunction with disturbed oestrogen metabolism leads to anovulation, amenorrhea and infertility.(96, 97) LT often reverses infertility associated with chronic liver disease and up to 80% of women will have a normal menstrual cycle and return of fertility within 8 months of LT. (96, 222-224) If these women are not educated about this change in fertility, then, unwanted or unplanned pregnancies may occur. This is important since in this series a TOP was associated with an adverse event in 25% of instances including severe haemorrhage, precipitation of ACR and sepsis necessitating auxiliary graft removal. Therefore, TOP should not be considered as a “routine” procedure in this cohort and preventing an unwanted or unsafe pregnancy with appropriate contraception should be the aim.

Another important factor in patient education is the ideal timing of a post LT pregnancy. Whilst successful pregnancies can occur in the first year post transplant, (179, 181) this study and earlier studies, have shown that the risk of developing an episode of ACR is significantly increased in those pregnancies occurring within 12 months of transplantation ($p=0.001$). The

reason for this is likely to reflect that in the early post LT period, rejection episodes are more frequent, irrespective of pregnancy, due to unstable immunosuppression levels and increased infection risk. This increased risk of rejection has resulted in the NTPR advising that pregnancy should be delayed for at least 12 months following LT. (184)

The effect of ACR on the foetus and the longer term graft function remains to be defined. A previous series by Armenti at al. demonstrated that biopsy proven ACR during pregnancy was associated with worse new-born outcomes and an increased risk of recurrent rejection post-partum.(225) In this study we found no association between an episode of ACR during pregnancy and adverse foetal outcomes including delivery gestation (p=0.67), SCBU admission (p=0.26), the live birth weight (p=0.13) or congenital abnormalities. There was however a trend toward need for caesarean section (p=0.07) in women who had developed ACR, suggesting obstetric concern.

In women who developed ACR, follow-up over a median period of 60-months indicated that they were more likely to require re-transplantation in future years (p=0.001) when compared to those women who did not develop ACR in pregnancy. This is interesting as in the renal transplantation literature, pregnancy has been shown to have no long term effect on graft function when compared to case control groups. (226) The findings of this study coupled with data from the NPTR raises the question as to whether an episode of graft rejection in pregnancy could be associated with an increased risk of graft loss in the longer term. It is likely that the pregnancy itself does not cause or predispose a patient to rejection or graft loss, but perhaps identifies those women who are already at an increased risk of graft loss due to poor graft tolerance and may therefore benefit from augmented baseline immunosuppression. A large case controlled study would be needed to answer the question whether pregnancy has an adverse effect on graft outcome and this study is yet to be undertaken in the liver transplant population.

In this study the incidence of pre-eclampsia was 14% compared to an incidence of between 2-6% reported for the general population. Furthermore the development of pre-eclampsia and was found to be significantly associated with prematurity (p=0.001) and low birth weight (p=0.001), likely in part due to iatrogenic premature delivery in order to maintain maternal safety. The increased incidence of pre-eclampsia in the LT cohort is yet to be fully explained but is likely due the vasoconstrictive effects of calcineurin inhibitors, chronic corticosteroid usage and possibly an increased incidence of underlying renal dysfunction.

The foetal outcomes reported are favourable with a live birth rate of 73%, no congenital abnormalities and only 1 child born at 24 weeks with delayed developmental milestones. However the prevalence of low (19%) and very low birth weight (10%) is considerably higher than that of the general population where in England and Wales it is reported to be 7.2% and 1.2% respectively. (227) This finding is likely linked to the high incidence of prematurity (31%) in this cohort. The cause for the high incidence of prematurity and low birth weight in babies born to LT recipients remains unclear and is likely to be multi-factorial, contributed to by immunosuppression, the high incidence of pre-eclampsia / eclampsia and iatrogenic delivery, ACR and maternal co-morbidity.

Finally the concept of an “ideal” pregnancy without medication or increased risk of complications is perhaps not obtainable in this unique cohort due to the complex medical problems which occur in these patients and the need for continuous immunosuppressive therapy. Therefore, comparing data with the healthy population will show increased maternal risk and poorer foetal outcomes. What this study and the current literature tell us is that pregnancies in women post-LT can occur with successful outcomes but must be considered high risk and monitored regularly by transplant clinicians and specialist obstetricians. With transplant registries and repeated case series, pregnancy in LT recipients will define its own outcome

standards and it is already clear from this study and others that successful and safe pregnancies can occur in women post LT.

CHAPTER 8: Outcomes of Pregnancy in cholestatic liver conditions

8.1 Introduction

Pregnancy in women with cholestatic liver diseases is rare and there is a scarcity of data detailing the effect of pregnancy on both the mother and the foetus. This means that counselling and managing women with cholestatic liver diseases who are pregnant or wanting to become pregnant is difficult. Outcomes in the reported literature (as discussed on chapter 1) are varied depending on the aetiology of the underlying cholestatic liver disease. In women with PSC reports of pregnancy on maternal disease vary from improving biochemical parameters to severe pruritus and development of biliary strictures. (154, 155) In those women with PBC, the literature suggests that pregnancy is largely uneventful. (158-161) Finally rarer cholestatic liver diseases such as AISC exist with either no case reports of pregnancy or isolated case reports.

8.2 Aims

In light of the above, the aim of the work detailed in chapter 8 is:

- To describe the outcomes / complications of pregnancy in women with cholestatic liver diseases
- To describe the effect if any of pregnancy on hepatic biochemistry
- To facilitate pre-conceptual counselling in the future for women with cholestatic liver disease
- To assess foetal outcomes
- To assess maternal safety
- To separately assess outcomes in AISC

8.3 Patients and Methods

All patients with a diagnosis of either PBC, PSC or rarer cholestatic liver diseases who reported pregnancy at our institution between 1984 and 2009 were identified. The clinical records were reviewed in all patients and data extracted in a standard fashion. The diagnosis of PBC was made if two of three objective criteria are present: serum AMA at titers ≥ 1:40, unexplained elevated ALP ≥ 1.5 times the upper normal value for over 24 weeks and compatible liver histology. (228) Patients were confirmed as having PSC if they had cholestatic liver enzymes and compatible radiology and / or histology. (145) A diagnosis of autoimmune sclerosing cholangitis (AISC) was based on histological evidence of AIH on liver biopsy and alterations of the bile ducts characteristic of sclerosing cholangitis on cholangiography in conjunction with seropositivity for ANA and/or SMA. (164)

Data was extracted in a standardised fashion, as described previously. Patient details including liver function tests at conception, throughout pregnancy and the post-partum period was collected. Fetal and maternal complications were collected.

8.4 Results:

We identified 27 conceptions in 20 women with cholestatic liver disease. The underlying hepatological diagnosis was primary biliary cirrhosis (n=6), primary sclerosing cholangitis (n=3), autoimmune sclerosing cholangitis (n=5) and genetic congenital syndromes (n=6, (alagilles n=4, PFIC n=2)). The median age at conception was 28-years. There were 4 conceptions in two women with cirrhosis. At conception the median alkaline phosphatase was 200 IU/L (55-709 IU/L), GGT was 150 U/L (43-439 U/L) and bilirubin was 10 µmol/L (4-56 µmol/L).

8.4.1 Foetal Outcomes

The live birth rate was 81% (22/27), there were 4 miscarriages (2 in women with cirrhosis) and one termination of pregnancy. All neonates survived to hospital discharge and no congenital abnormalities were noted. The median gestation was 37-weeks (33-39-weeks). Four neonates required elective early delivery as a result of maternal cholestasis and pruritus, and clinical difficulties differentiating it from ICP.

8.4.2 Maternal Outcomes

The most common maternal complication was pruritus in the third trimester occurring in 13 (48%) pregnancies. The underlying diagnosis was not helpful in identifying which patients were likely to develop pruritus. Four out of the thirteen women (31%) who developed pruritus in the 3rd trimester required premature delivery due to severe maternal cholestasis and pruritus and concerns for foetal wellbeing.

