Original Article

Abnormal Liver Function Tests in the Symptomatic Pregnant Patient: The Local Experience in Singapore

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Abstract

Introduction: The causes of abnormal liver function tests in pregnancy are varied and may or may not be pregnancy related. Often, the diagnosis can be difficult. This study looked at the causes of deranged liver function tests in obstetric patients with significant symptoms and signs. Materials and Methods: Data from 50 cases of abnormal liver function tests in pregnant patients, who presented from 1998 to 2001, were analysed. Their presenting symptoms included persistent vomiting (48%), pruritis (14%), jaundice (26%), upper abdominal discomfort (24%) and hypertension (46%). Results: Pregnancy-related causes accounted for 84% of the abnormal liver function tests. Abnormal liver function tests occurred more frequently in the first (34%) and third (58%) trimesters than in the second trimester (8%). Hyperemesis gravidarum (94%) and partial haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome (31%) were the commonest causes in the first and third trimesters respectively. Hepatitis B flare resulted in 2 maternal deaths. Seven patients with pre-eclampsia toxaemia, acute fatty liver of pregnancy or partial/complete HELLP syndrome had their liver function tests measured sequentially before and after delivery. All of them showed rapid improvement postpartum with their alanine aminotransferase (ALT) dropping 50% within 3 days. Conclusions: The majority of patients with abnormal liver function tests had a cause related to pregnancy, and pregnancy-related causes in the third trimester improved rapidly postpartum. Hepatitis B flare was a significant non-obstetric cause leading to maternal mortality. This diagnosis must therefore be considered in ethnic groups where the incidence of chronic hepatitis B infection is high, especially in chronic hepatitis B carriers with suspected pregnancy-related disease who deteriorate postpartum.

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Key words: HELLP syndrome, Hepatitis B, Liver function tests, Pre-eclampsia, Pregnancy

Introduction

The diagnostic work-up of abnormal liver function tests (LFT) in pregnancy is challenging, as the conditions peculiar to pregnancy have to be considered in addition to the causes affecting the non-pregnant population.[1,2] The spectrum of disease is varied and the abnormal LFT can be mild with no long-term consequence, or it can be severe, leading to both maternal and foetal mortality.[3] As such, gastroenterologists and obstetricians are often faced with the dilemma of whether the abnormal LFT is related to pregnancy and whether immediate obstetric intervention is necessary. Knowing the distribution of the various probable causes of abnormal LFT in the pregnant population would therefore be useful in guiding clinical practice.

Of pregnancy-related causes of abnormal LFT in the third trimester, acute fatty liver of pregnancy, haemolysis, elevated liver enzymes and low platelets (HELLP) syndrome, pre-eclampsia toxaemia (PET) and partial HELLP syndrome can potentially be fatal, but the LFT abnormalities usually resolve after delivery.[4] We also looked at the LFT in patients with these diagnoses postpartum to study the time course to resolution.

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Materials and Methods

This is a retrospective study of patients, at a major obstetric hospital in Singapore from 1998 to 2001, who were referred to the obstetric physician and had abnormal LFT. The medical records of these patients were obtained and information relating to the episode of abnormal LFT were analysed. Routine LFT are not done in all patients in this hospital and performed only in the presence of symptoms or abnormalities on physical examination. This comprised persistent vomiting (48%), pruritis (14%), jaundice (26%), upper abdominal discomfort (24%) and hypertension (46%).

The definition of abnormal LFT pertained to values higher than the normal range as defined by the local laboratory (bilirubin >24 μmol/L, alkaline phosphatase (ALP) >103 U/L, gamma-glutamyltranspeptidase (GGT) >26 U/L, ALT >51 U/L, aspartate aminotransferase (AST) >33 U/L). Hyperemesis gravidarum was defined as persistent vomiting with the onset occurring before 13 weeks of gestation, and of such severity that the patient is unable to retain solids and liquids and requires hospital admission for intravenous hydration.[5] In this study, the diagnosis of HELLP syndrome required the presence of the following criteria: ALT greater than and haptoglobin less than the range defined by the local laboratory (haptoglobin <0.37 g/L) and platelets of less than 100 x 10^9/L. If the patients had a raised ALT but only 1 of the 2 remaining criteria, they were diagnosed as having partial HELLP syndrome. PET was defined as the development of hypertension after 20 weeks' gestation according to the Australasian Society for the Study of Hypertension in Pregnancy criteria.[6] There are no established diagnostic criteria for acute fatty liver of pregnancy. Although liver biopsy is the gold standard for the diagnosis of acute fatty liver of pregnancy, the diagnosis can be made in most cases clinically with liver biopsies indicated only for patients with atypical presentations.[3,4,7,8] The diagnosis of acute fatty liver of pregnancy in our study was made on clinical grounds in patients with acute hepatic failure in the third trimester who had reduced synthetic function of the liver with coagulopathy and impaired renal function as prominent features as discussed by Castro et al.[8] In addition, non-obstetric causes of acute hepatic failure such as hepatitis A, hepatitis B, hepatitis C and drug-induced hepatitis were excluded in these patients. Lastly, their clinical parameters improved after delivery. The diagnosis of intrahepatic cholestasis of pregnancy was made on clinical grounds as described by Davidson.[9] These patients presented with pruritis as a prominent symptom without skin lesions in late pregnancy. The pruritis generally begins in the palms and soles, and may extend to the trunk. The pruritis resolves within days of delivery. Serum bile acids were not assessed in our patients as this test is not available locally.