Those women that reported pruritus had a significantly higher preconception GGT (p=0.002) and ALP (0.07) when compared to those women who did not develop pruritus. Similarly third trimester GGT (p=0.01) and ALP (p=0.04) levels were higher in those women who developed pruritus. Furthermore, the increment (Δ) in GGT (p=0.045) and ALP (p=0.05) between preconception and the 3rd trimester was higher in those patients reporting pruritus. Underling aetiology of liver disease was not indicative of a higher Δ GGT or Δ ALP. (Table 8.4.2)

Table 8.4.2 Biochemical characteristics in patients with cholestatic liver diseases with and without the development of pruritus

	No Pruritus Median (range)	Pruritus Median (range)	p value
Pre conception GGT (IU/L)	138 (43 – 237)	289 (167- 439)	0.002
Pre conception ALP (IU/L)	154 (55-321)	368 (193-709)	0.07
3rd Trimester GGT (IU/L)	156 (48 – 293)	387 (243 – 590)	0.01
3rd Trimester ALP (IU/L)	189 (69 – 401)	473 (250-796)	0.04
Δ GGT (IU/L)	40 (5-63)	102 (56-151)	0.05
Δ ALP (IU/L)	53 (14-80)	122 (57-139)	0.05

Twenty-three conceptions (85%) occurred on ursodeoxycholic acid (UDCA), of which 15 women continued it throughout their pregnancy. The mean dose was 1000mg/day (range 500-1500mg/day). Treatment with UDCA was not found to be protective against the development of pruritus. Women taking UDCA throughout pregnancy had a trend towards a lower increment in ΔGGT (p=0.09) and ΔALP (p=0.1) in the third trimester when compared to those women who discontinued it. No congenital anomalies were reported.

Eight women had worsening of their liver function tests post-partum; 3 had AISC and developed elevated aminotransferases which was subsequently controlled with steroids, 5 women developed worsening of their cholestatic parameters which settled with either re-introduction or augmentation of their UDCA. At one-year post-partum there was no significant change from pre-conception GGT and ALP levels.

There were no maternal deaths. However one women (with cirrhosis) required admission to intensive care for 24 hours post-partum with an unexplained metabolic acidosis and a second had a significant post-partum haemorrhage.

8.4.3 Pregnancy in Autoimmune sclerosing cholangitis

There were 8 conceptions reported in 5 women. All women had been diagnosed with AISC in childhood, at a median age of 12-years (range 5-15 years). Three of five women were cirrhotic at the time of conception. Pregnancy was planned and discussed with the physician in all cases. All women conceived naturally. Regarding medication, all women were taking prednisolone prior to conception and no patient discontinued this medication whilst pregnant. Seven women were taking UDCA prior to conception, one woman discontinued it prior to pregnancy (patient choice). Two women were taking azathioprine for disease control and one discontinued it for pregnancy (patient choice). Below the specific details of each conception are outlined. Table 8.4.3 shows the outcomes of the 8 conceptions for both mother and baby. Figures 8.4.3.1 and 8.4.3.2 show the changes in AST and GGT activity respectively in relation to the different stages of pregnancy.

Table 8.4.3: Foetal and maternal outcomes of 8 conceptions in 5 women with AISC

Woman	Age at conception	Cirrhotic	Foetal Outcome	Maternal outcome
1	28	No	Live Birth	Post-partum flare, settled with steroids and azathioprine
2	36	No	Live Birth – Died at 12 weeks from sepsis	Post-partum flare, settled with steroids and UDCA
	37	No	Live Birth	Post-partum flare, settled with steroids and UDCA
3	25	Yes	Live birth at 31-weeks, needed SCBU	Died 48 hours post-delivery – ruptured splenic varices
4	24	Yes	Live Birth	No significant effect
	26	Yes	Live Birth	No significant effect
5	28	Yes	Miscarriage 8 weeks	No effect
	29	Yes	Live Birth	Ventilated for 24 hours post-partum, no change in LFT's

Woman 1: This 28-year old patient had non cirrhotic AISC and was maintained on UDCA (600mg/day) and prednisolone (5mg/day). Preceding pregnancy her liver function tests had been stable for more than 1 year and prior to conception her GGT was 135, ALP was 215 and AST was 60. Her pregnancy was uneventful, she remained on her baseline immunosuppression and no changes in her liver functions tests were noted. In the week prior to delivery she complained of mild pruritus and delivered a healthy baby at 38-weeks' gestation. Immediately post-partum she had a significant flare in her liver disease with a peak AST of 257 IU/L and GGT

of 337 and ALP of 367. She required treatment augmentation with prednisolone (30mg/day) and azathioprine (125mg/day), which resulted in normalisation of her hepatic biochemistry. There was no hepatic decompensation as a result of the disease flare. Both the patient and child remain well 7-years from delivery.

Woman 2: This patient had 2 pregnancies at ages 36 and 37-years. She was non cirrhotic and personally chose to discontinue both her UDCA (1250mg/day) and azathioprine (100mg/day) for both pregnancies but remained on 5mg of prednisolone. Both gestational periods were uneventful with no change in her AISC activity. She delivered both her babies vaginally at 38-weeks gestation. The babies were both healthy and required no immediate medical input. Her 1st baby died suddenly at 12 weeks from severe sepsis thought to be unrelated to maternal disease or medication. Following both pregnancies she developed a flare in her inflammatory activity with her AST peaking at 160 and 140 respectively (previously normal), her GGT peaking at 603 and 417 and her ALP peaking at 307 and 348. In both cases she needed augmentation of her prednisolone to 20mg/day and her UDCA was restarted. The patient remains well on long term follow-up.

Woman 3: This 25 year old patient with AISC was cirrhotic based on radiological and blood parameters with a MELD score prior to conception of 10. She was known to have portal hypertension and was advised against pregnancy due to a high risk of hepatic decompensation. Her medications pre-conception and throughout pregnancy were UDCA (1250mg/day), azathioprine (100mg/day) and prednisolone (5mg/day). She underwent a screening endoscopy in her second trimester and oesophageal varices were confirmed and a caesarean section at 35-weeks was planned. At 31-weeks she was admitted as an emergency for foetal distress and underwent an emergency caesarean section. Forty-eight hours post-surgery she developed hypovolaemic shock. A laparotomy revealed severe haemorrhage from splenic varices. A

splenectomy was undertaken but she died shortly after from a hypovolemic cardiac arrest. The child survived after a short stay in the special care baby unit.

Woman 4: This patient had histologically proven cirrhosis with a MELD score prior to conception of 6. She had 2 pregnancies at aged 24 and 26. Her baseline immunosuppression consisted of prednisolone (5mg/day) and UDCA (500mg/day) and this was maintained throughout both pregnancies. Pregnancy had no impact on her hepatic biochemistry in the gestational or post-partum period. She delivered 2 healthy babies at 37 and 38 weeks gestation. Both the patient and children remain well at 5 years follow-up.

Woman 5: This patient had biopsy proven cirrhosis with a MELD score prior to conception of 6. She was maintained on UDCA (1250mg/day) and prednisolone (2.5mg/day) prior to and during both pregnancies. Her 1st pregnancy miscarried at 10 weeks. There was no change in her hepatic biochemistry related to the miscarriage. The second pregnancy was uneventful with a healthy baby delivered vaginally at 37 weeks gestation. The patient developed no change in her baseline hepatic biochemistry during the pregnancy or in the post-partum period. Immediately post-partum she required admission to intensive care and was ventilated for 24 hours due to hypoxia. The cause was unclear but resolved and was not thought to be liver related.

Figure 8.4.3.1: Trend in AST values throughout pregnancy in patients with AISC

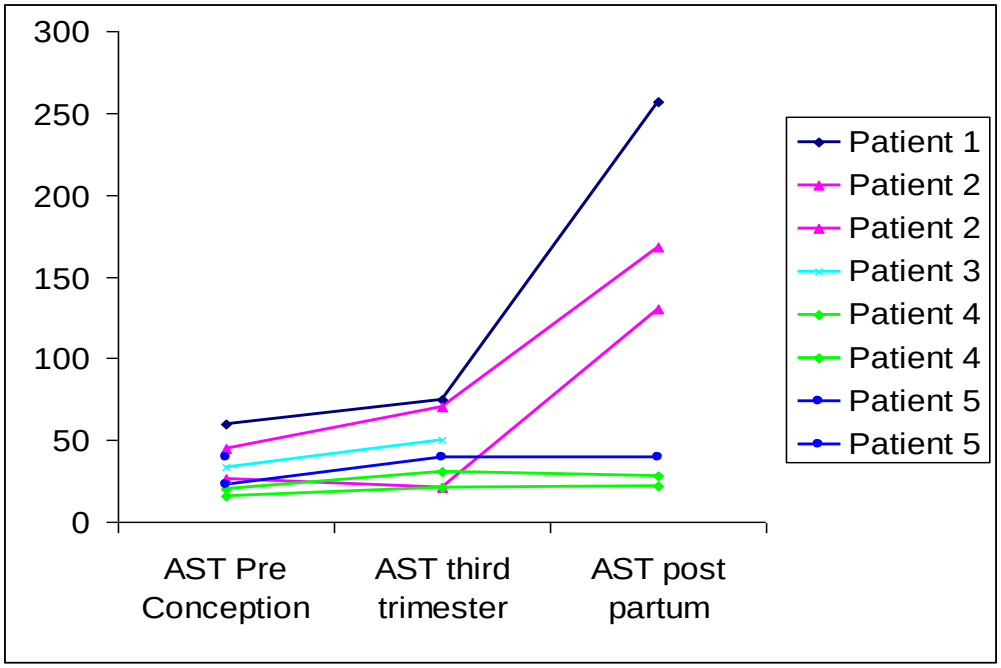
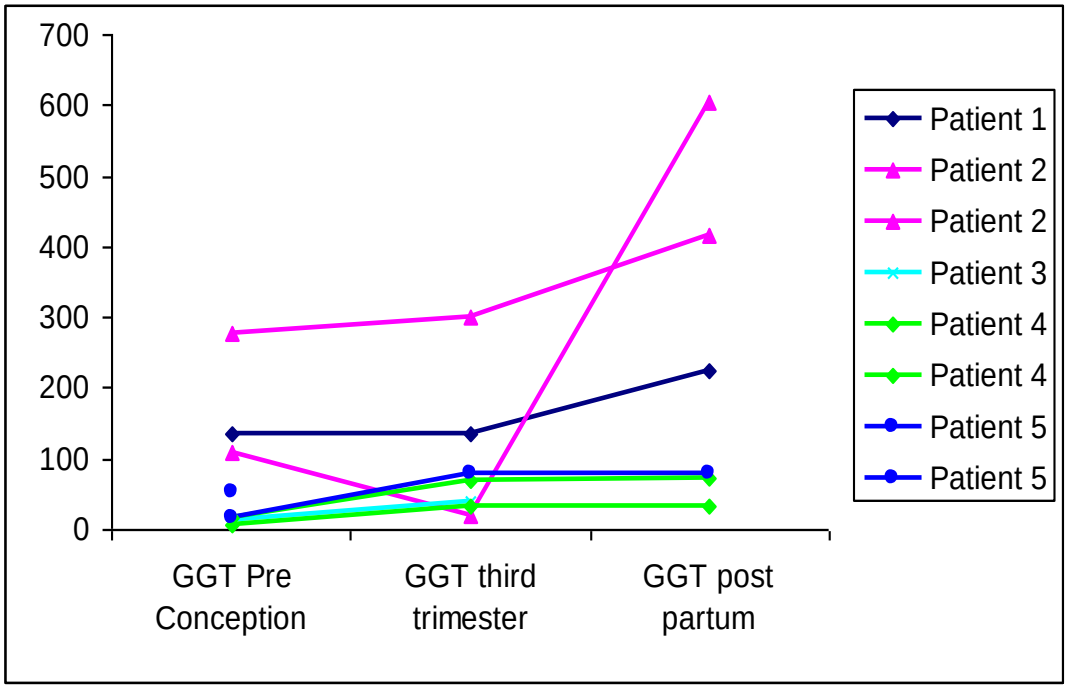


Figure 8.4.3.2: Trend in GGT values throughout pregnancy in patients with AISC



8.5 Discussion: Pregnancy in Cholestatic liver diseases

Foetal outcomes in women with cholestatic liver diseases appears acceptable with a favourable live birth rate of 81% and no obvious neonatal concerns or congenital anomalies. These findings are in keeping with other case series published in PBC and PSC. (155, 160, 229) Pruritus development in the third trimester was the commonest maternal symptom occurring in 48% of women. Pruritus was more common in those women with a higher pre-conception and third trimester GGT and ALP. In addition women taking UDCA throughout pregnancy had a trend towards a lower increment in ΔGGT (p=0.09) and ΔALP (p=0.1), suggesting response to UDCA, either pre or during pregnancy, may be of interest in the development of pruritus. Reassuringly in all cases, pruritus and biochemical abnormalities returned to baseline at 1-year post-partum, perhaps suggesting pregnancy has no or little impact on the long term natural history of the cholestatic liver disorders. This hypothesis remains to be proven via long-term follow-up studies.

In this report there were no late foetal losses. Premature delivery of the foetus is a concern, with 31% of those women who develop pruritus and cholestasis requiring early delivery. In this case series, the premature delivery, was due to an inability to confidently distinguish the development of ICP and its associated increased foetal morbidity from worsening of baseline cholestatic parameters. The challenge in women with cholestatic liver diseases arises in distinguishing worsening of the underlying cholestatic liver disease (which from the published literature does not appear to have a negative impact on foetal wellbeing) and the development and intrahepatic cholestasis of pregnancy which is associated with an increased foetal mortality and morbidity. (31, 155, 160) Polymorphisms in the ABCB4 gene are common to both conditions and raise the question as to whether IHCP is more common in patients with PSC, however this currently remains speculation.

In women with AISC and pregnancy, the maternal outcomes in this report appear favourable. The commonest complication was a flare in inflammatory activity in the post-partum period, which occurred in 3/8 pregnancies. In all cases the flare was controlled using prednisolone and/or azathioprine and/or UDCA. The biochemical abnormalities returned to pre-conception levels in all cases within 3 months. This incidence of flares in disease activity was not an unexpected finding as in previous reports of pregnancy in patients with AIH, flares in disease activity were reported to occur in 7- 21% of patients in the gestational period and between 11-86% of patients in the post-partum period. (14, 140-142) Moreover, a recent study by Wellge et al. described 25 pregnancies in patients with PSC. They reported an increase in liver enzymes, particularly serum aminotransferases (AST) in 20% and a post-partum increase in liver enzymes in 31%. (155) Caution is needed however, as although in this current case series all flares were easily controlled with medication augmentation, in larger series of women with AIH, reports of hepatic decompensation, liver transplantation and death have all been reported as a consequence of hepatic flares and pregnancy in AIH. (140-142)

In women with AISC and cirrhosis, there were five conceptions in 3 women with underlying cirrhosis. In this group there was one maternal death secondary to a hypovolaemic cardiac arrest subsequent to ruptured oesophageal varices. The second serious adverse event was admission of a woman to intensive care for 24 hours post-partum. Pregnancy in women with underlying cirrhosis is known to carry increased risks irrespective of underlying pathology, (230, 231) and need to be counselled pre-conception appropriately.

In this series 7/8 pregnancies resulted in a live birth, with 1 miscarriage at 8-weeks. One child died 3-months post-partum from overwhelming sepsis thought to be unrelated to maternal disease or medication. One neonate was born at 31-weeks and required admission to the special care baby unit. This neonate was born to the mother with a MELD score of 10. The above child and the remaining 5 births all remain well on long term follow-up with no

abnormalities reported. It is worthy of note that women with underlying cirrhosis are at an increased risk of having a premature birth and in the above case it is likely that the prematurity was as a result of the mothers underlying cirrhosis rather than AISC.