Results

Patient Demographics

There were 48 patients seen during the study period with 49 pregnancies associated with abnormal LFT and the presence of significant symptoms and signs. One woman had 2 pregnancies during the study period with abnormal LFT for which 2 different causes were found. Another woman had 2 different causes for the abnormal LFT during the same pregnancy. The median age for the whole study group was 31 years (range, 19 to 40 years). Forty-six per cent of this population was primiparous. The ethnic distribution was as follows: Chinese (34%), Malay (38%), Indian (20%) and minority ethnic groups (4%).

Causes of Abnormal LFT

The causes of abnormal LFT are shown in Table 1. The majority of LFT abnormalities in this study were related to pregnancy (84%). Most episodes of abnormal LFT occurred in the first (34%) and third (58%) trimesters. In contrast, the occurrence of abnormal LFT was uncommon during the second trimester (8%). The commonest cause of abnormal LFT in the first trimester was hyperemesis gravidarum (94%). The causes of abnormal LFT in the third trimester were the most varied, with partial HELLP syndrome (31%) and PET (21%) comprising the commonest diagnoses. The only patient with drug-induced hepatitis was on isoniazid and rifampicin for treatment of pulmonary tuberculosis.

There were 2 deaths in this study which were due to hepatitis B flare. Both patients had emergency Caesarean sections as their abnormal LFT were thought to be related to pregnancy, but their liver impairment did not recover and they died subsequently. The first patient was diagnosed to be a chronic hepatitis B carrier during routine antenatal

Table 1. Causes of Abnormal LFT in the Study Population Stratified According to Trimester

	Diagnosis	No.	%
1st trimester	Hyperemesis gravidarum	16	94
	Typhoid	1	6
2nd trimester	Hyperemesis gravidarum	2	50
	Choledocholisthesis	2	50
3rd trimester	Acute fatty liver of pregnancy	2	7
	Drug induced	1	3
	HELLP syndrome	3	10
	Hepatitis B flare	3	10
	Unknown	1	3
	Intrahepatic cholestasis of pregnancy	4	14
	PET	6	21
	Partial HELLP syndrome	9	31

HELLP: haemolysis, elevated liver enzymes, low platelets;
PET: pre-eclampsia toxaemia

screening. In the third trimester, she developed jaundice associated with disseminated intravascular coagulation and renal impairment. She was suspected to have acute fatty liver of pregnancy with a differential diagnosis of hepatitis B flare. The foetus was delivered immediately as this is the treatment of choice for acute fatty liver of pregnancy. However, the patient deteriorated post-delivery with worsening LFT and renal function, not typical of acute fatty liver of pregnancy. With the exclusion of acute fatty liver of pregnancy, the diagnosis of a hepatitis B flare was made. Her HBsAg was positive, HBeAg was negative and Anti-HBeAb was positive. Her HBV DNA test result was subsequently available and was 1295.0 MEq/mL. She could have had a pre-core mutant infection or a fatal seroconversion reaction. The patient was referred for liver transplantation, but she deteriorated rapidly with cerebral oedema and septic shock, and died before liver transplantation could be initiated. The second patient was a chronic hepatitis B carrier diagnosed to have PET as she had proteinuria, a raised uric acid and severe hypertension requiring IV hydralazine. Following an emergency Caesarean section, her blood pressure normalised and her LFT improved and she was discharged 3 days postpartum. She was re-admitted 2 weeks later with vomiting, jaundice and drowsiness. There was a marked deterioration in her LFT and she lapsed into fulminant liver failure rapidly. The diagnosis of a hepatitis B flare was made only after the second rise in her LFT. Her HBsAg and HBeAg were positive and HBV DNA was 66.3 MEq/mL. She was referred for liver transplantation, but she developed septicaemia which led to her death before liver transplantation could be made. The diagnosis of hepatitis B was difficult to make in this case as she had co-existing PET which improved postpartum.