In conclusion, this case series in women with cholestatic liver diseases has demonstrated that the majority of women have an uneventful pregnancy. Worsening of pruritus and liver function tests can occur but these resolve post-partum, with the main risk being premature delivery due to the difficulties in separating distinguishing worsening of the underlying cholestatic liver disease and the development and intrahepatic cholestasis of pregnancy. In women with cirrhosis the risks encountered are due to the severity of the underlying cirrhosis as opposed to the specific disease and these have been discussed extensively in chapter 5. Specifically in women with AISC there is a risk that pregnancy may precipitate a flare in disease activity, similar to that reported in the AIH literature but overall outcomes appear favourable in the absence of underlying cirrhosis.

CHAPTER 9: Assisted Conception in women with liver disease

9.1 Introduction:

Women with chronic liver disease and cirrhosis have reduced fertility and may request advice regarding the safety and success rates of assisted conception. To-date, no published data, information or guidelines exist regarding the maternal safety and success rates of assisted conception in women with underlying liver disease. Theoretically pregnancy could carry an unacceptably high risk (hepatic decompensation and death) in those patients with cirrhosis of sufficient severity to impair ovulation, with failure of ovulation perhaps a naturally protective mechanism for the mother given the severity of her underlying liver disease. Furthermore, one must consider that the intensive hormonal ovulation induction regimens could potentially have an adverse effect in patients with non-cirrhotic autoimmune and cholestatic liver conditions or in patients following liver transplantation.

9.2 Aims

In light of the above, the aim of the work detailed in chapter 9 is:

- To assess the success rates of IVF in women with cirrhotic and non-cirrhotic liver disease
- To assess the success rates of IVF in the post liver transplant cohort
- To assess foetal outcomes
- To assess maternal safety

9.3 Patients and Methods

All patient records of patients who had enquired or had been seen with regards to infertility, assisted conception or in vitro fertilisation at our institution between 1984 and 2009 were reviewed. Clinical data was extracted in a standardised fashion with information on liver disease, severity, assisted conception, outcomes and complications. Specifically, data on maternal complications including worsening of parenchymal liver disease, hepatic decompensation, flares in disease activity, thrombotic complications were recorded. Regarding foetal outcomes, data on miscarriage, gestational duration, live birth rate and foetal outcomes was collated.

9.4 Results

Eighteen women with liver disease were identified as being assessed for assisted conception. The median age at referral was 38 years (range 26-45 years) and seven of the women had underlying cirrhosis based on histology or a combination of laboratory and radiological parameters. The cause of their underlying liver condition was AIH (n=6), PBC (n=2), hepatitis B (n=1), Budd Chiari syndrome (n=1), non-cirrhotic portal hypertension (n=1) and post liver transplant (n=7).

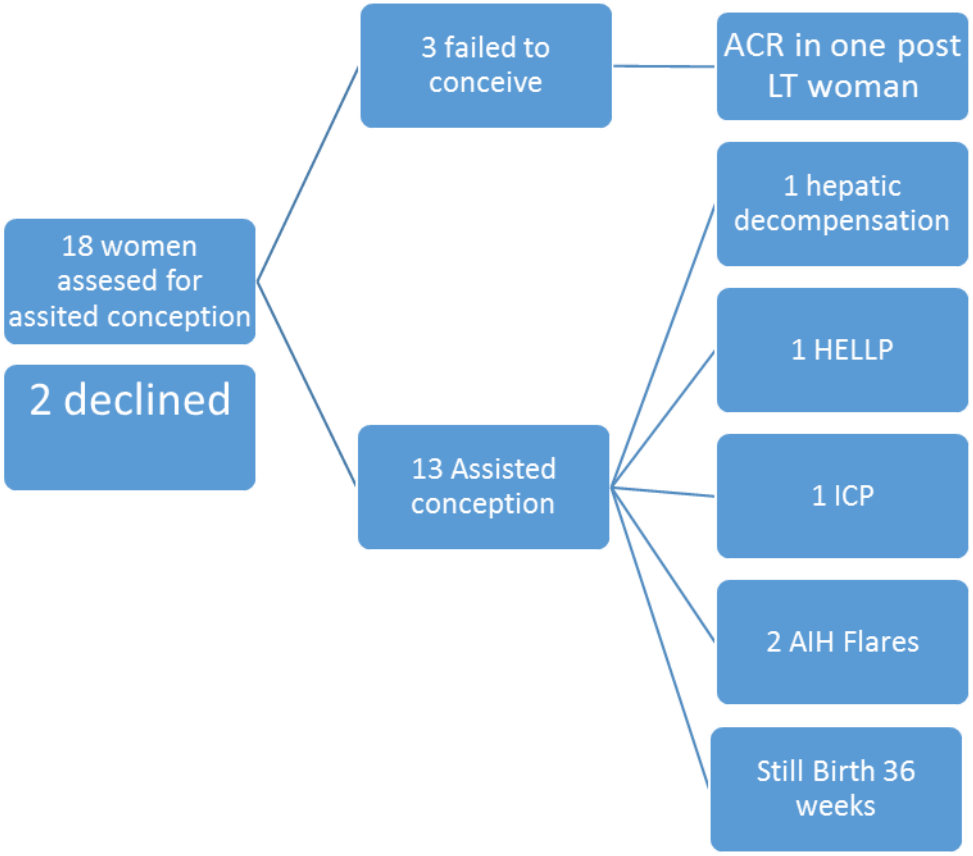
Two women, with underlying cirrhosis were declined assisted conception due to concerns about the effect of hormonal therapy and pregnancy on maternal health. Neither of these two women had decompensated and their MELD, UKELD and CP scores were not significantly different from those women with cirrhosis who underwent assisted conception. Both women had a MELD score of 6 and UKELD of 47.

In total 16 women underwent in vitro fertilisation (IVF). Three women failed to conceive after 3 cycles of IVF. Of these women 2 had no ill effects from IVF however, one women (post LT) developed graft dysfunction after her 3rd cycle of treatment with a liver biopsy confirmed acute cellular rejection. She was treated with augmented steroid therapy.

There were 16 conceptions in the remaining 13 women; no multiple pregnancies occurred. The median gestation was 36 weeks (range 28-38 weeks). In women with underlying cirrhosis the live birth rate was 50%. There was one major adverse event with one woman developing hepatic decompensation (ascites and encephalopathy). She was delivered at 28 weeks gestation. The baby had cerebral palsy, needed admission to the special care baby unit, but survived. Assisted conception in the 6 women who had been transplanted resulted in a live birth rate of 50%. Adverse events occurring in this cohort included a case of HELLP syndrome and in a separate woman, the development of obstetric cholestasis of pregnancy, both of which resulted in a pre-term delivery. A third woman had a still birth at 36 weeks (cause unknown).

Finally in the non-cirrhotic, non-transplanted cohort the live birth rate was 67%. This included 2 women with autoimmune hepatitis who developed a flare in their disease activity in the post-partum period which was controlled with immunosuppression augmentation.

Figure 9.4 Maternal outcomes of assisted conception in women with liver disease



9.5 Discussion

In this series of women with liver disease undergoing assisted conception, we report a conception rate of 81% in a heterogeneous cohort of women with underlying liver disease and a live birth rate of between 50-67%.

Following liver transplantation in women of child bearing age, it is normal for fertility to recover and women often enquire about having children. (90) Previous published series and the work detailed in chapter 7 show that a live birth can be expected in the majority of women. There will inevitably be some women post-transplant who are unable to conceive for a variety of reasons and may enquire about the safety and success rates of assisted conception. There are no published case series of women conceiving with assisted conception following liver transplant and therefore the safety of IVF for the mother, baby and graft is unknown. In the renal transplant population, a recent series describes 7 singleton and 1 twin pregnancy after IVF and compared them to matched renal transplant patients who conceived naturally. (232) Interestingly, they describe that the rates of pre-eclampsia, prematurity, low birth weight and neonatal morbidity and mortality were all significantly higher in IVF conceptions compared to those women who conceived naturally. (232) From our own data, we have shown that IVF following transplantation can result in a heathy live birth, but potentially carries a significant risk, with the real possibility of hormonal manipulation acting as a trigger for ACR, prematurity and still birth. Further larger case series are needed to explore the safety of IVF following liver transplantation further.

In women with cirrhosis, conception and a successful pregnancy can occur. Data discussed in chapter 5 has shown that pregnancy in patients with cirrhosis carries a high incidence of maternal morbidity (10%), a live birth rate of 58%, with 75% of neonates born prematurely and 17% of live births requiring neonatal intensive care support. The decision on whether to assist conception in women with underlying cirrhosis is more challenging than in

post LT patients. These women may not ovulate due to the effects of cirrhosis and this may represent a protective measure due to the body not being able to cope with the demands of pregnancy in the context of underlying cirrhosis. We describe IVF resulting in a successful implantation in 4 women with well compensated underlying cirrhosis. The live birth rate was 50% and although 1 woman had hepatic decompensation resulting in a pre-term delivery at 28 weeks. Further larger case series are required before conclusions are made about the safety of assisted conception in women with cirrhosis. Currently, until further information is awaited women need to be counselled regarding the risk of decompensation and avoid assisted conception if MELD is 10 or above.

CHAPTER 10: Discussion

10.1 General discussion

This thesis has documented in detail the risks related to pregnancy for mother and baby in the context of varied liver pathologies and disease severity. Moreover, it has identified pre-conception parameters that are associated with adverse pregnancy outcomes. This body of work will therefore enable physicians to give individualised disease specific advice regarding the associated risks and outcomes of pregnancy. The following discussion highlights the major findings of this thesis and places them in the context of the literature. However, it must be emphasised that to-date, the aims outlined in this thesis have heretofore never been explored. Finally the limitations of the thesis are discussed along with potential areas for future work and development.

10.1.1 Outcomes of severe pregnancy related liver disease; refining the use of prognostic markers and the role of liver transplantation

A better understanding of parameters which indicate that a patient with pregnancy associated acute liver failure is at an increased risk of death and as a consequence might benefit from LT is an unmet need in the pregnancy specific liver diseases. In chapter 4 we demonstrate an unacceptably high maternal mortality rate of 13% with an additional 6% requiring liver transplantation. These poor outcomes occurred despite 90% of babies being delivered within 24 hours of presentation and the remainder within 48 hours of presentation to hospital. Moreover we highlight that mortality rates in women with severe pregnancy associated liver disease has not changed in over 2 decades. Whilst it is also well accepted that prompt delivery of the foetus is a key intervention that halts disease progression in the pregnancy associated liver diseases;

(42) this body of work highlights that at the severe end of the spectrum despite this intervention mortality or need for liver transplantation can be as high as 1 in 5 cases.

We also highlight for the first time that in women with severe pregnancy associated liver dysfunction of such severity as to require admission to high dependency or intensive care unit, that the well published and validated King's College Criteria for poor prognosis in acute liver failure are not predictive of risk of death and/or need for liver transplantation. (78, 233) In our cohort, no patient that died or underwent liver transplantation fulfilled the King's College Hospital poor prognostic criteria for non-acetaminophen acute liver failure. (77, 78) Although, all patients had encephalopathy, none fulfilled the requirement of either an INR greater then 6.5, or any three parameters from the variables of age greater than 40 years, unfavourable aetiology, INR greater than 3.5, serum bilirubin greater than 300µmol/L or interval of jaundice to development of encephalopathy of greater than 7 days. (78) Encephalopathy although sensitive in predicting need for transplant in our cohort was not specific occurring in 43% of medical survivors. The lack of defined criteria to identify which patients are at high risk of death without LT, or indeed identification of those patients who are likely to survive with medical therapy alone is of critical importance. Inaccurate selection criteria will result in subjecting a patient that would have recovered with medical management to the risk of liver transplant surgery, a life of immunosuppression, its side effects and increased mortality. Furthermore, failing to identify a patient with ALF who would survive only with LT, is meaning their death is inevitable.

In this chapter we proceeded to identify that an admission a lactate of greater than 2.8g/dl combined with the presence of any grade of encephalopathy has a 90% sensitivity and 86% specificity for identifying those patients that died or underwent liver transplantation in our cohort. The negative predictive value was 97%. The one patient which was not identified by these criteria died from associated pancreatitis and although had liver dysfunction and

coagulation abnormalities did not clinically have any other features of liver failure and hence in “real life” the clinician would not be proposing LT as a treatment modality. With this patient excluded from analysis the criteria we propose are 100% specific for identifying those patients at risk of death from acute liver failure / need for liver transplantation.

The criteria suggested by this thesis to identify patients at increased risk of death / LT with pregnancy associated acute liver failure need to be prospectively validated in a cohort of women outside of King’s Liver intensive care unit to confirm there sensitivity and specificity before they are incorporated into clinical care and used to make decisions regarding listing for LT. Once accurate criteria are established, it appears reasonable that pregnancy induced acute liver failure should have its own listing criteria for LT as in this specific group, for the reasons explored in chapter 4 and demonstrated in this thesis the current criteria are inadequate.

Of interest, this body of work has highlighted the high incidence of significant bleeding complications (59%) encountered in women with severe pregnancy associated liver dysfunction. Bleeding sites were gynaecological (66%) or hepatobiliary (47%) or combined (13%) with surgical intervention required in 72%. No predictors of bleeding complications were identified and the incidence was no different in those women who delivered vaginally compared to caesarean section. When bleeding complication occurred the incidence of infection and length of ITU stay was significantly longer than those women without bleeding complications. This highlights the need for a high index of suspicion for bleeding in such women, potentially early *radiological / surgical intervention and prophylactic antibiotics.

10.1.2 Utilisation of prognostic scoring systems to predict outcomes in pregnant women with cirrhosis

Women with cirrhosis who are of childbearing age often enquire about the safety of pregnancy. Obstetricians and hepatolgists have very limited information to give these women as available data is limited to case reports and small historic series as discussed in the introductory chapter. (102, 105) Furthermore it is well recognised that cirrhosis represents a spectrum of disease and hence it is reasonable to speculate that the risk pregnancy would confer is likely related to the severity of cirrhosis.

In chapter 5 we have demonstrated that pregnancy in patients with established cirrhosis is associated with a high incidence of hepatic decompensation (10%) and a maternal mortality rate of 1.6%. Oesophageal varices were reported in 50%. The live birth rate was significantly reduced (58%) and of those 75% are born prematurely and 17% require neonatal intensive care support.

We demonstrate in this thesis for the first time, that these adverse outcomes (maternal and foetal) in the context of cirrhosis, can be predicted pre-conception by using established prognostic scoring systems. (120, 126, 137)

Regarding foetal outcomes, higher MELD score (p=0.01), MELD-Na score (p=0.01), UKELD score (p=0.01), and CP score (p=0.03) at conception are associated with a birth prior to 37 weeks gestation. The need for admission of a neonate to intensive care was associated with higher maternal MELD score (p=0.04) and UKELD score (p=0.04) but not CP score (p=0.35) or MELD Na (p=0.28) at conception. Although we demonstrated a significant foetal loss rate we were unable to find an association with the severity of the underlying cirrhosis as measured by MELD, UKELD and CP score pre-conception. This may be related to several factors, the first being that cirrhotic women have irregular menstruation as cirrhosis advances and that consequently, an early pregnancy loss in patients with more advanced cirrhosis could be missed.

Secondly, due to the limitations of the retrospective nature this study, many early losses may not have been reported to us. Indeed, previous published reports have estimated the spontaneous abortion rate to be higher, reported between 30% and 40% of pregnancies in women with cirrhosis. (210)

Hepatic decompensation (variceal bleeding, ascites, hepatic encephalopathy) occurred in 6 women which equated to 10% of all conceptions. A higher median MELD score (p=0.01) and UKELD score (p=0.02) at conception was significantly associated with an increased risk of the mother developing a decompensating event. Evaluation of the receiver operator characteristic (ROC) curves for MELD and UKELD scores at conception and the development of a significant liver related complication for the mother both demonstrated an area under the ROC curve (AUC) 0f 0.8. Furthermore, a MELD score of greater than 10 points demonstrated 83% sensitivity and 83% specificity for predicting which patients with cirrhosis were likely to experience a significant liver related complication during pregnancy. Regarding UKELD, a score of greater than 47 demonstrated an 83% sensitivity and a 79% specificity for predicting which patients with cirrhosis are likely to experience a significant liver related complication. Interestingly no patient who had a MELD score of 6 or a UKELD score of less than 47 developed any significant hepatological complications related to their pregnancy.