Our patients with PET, HELLP, partial HELLP and acute fatty liver of pregnancy were treated by urgent delivery of the foetus. Apart from the patient described above who had co-existing PET and hepatitis B flare, and 1 patient with PET who absconded from the ward and was subsequently lost to follow-up, the remaining 18 patients recovered uneventfully after delivery of the foetus.

Laboratory Tests

The median LFT for the 3 commonest diagnoses of hyperemesis gravidarum, PET and partial HELLP are listed in Table 2. Postpartum LFT were measured sequentially in 7 patients of whom 3 had partial HELLP syndrome, 2 had acute fatty liver of pregnancy, 1 had HELLP syndrome and the last had PET. The median time taken for the ALT to fall to 50% of the highest recorded level was 2 days (range, 1 to 3 days).

Discussion

There have been numerous publications on the specific causes of abnormal LFT in pregnancy[4,8-11] but this study focuses on the probable diagnoses that a physician would expect when faced with a pregnant woman with symptoms and signs associated with an abnormal LFT. It is therefore pertinent that the study looked at patients who had their LFT tested only when indicated clinically rather than as a result of blanket screening, because the use of laboratory investigations in the appropriate clinical setting reflects our local medical practice at present.

Hyperemesis gravidarum was by far the commonest cause of raised LFT during the first trimester in our study. Abnormal LFT have been reported previously in 16% to 25% of patients with severe hyperemesis gravidarum who required hospitalisation.[12,13] Elevations in ALT are usually mild and less than 4 times the upper limit of normal.[13] The ALT levels in our patients with hyperemesis gravidarum were similar, with a median value of 103 U/L. However, there have been occasional case reports of ALT rising more than 1000 U/L in patients with hyperemesis gravidarum.[14] The cause of LFT abnormalities in hyperemesis gravidarum is not known, but is thought to be related to fasting and poor nutrition.[12] However, Morali and Braverman[13] reported that the degree of ketonuria and level of LFT abnormality did not correlate in patients with hyperemesis gravidarum, suggesting that other mechanisms may be responsible.

Many definitions of the clinical parameters of HELLP

Table 2. The Median (Range) LFT for Patients With Hyperemesis Gravidarum, PET and Partial HELLP Syndrome

	Hyperemesis gravidarum (n = 18)		PET (n = 6)		Partial HELLP syndrome (n = 9)	
Total bilirubin (μmol/L)	21.5	(11-90)	14	(6-16)	15	(8-222)
ALP (U/L)	51.5	(34-90)	203.5	(67-314)	195	(86-276)
GGT (U/L)	45	(12-154)	17	(7-59)	35	(2-286)
ALT (U/L)	103.5	(44-405)	115	(20-342)	149	(22-1048)
AST (U/L)	73	(25-154)	66	(30-407)	81	(44-735)
Albumin (g/L)	36	(31-45)	28.5	(22-32)	31.5	(21-34)

ALT: alanine aminotransferase; ALP: alkaline phosphatase; AST: aspartate aminotransferase; GGT: gamma-glutamyltranspeptidase; HELLP: haemolysis, elevated liver enzymes, low platelets; LFT: liver function tests; PET: pre-eclampsia toxaemia

syndrome have been proposed in the literature. We have chosen to use a decreased haptoglobin in our study as an indicator of haemolysis rather than a raised LDH, raised total bilirubin or a falling haematocrit used in previous studies.[15] The reasons are that LDH and total bilirubin are also raised as a result of liver impairment.[16] Furthermore, it is difficult to attribute a falling haematocrit to haemolysis alone as blood loss following delivery, especially Caesarean section, can contribute to a falling haematocrit. A reduced haptoglobin may be a better indicator of haemolysis as Wilkie et al[17] reported reduced levels of haptoglobin in all 25 patients with HELLP syndrome in their study. In contrast, in 5 patients with HELLP syndrome where they measured LDH isoenzymes, elevated plasma LDH in 4 patients were of liver origin rather than from haemolysis.

PET, partial HELLP and HELLP are thought to be related entities with different clinical manifestations of the same underlying disease process. Liver biopsies of patients with HELLP syndrome showed fibrin deposition in the periportal sinusoids and hepatocellular necrosis[18] similar to that found in pre-eclampsia.[19] The mortality with PET is lower than that of HELLP syndrome, with rates of less than 1% and 1% to 3%, respectively.[4] The clinical distinction between patients with full blown HELLP syndrome and partial HELLP syndrome also carries prognostic significance. Audibert et al[20] reported that patients with HELLP syndrome developed more complications than patients with partial HELLP syndrome. PET and partial HELLP syndrome were the commonest causes of raised LFT in our study population during the third trimester, occurring with a frequency of 21% and 31%, respectively. The median ALT for PET and partial HELLP were 115 U/L and 149 U/L, respectively, in our study. The rise in aminotransferases is usually not severe, with mean levels of 60 U/L in pre-eclampsia and 150 U/L in HELLP reported previously.[4]