The novel data generated form this thesis is of critical importance as it allows accurate identification of those women who can be reassured pregnancy is likely to have a good outcome (MELD 6 or UKELD <47) and perhaps more importantly identifies a group of women that should be advised against pregnancy due to the high risk of associated hepatic decompensation (MELD>10 and UKELD>47).

Regarding screening for the presence of varices, 93% of women underwent a gastroscopy in their second trimester and half were found to have oesophageal varices, reporting a similar incidence to other published series.(212) Prognostic scores at conception

could not predict the presence or absence of varies. The pre-conception platelet count was strongly associated with the presence of oesophageal varices ($p<0.001$), and ROC analysis concluded that using a platelet count cut off of 110 cells/mm3 gives an 89% specificity in predicting the presence of oesophageal varices. The use platelet count as a non-invasive marker of portal hypertension to predict the presence of varices, has been shown to be of use in patients with cirrhosis outside of pregnancy. However to-date non-invasive markers of portal hypertension are insufficient to confidently diagnose / exclude the presence of varices in clinical practice.

In this study, variceal haemorrhage occurred in 3 cases, which is much lower than previous reports where the incidence of bleeding has been reported to be as high as 50%.(105, 111) The lower incidence of haemorrhage, in this study is unclear, but may reflect the use of beta blockers, less severe portal hypertension or even the fact that enrolment in a screening program for varices might have resulted in a higher beta blocker prescription rate. An episode of variceal haemorrhage could not be predicted by prognostic scores or preconception platelet count.

Finally we noted in women who had an episode of hepatic decompensation in pregnancy, long term prognosis was reduced. One patient died directly as a result of the complication, and a further 2 patients that had a significant complication during pregnancy died at 6 and 16 months following delivery. This raises the question as to whether patients that decompensate during pregnancy reflect a group that lack functional hepatic reserve and should be monitored even more closely or even considered for transplantation post-delivery even if their synthetic function recovers. This however would be controversial, since their prognostic scores are significantly lower than those at which transplantation would ordinarily be considered. The numbers in this piece of work are too small to make any meaningful conclusions, but this does suggest an area for potential further research in the future.

10.1.3: Predicting outcomes of pregnancy in women with autoimmune hepatitis

We have also reported in this thesis on 81 pregnancies in 53 women with AIH. We have confirmed in our series that pregnancy in AIH can be associated with a high incidence of disease flares (33%) and serious maternal adverse events (11%). We have demonstrated for the first time that disease flares are associated with poor disease control in the year preceding pregnancy (p=0.03), the absence of therapy whilst pregnant (p=0.047) and older age at conception (p=0.048). Moreover we demonstrated that a flare in autoimmune activity associated with pregnancy is a clinically important event as they are associated with a significantly increased risk of hepatic decompensation (p=0.01) and an increased need for neonatal admission to special care baby units (p=0.047). This work has demonstrated that continuing immunosuppression throughout pregnancy in women with AIH is relatively safe with no apparent increased risk of adverse effects on either live birth rate or congenital anomalies. In this work immunosuppressive therapy was associated with a significantly reduced maternal AIH flare rate (p=0.047) when compared to women with AIH not on therapy and foetal prematurity was more common in mothers not immunosuppressive on therapy, however this did not reach statistical significance (p=0.07). This study therefore adds growing support to the theory that the greatest chance of a healthy baby in patients with AIH is attained by continuing therapy with the aim of achieving a healthy mother throughout pregnancy via good disease control.

The incidence of a serious maternal adverse event (death or decompensation) occurred in 9 conceptions (11%). This is significantly higher than that of the general population.(219) The increased incidence of a serious maternal adverse event in association with pregnancy in women with AIH has been reported in other series; Schramm et al. and Terrabuio et al. both describe a serious maternal complication rate of 9% and 7.8% respectively. (141, 142) To-date, identifying which women with AIH are likely to have a risk free pregnancy and who are at an increased risk of developing serious complications has been challenging. Whilst this study failed

to identify specific preconception parameters that predicted a serious maternal complication rate, we have identified that sub-optimal disease control in the year prior to conception (p=0.03), the absence of therapy during pregnancy (p=0.047) and increasing maternal age (p=0.047) predispose to a disease flare, which if it occurs confers a significantly increased risk of hepatic decompensation (p=0.01).

Of concern in out cohort of 53 women, was 1 maternal death in association with pregnancy, 3 maternal deaths within 12 months of delivery and 2 women undergoing liver transplantation within 12 months of delivery. This equates to 11% of women and the only preconception parameter that conferred an increased risk of the above events was the presence of underlying cirrhosis. Therefore, as discussed previously, it behoves us as clinicians to evaluate closely patients in the year following delivery, particularly, those patients with underlying cirrhosis, portal hypertension and a history of poor disease control.

10.1.4 Pregnancy following liver transplantation: predicting outcomes

In this section, we described the outcomes of 117 conceptions in women post LT. We demonstrated that a successful and safe pregnancy could be achieved for the majority of women.

The live birth rate was 73% without congenital abnormalities being reported. The rate of spontaneous miscarriage was 17% with no identifiable predictors pre-conception, 10% of women had elective terminations of pregnancy and there was one still birth. Thirty one percent of neonates were premature (gestation ≤37 weeks) which was associated with a reduced birth weight, need for admission to a special care baby unit and maternal development of pre-eclampsia (likely iatrogenic to maintain maternal safety). No pre-conception parameters were associated with prematurity. The prevalence of low (19%) and very low birth weight (10%) is considerably higher than that of the general population where in England and Wales it is

reported to be 7.2% and 1.2% respectively. (227) The cause for the high incidence of prematurity and low birth weight in babies born to LT recipients remains unclear and is likely to be multi-factorial, contributed to by immunosuppression, the high incidence of pre-eclampsia / eclampsia and iatrogenic delivery, ACR and maternal co-morbidities.

In the post-transplant phase, the education of women in relation to pregnancy and the likely outcomes is important. Often, pre-transplantation, women are infertile and amenorrhoeic due to the combined impact of cirrhosis on metabolic, nutritional, and hormonal function. Following transplantation, fertility can be restored as early as 1 month following LT and pregnancy can occur. Our data has highlighted that a termination of pregnancy post LT is associated with an adverse event in 25% of cases with complications including severe haemorrhage, precipitation of ACR and sepsis necessitating auxiliary graft removal. Therefore a TOP should not be considered as a “routine” procedure in this cohort and prevention of an unwanted or unsafe pregnancy with appropriate pre-pregnancy counselling and contraception should be the norm and the paradigm of best clinical practice.

The rate of acute cellular rejection in association with pregnancy was 15% (n=18) and was associated with conception occurring within a year of LT, but not with any specific immunosuppression regimen (p=0.08). An episode of acute cellular rejection did not have any effect on foetal outcomes (gestational week, birth weight need for admission to a special care baby unit). This finding mirrors other studies. The reason for which this is likely to reflect that in the early post LT period, rejection episodes are more frequent, irrespective of pregnancy, due to unstable immunosuppression levels and increased infection risk.

Additional maternal complications encountered during pregnancy included hypertension (n=22), pre-eclampsia (n=16), eclampsia (n=3) and gestational diabetes (n=8), there were no pre-conception parameters that allowed identification of these complication. The incidence of pre-eclampsia was 14% compared to an incidence of between 2-6% reported for

the general population. The increased incidence of pre-eclampsia in the LT cohort is yet to be fully explained but is likely due the vasoconstrictive effects of calcineurin inhibitors, chronic corticosteroid usage and possibly an increased incidence of underlying renal dysfunction.

Interestingly we found that in women who developed ACR, follow-up over a median period of 60-months indicated that they were more likely to require re-transplantation in future years (p=0.001) when compared to those women who did not develop ACR in pregnancy. In the renal transplantation literature, pregnancy has been shown to have no long term effect on graft function when compared to case control groups. (226) It is likely that the pregnancy itself does not cause or predispose a patient to rejection or graft loss, but perhaps identifies those women who are already at an increased risk of graft loss due to poor graft tolerance and may therefore benefit from augmented baseline immunosuppression.

10.1.5 Pregnancy in cholestatic liver conditions and assisted conception

We have reported in chapters 8 and 9 that women with cholestatic liver disease have favourable outcomes regarding pregnancy. The live birth rate was 81% with no late foetal losses or congenital abnormalities. Pruritus was the commonest maternal complication occurring in 65% of women and was associated with higher pre-conception GTT and ALP levels in conjunction with a higher increment in GGT and ALP between pre-conception and the levels measured in the third trimester. Pruritus was relieved by delivery and at 1 year post-partum, there was no significant change in GGT and ALP levels form preconception parameters. Urosdeoxycholic acid was tolerated well, and in this small cohort did not have any adverse effect on the pregnancy or foetal outcomes. Iatrogenic prematurity due to difficulty distinguishing between worsening cholestatic liver disease or ICP is a risk for such patients.

Neither published data, nor guidelines exist regarding the maternal safety and success rates of assisted conception in women with liver disease. Theoretically, pregnancy is likely to

carry an unacceptable high risk (hepatic decompensation and death) especially in those patients with cirrhosis of a severity to impair ovulation. Furthermore the intense hormonal ovulation induction regimens may potentially have an adverse effect in patients with non-cirrhotic autoimmune and cholestatic liver disease or in those patients after liver transplantation.

In this thesis, despite a retrospective look-back over 20-years, only 18 women with established liver disease were assessed for assisted conception. The cohort of women are heterogeneous with a variety of underlying liver pathologies including post LT patients. This makes it difficult to draw definitive conclusions. What is apparent however, is that obstetricians and hepatologists have significant reservations about AC in such women due to the potential risks discussed in previous chapters. Moreover, what we can also conclude that the risk of assisted conception is certainly higher than women with infertility and the absence of liver disease. There is also the potential to precipitate ACR in LT patients and hepatic decompensation in cirrhotic patients, both of which carry significant morbidity and mortality.

10.2 Limitations of thesis

Although, this body of work has largely achieved its goal of defining the natural history of pregnancy in patients with underlying liver disease in addition to identifying poor prognostic factors in women with liver disease wanting to become pregnant or in those who develop severe pregnancy associated liver dysfunction, there are however several limitations to the work that warrant discussion.

In evaluating and interpreting the results of these studies and their translation into current practice, it is pertinent to note the retrospective nature of the data collected and the limitation that the results in this thesis are dependent on the completeness of the databases and their interrogation. Databases dating back to as early as 1979 were interrogated and all patients identified were included for data collection. Ninety two percent of patients included in this thesis reported pregnancy after 1990, and this in itself is likely to represent an era effect of physicians starting to accept that pregnancy could be a safe and viable option for women of child bearing age with liver disease. The historic nature of the data is important as there have been several key developments in hepatological, obstetric and neonatal care over this time period, including corticosteroids for foetal lung maturity, endoscopic techniques for ablation and treatment of varices and recognition of immunosuppression safety and importance in relation to pregnancy. (90, 211) These developments should result in an overall increased survival rate over time for such patients and therefore analysing the data as a whole may provide more negative results regarding outcomes than what would be expected in the current day. The era-effect in women admitted to intensive care with pregnancy associated liver dysfunction was assessed and of great concern is that mortality rates for such women has not changed significantly over a 20 year period.

Another recognition of the retrospective review of outcomes in women with liver disease and pregnancy is that there has been no standard monitoring or treatment of women

throughout the study period. Furthermore, choices regarding continuing/discontinuing medication and altering doses has not been standardised or randomised and therefore, any conclusions drawn could be subject to bias, An example in point is that although we found a lack of immunosuppression in AIH and pregnancy to be statistically associated with the development of a disease flare, when the reasons for absence of therapy are reviewed the group is widely heterogeneous.

There were 2 de novo presentations of AIH in association with pregnancy, 5 were cirrhotic with burnt out disease, 6 were in biochemical and histological remission and had subsequently had treatment discontinued and the remaining 7 had their medication stopped either due to personal wishes or on medical advice with regard to their wish to become pregnant. Moreover, the frequency of blood monitoring during the gestational and post-partum period varied widely throughout the cohort. In light of this a generalised statement suggesting lack of immunosuppressive therapy is associated with a disease flare, although correct is limited due to heterogenous group and varied monitoring schedules.

Pregnancy was also self-reported by patients and had to be recorded in the medical notes to be captured by our data search. This means that whilst we are likely to have captured all pregnancies that resulted in a delivery, it is also likely that many early miscarriages were not captured. This is likely due to a combination of factors, the first being that in women with advanced liver disease, menstrual patterns can become erratic and consequently, early pregnancy loss in patients with more advanced cirrhosis would be missed and hence, under-reported. Secondly many early losses may not have been reported to us or not documented in the medical notes by the reviewing physician. This again means any statements regarding association of liver disease and pregnancy loss may be under-recognised due to the likelihood that early pregnancy losses are under-represented in this retrospective data set.

King's College Hospital in itself represents a further source of bias. It represents both a tertiary hepatology referral centre and a large volume transplant centre. This is likely to mean that an ascertainment bias exist towards women with more severe disease. Certainly, in chapter 4, the women transferred to the liver intensive care unit had already been pre-selected by referring centres as those women who potentially might require either hepatobiliary surgical intervention or liver transplantation. This therefore needs to be recognised when interpreting the high incidence of bleeding complications, length of ITU stay, mortality and need for liver transplantation in this study. The incidences reported are thus not transferrable to all women with pregnancy associated liver dysfunction who require intensive care support.

Finally, pre-conception parameters associated with adverse pregnancy outcomes were identified using univariate analysis due to the relatively small numbers in each cohort of patients and it needs to be noted that identified parameters may not be individually associated on multivariate analysis.

Although the retrospective nature of this thesis means that results should be interpreted with this in mind, the frequency of pregnancy in women with liver disease or women requiring intensive care for pregnancy associated liver injury is such, that no single centre could generate a prospective study with adequate recruitment numbers. Furthermore the data collected in this thesis is the largest report of outcomes in women with liver disease and pregnancy and comparable information does not exist even in multicentre collaborations.

10.3 Unmet needs and future work

The data and results generated from this thesis has added significantly to the published literature and our knowledge and understanding of what adverse outcomes women with liver disease may encounter and how such adverse outcomes may be identified pre-conception. This body of work will hopefully result in better individualised education of women with liver disease wanting to consider pregnancy and reduce maternal and foetal adverse outcomes. It has however highlighted several unmet needs, areas for potential ongoing research and the need for multicentre collaboration. Achieving this will ultimately improve preconception counselling, the assessment and management of such women during pregnancy and in the post-partum period and define need for liver transplantation in women with severe pregnancy associated liver failure. Achieving this will hopefully transfer to a reduction in morbidity and mortality for women with liver disease.

A large unmet need in women of child bearing age with liver disease or those post LT is their ability to access good advice regarding contraception and education about their fertility. For example this thesis highlights a termination of pregnancy post LT is associated with an adverse event in 25% of cases with complications including severe haemorrhage, precipitation of ACR and sepsis necessitating auxiliary graft removal. Moreover in our cohort of 9 patients with cirrhosis who underwent medical termination, one patient had a deterioration of hepatic function and needed transplantation. Therefore a TOP should not be considered as a “routine” procedure in this cohort and preventing an unwanted or unsafe pregnancy with counselling and education on appropriate and safe contraception should become normal practice. Education of women with liver disease who are of child bearing age regarding contraceptive use, their fertility and risks of pregnancy should become routine. Delivery of this advice is the challenge. General practitioners are unlikely to be confident in advising women with liver disease about

contraception, pregnancy and its associated risks, especially as the advice will be specific to that individual and the severity of their underlying liver disease. Therefor the responsibility lies with the individual patient and their hepatologist. Education about contraception, fertility and pregnancy should be discussed with all women of a child bearing age and they should be informed that should they have the desire to become pregnant a detailed discussion with their physician prior to trying to conceive is warranted. This way women can have their medications reviewed, be educated regarding the outcomes and associated risks and make a fully informed decision if pregnancy is something they wish to pursue.