In their series of 28 patients with acute fatty liver disease of pregnancy, Castro et al[8] reported that the cardinal features were that of impaired coagulation and renal impairment. However, HELLP too can lead to disseminated intravascular coagulation and renal impairment with a reported incidence of 21% and 7.7%, respectively.[11] Indeed, it has been suggested that acute fatty liver of pregnancy may form the extreme end of the spectrum of pre-eclamptic disease. This is supported by the findings of Minakami et al,[21] in which liver biopsies were taken from 41 patients with acute fatty liver of pregnancy, HELLP syndrome, PET with normal AST and PET with raised AST, and the liver tissue stained with oil red O. All liver biopsy specimens showed microvesicular fat droplets in varying degrees suggesting a common pathology. Interestingly, patients with HELLP and acute fatty liver of pregnancy tended to have a higher liver fat density than patients with PET, but it was not possible to distinguish these diagnoses histologically.

We found that the large majority of abnormal LFT in pregnancy was related to the pregnancy. This occurred primarily in the first and third trimesters. However, despite the observation that 83% of abnormal LFT in the third trimester was related to pregnancy, the non-obstetric causes were important as the deaths in our study were secondary to hepatitis B flare. Both patients had raised LFT in the third trimester which were initially thought to be due to acute fatty liver disease of pregnancy and PET respectively as discussed previously. Lin et al[22] reported in their study that 5 out of 30 patients who were hepatitis B carriers sero-converted in the first 3 months postpartum. In contrast none of the patients in the control group seroconverted. This increased rate of seroconversion may be related to postpartum immune rebound.[23] The level of endogenous cortisol in pregnancy rises in the second trimester, reaching levels of 2 to 3 times normal in the third trimester. Following delivery, the cortisol falls rapidly to pre-pregnancy levels.[24] This phenomenon is reminiscent of that following withdrawal of corticosteroids in non-pregnant individuals with chronic hepatitis B. A similar phenomenon has been observed with chronic hepatitis C carriers in whom the histopathological grading was found to be more severe in patients postpartum than in controls.[25] In patients with abnormal LFT due to an attempt at hepatitis B sero-conversion during the third trimester, emergency delivery of the foetus reduces circulating cortisol rapidly and this may ironically worsen the seroconversion reaction as may have been the case in both maternal deaths in our study.

The diagnosis of the pre-eclamptic diseases and acute fatty liver of pregnancy may be difficult to distinguish from hepatitis B flare as illustrated in our cases. Moreover, patients with chronic liver disease may have co-existing pre-eclamptic disease, as it has been reported that patients with chronic active hepatitis have an increased risk of developing PET.[26] A major difference between obstetric and non-obstetric causes of abnormal LFT is that acute fatty liver of pregnancy and the pre-eclamptic diseases respond well to delivery of the foetus.[4] Our study showed that patients with acute fatty liver of pregnancy, HELLP syndrome, partial HELLP syndrome and PET had rapid improvement in the LFT postpartum, whereas patients with hepatitis B flare deteriorated rapidly postpartum. As hepatitis B is common in the Asia-Pacific region with a prevalence of the carrier state of greater than 10%,[27] a high index of suspicion for a hepatitis B flare is required in patients with suspected pregnancy-related liver disease from these countries when their LFT do not improve rapidly within a few days postpartum.

Although we do not advocate checking LFT in asymptomatic pregnant patients, it may be worthwhile performing screening LFT in asymptomatic hepatitis B carriers, because of the possible effects of pregnancy as discussed previously. In addition, these patients should have their 'e' status evaluated if this was not done recently. For patients with abnormal LFT on screening, a baseline HBV DNA should be done as subsequent measurements of HBV DNA may be useful in distinguishing pregnancy-related causes of abnormal LFT from a hepatitis B flare. However, many questions regarding this special group of pregnant patients remain unanswered. For example, what is the optimal frequency of LFT evaluation in pregnant hepatitis B carriers with abnormal LFT? Is lamivudine indicated in pregnant patients with a hepatitis B flare? Large prospective trials are needed to answer these complex yet important clinical questions.

Conclusion

Knowing the likely causes of an abnormal LFT in the various stages of pregnancy helps allay much anxiety and allows appropriate obstetric planning with regards to the timing of delivery. Extra caution should be exercised in interpreting the abnormal LFT of a HBsAg positive obstetric patient bearing in mind the consequence of a more serious outcome in a seroconversion reaction occurring in the immediate postpartum period. Early referral to a hepatologist would be important in the management of hepatitis B flare in pregnancy.

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