The outcomes of pregnancy documented in this thesis in women with liver disease and pregnancy along with the pre-conception markers of adverse outcome have all been derived from a single, large volume, tertiary liver centre. Ideally these findings should be validated by other centres. The data for this thesis was generated from over 20 years of records and patient attendances at the hospital and a potential criticism would still be the relatively small numbers, along with now historic data and hence repeating this work at another single centre is likely to add very little. Ultimately the next step should be a national review of patients with pregnancy and liver disease, their outcomes and a prospective validation of the findings suggested by this thesis.

Additionally, this body of work has postulated that how a liver “reacts” to the stress or immunological changes in pregnancy, may provide valuable prognostic information about that individuals liver disease. For example, women with an episode of ACR in association with pregnancy had higher risk of graft loss over time and those women with hepatic decompensation in pregnancy had significantly reduced long term survival from what their prognostic scores would suggest. Whilst these associations appear reasonable, it is critical to understand mechanistically and immunologically why a liver transplant patient who has an episode of rejection in pregnancy might have an increased risk of graft loss from rejection. This

may in turn help us to develop an enhanced understanding of immune tolerance and result in an altered immunosuppression strategy for such women to try and prevent graft loss.

In women with cirrhosis that decompensate in the context of pregnancy the data from this thesis suggest a 50% 2 year survival. This also raises the question as to whether patients that decompensate during pregnancy should be considered for transplantation post-delivery even if their synthetic function recovers. Similarly, it suggests that although the prognostic scores such as MELD or UKELD are significantly lower than those at which transplantation would ordinarily be considered, patients that decompensate during pregnancy represent a group that lack functional hepatic reserve and therefore may benefit from earlier transplantation or much closer clinical monitoring in the first year following delivery. Due to the small number of patients involved, a national or international study group needs to be created to facilitate appropriate case acquisition and allow the answering of such important questions.

Finally, and perhaps of greatest concern from the data generated from this work is the suggestion that no apparent increment in survival has occurred in women who present with severe pregnancy associated liver disease over the last 2 decades. This is in contrast to outcomes for ALF secondary to other aetiologies, although, again, an ascertainment bias may be in-part responsible for these results. (234) Moreover, the multi-system nature of organ dysfunction in these conditions may also reflect the severity of disease and the extreme phenotypic presentation of this type of case. For AFLP and the hypertensive liver disorders, national studies are required to aid diagnosis, management strategies and define need for liver transplantation.

Appendix A: Publications, Presentations and Prizes as a result of this thesis

Publications:

Westbrook RH, Dusheiko G, Williamson C
Pregnancy and Liver Disease
Journal of Hepatology 2016 Apr;64(4):933-45

Westbrook RH, Yeoman AD, Agarwal K, Aluvihare V, O'Grady J, Heaton ND, Penna L, Heneghan MA
Outcomes of pregnancy following liver transplantation: The King's College Hospital Experience
Liver Transplantation 2015. Sep;21(9):1153-9

Westbrook RH, Yeoman AD, Kreise S, Heneghan MA
Outcomes of pregnancy in women with autoimmune hepatitis
Journal of Autoimmunity. 2012 May;38(2-3):J239-44.

Westbrook RH, Yeoman AD, O'Grady, Harrison PM, Devlin J, Heneghan MA
Model for end stage liver disease (MELD) score predicts outcome in cirrhotic patients during pregnancy
Clinical Gastroenterology Hepatology 2011 Aug;9(8):694-9

Westbrook RH, Yeoman AD, Joshi D, Heaton ND, Quaglia A, O'Grady JG, Auzinger G, Bernal W, Heneghan MA, Wendon JA
Outcomes of severe pregnancy related liver disease: Refining the role of transplantation.
American Journal of Transplantation 2010 Nov;10(11):2520-6.

Joshi D, James A, Quaglia A, **Westbrook RH**, Heneghan MA.
Liver Disease in Pregnancy
Lancet 2010 Feb 13;375(9714):594-605.

Abstract Publications:

Westbrook RH, Hughes S, O'Grady J, Harrison P, Heneghan MA.
Pregnancy in cholestatic liver disease.
Hepatology, 2011, Vol 54, pp 926A-926A

Westbrook RH, O Grady J, Harrison P, Devlin J, Heneghan MA.
Assisted conception in patients with liver disease.
J Hep, Vol 54, pp S83

Westbrook RH, Yeoman AD, Agarwal K, Aluvihare V, O'Grady J, Suddle A, Heaton N, Heneghan MA.
Outcomes of pregnancy following liver transplantation.
Hepatology 2010, Vol 52, pp835A – 835 A.

Westbrook RH, Yeoman AD, Agarwal K, Aluvihare V, O'Grady J, Suddle A, Heaton N, Heneghan MA.
Outcomes of pregnancy following liver transplantation.
Gut 2010, Vol 59, supp 2, 49A – 49A

Westbrook RH, Yeoman AD, McFarlane IG, O'Grady JG, Harrison PM, Devlin J, Heneghan MA.
Pregnancy outcomes in Autoimmune Hepatitis
Hepatology 2009, Vol 50, pp1012A – 1013A

Westbrook RH, O'Grady JG, Harrison PM, Devlin J, Heneghan MA.
Pregnancy in patients with cirrhosis – Can adverse outcomes be predicted prior to conception?
Hepatology 2009, Vol 50, pp 455A – 455A

Westbrook RH, Yeoman AD, Joshi D, Rela M, Quaglia A, O'Grady JG, Bernal W, Heaton ND, Wendon JA, Heneghan MA.
Outcomes of severe pregnancy related liver disease – should standard transplant listing criteria be applied?
Liver Transplantation, 2009, vol 15, pp S71 –S72

Westbrook RH, Yeoman AD, Agarwal K, Aluvuhare V, O'Grady JG, Bowles M, Rela M, Heaton ND, Wendon JA, Heneghan MA.
Pregnancy following liver transplantation: A 20 year experience
Liver Transplantation, 2009, Vol 15, pp S202 – S202

Oral Presentations at conferences:

Pregnancy in patients with cirrhosis – Can adverse outcomes be predicted prior to conception?
Westbrook RH, O'Grady JG, Harrison PM, Devlin J, Heneghan MA
Plenary oral presentation at the British Society of Gastroenterology Regional Meeting – 2011

Outcomes of severe pregnancy related liver disease and liver transplantation
Westbrook RH, Yeoman AD, Joshi D, Rela M, Quaglia A, O'Grady JG, Bernal W, Heaton ND, Wendon JA, Heneghan MA.
"The Presidents pick – Tomorrows stars" Oral presentation at the British Association for the Study of Liver Disease Annual Meeting - 2009

Outcomes of severe pregnancy related liver disease – should standard transplant listing criteria be applied?
Westbrook RH, Yeoman AD, Joshi D, Rela M, Quaglia A, O'Grady JG, Bernal W, Heaton ND, Wendon JA, Heneghan MA
Plenary oral presentation at the International Liver Transplant Society Annual Meeting - 2009

Book Chapters:

Autoimmune hepatitis: A guide for practicing clinicians
Chapter 10: Autoimmune hepatitis and pregnancy **– Rachel Westbrook** and Michael Heneghan
ISBN 978-1-60761-568-2

Awards:

British Society of Gastroenterology regional meeting 2011 – Best Clinical Poster presentation £100
European Association for the Study of Liver Disease 2011 – Young Investigators Bursary £650
British Association of Liver Disease 2010 - Travel award £250
International Liver Transplant Society 2010 – "rising star award" $1500
European Association for the Study of Liver Disease 2010 – Award to attend EASL school of hepatology in Autoimmune Hepatitis, PBC and PSC - December 2009
British Association of Liver Disease – 2009 Travel award £500
British Association of Liver Disease – 2009 "rising star award"
International Liver Transplantation Society – 2009 – Travel Award $1000

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