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Increasing LFT in foetal outcome

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Abstract

Objective: Abnormal liver function tests (LFTs) in pregnancy require proper interpretation in order to avoid pitfalls in the diagnosis. The underlying disorder can have a significant effect on the outcome of both mother and foetus. The present study was done with the objective to study the clinical profile, incidence and possible causes of derangements of liver function tests.

Method: Eighty pregnant women with abnormal liver dysfunction were studied prospectively. Women with chronic liver disease and drug-induced abnormal liver function test were excluded. All available LFTs including LDH were studied along with some more definitive tests to aid identification of underlying cause. Foetomaternal outcome was noted in all.

Results: The incidence of abnormal LFT was 0.9 %. 13/80 (16.75 %) women had liver disorder not specific to pregnancy, whereas 67/80 (83.25 %) women had pregnancy specific liver dysfunction. Of these, 65(81.25 %) women with liver dysfunction had pre-eclampsia including 11 (13.75 %) with HELLP and six women with eclampsia. 48/65 (60 %) women had pre-eclampsia in the absence of HELLP syndrome or eclampsia. The mean value for bilirubin (mg %) in hypertensive disorders of pregnancy ranged from 1.64 to 3.8, between 5 and 10 for ICP and AFLP and [10 in infective hepatitis. Transaminases were highest in infective hepatitis, whereas alkaline phosphate was highest in ICP. Total 27 (33.75 %) women suffered from adverse outcome with four (5 %) maternal deaths and 23 (28.75 %) major maternal morbidities. 33/80 (41.25 %) women had intrauterine death. 26.25 % babies were small for date.

Conclusion: Pregnancy-specific disorders are the leading cause of abnormal liver function test during pregnant state particularly in the third trimester. Pre-eclampsia-related disorder is the commonest. Gestational age of pregnancy and relative values of various liver function tests in different pregnancy-specific and pregnancy nonspecific disorders appear to be the best guide to clinch the diagnosis.

Keywords: Abnormal liver function test in pregnancy Pre-eclampsia HELLP syndrome Acute fatty liver of pregnancy

Introduction

Abnormal liver function tests (LFTs) in pregnancy require proper interpretation in order to avoid pitfalls in the diagnosis. The underlying disorder can have a significant effect on the outcome of both mother and foetus, and a diagnostic workup must be initiated urgently. The abnormal liver function tests may be found in an asymptomatic pregnant woman, and on the other hand, a fulminant form may present with life-threatening complications [1].

The physiological changes in a pregnant woman can confuse the clinician by some nonspecific symptoms such as nausea, vomiting and abdominal pain. Alterations of laboratory test results representing the physiological changes of pregnancy include a threefold to fourfold increase in the level of alkaline phosphatase and also an increase in the synthesis of clotting factor, whereas there is a decrease in the level of antithrombin III and protein S, serum albumin and total proteins. There are no significant changes in the level of liver transaminase enzyme, serum bilirubin level and prothrombin time [2].

The pathological derangement in the liver functions may be related to pregnancy or may coexist with pregnancy and may be divided into three major groups [3]. First group includes liver disorders that are specific to pregnancy such as hyperemesis gravidarum, pre-eclampsia, eclampsia, syndrome of haemolysis, elevated liver test and low platelets (HELLP), acute fatty liver of pregnancy and intrahepatic cholestasis of pregnancy. These disorders are mostly trimester specific. Second group includes intercurrent liver disease occurring during pregnancy such as viral hepatitis and herpes simplex. Third group includes pregnancy with pre-existing liver disease such as chronic active hepatitis, Wilson's disease, cirrhosis of liver, portal hypertension, Budd-Chiary syndrome and hepatic tumour. The guidelines for pregnancy-related liver disorders are not very clear in India and abroad [4, 5].

The present study was done with the objective to study the clinical profile, incidence and possible causes of derangements of liver function test at the largest tertiary hospital as well as to study the foetomaternal outcome in these women.

Methods

Study Design: This is a prospective study carried out at Rajendra Institute of Medical Sciences, Ranchi within a year.

Methodology: After obtaining the demographic, menstrual and obstetric details, the specific symptoms related to liver dysfunction such as pruritus, persistent vomiting, yellowish discoloration of urine, blurring of vision, diminished urine output, upper abdominal discomfort and anorexia were asked.

A detailed history of any drug intake such as paracetamol, antitubercular drugs, oral contraceptive and history of sickling was noted. Specific history taken in view of abnormal liver function is history of blood

transfusion, tattoos, alcohol consumption, and hyper lipidaemia was noted.

A thorough general and obstetric examination was carried out in all. In all cases of severe gestational hypertension and pre-eclampsia, clinical signs and symptoms of ICP, infective hepatitis or other disorders, all available LFT including LDH were ordered. Some more definitive tests to aid identification of underlying cause such as platelet count viral serology for hepatitis, peripheral smear and haemoglobin electrophoresis were done whenever required. These women were followed up till delivery and along with their neonates, up to 7-day post-partum.

Diagnostic criteria for different underlying pathologies were based upon following parameters [6]:

HELLP syndrome: complete: raised bilirubin, elevated AST ([70 IU/L), low platelet count (\100,000/lL), haemolysis (suggestive peripheral smear with red cell fragmentocytes along with increased reticulocytes). Partial: elevated AST ([40 IU/L), low platelet count (\150,000/lL), the absence or presence of haemolysis. Pre-eclampsia-associated liver dysfunction: Elevated transaminases or bilirubin in the presence of hypertension to the extent of 140/90 mmHg or more on two occasions [6 h apart, proteinuria after 20 weeks of pregnancy]

Intrahepatic cholestasis of pregnancy (ICP): Pruritus without any skin problem or allergy with elevated transaminases. Relieved after delivery.

Acute Fatty Liver of Pregnancy (AFLP) Six or more of the following—vomiting, abdominal pain, polydipsia or polyuria, encephalopathy, leucocytosis, elevated bilirubin, elevated transaminases, marked hypoglycaemia, renal impairment, coagulopathy, elevated urate, ascites or bright liver on ultrasound.

Hepatitis: elevated transaminases or bilirubin in the presence of positive hepatitis viral serology. Sickling: positive haemoglobin electrophoresis.

Sample Size: 80 such women were included in the study.

Inclusion criteria: All pregnant women with abnormal liver dysfunction admitted in the obstetric unit of hospital were studied prospectively

Exclusion criteria: Women with chronic liver disease and drug-induced abnormal liver function test

Results

There were 80 women with deranged LFT amongst 8508 admissions giving the incidence of 0.9 % in our study. Majority of the women were young and aged less than 30 years, were un-booked, of low parity and belonged to lower socio-economic status; 87.5 % of pregnant women presented in third trimester of pregnancy. The most common presenting complaint was oedema (25 %) followed by yellow discoloration of urine and visual symptoms with headache.

In our study, 13/80 (16.75 %) women had liver disorder which were not specific to pregnancy and consisted of infective hepatitis, malaria and sickle cell disease, whereas 67/80 (83.25 %) women had pregnancy-specific liver dysfunction. Of these, 65 (81.25) women with liver dysfunction had pre-eclampsia including 11 (13.75) with HELLP syndrome and six women with eclampsia. 48/65 (60 %) women had pre-eclampsia in the absence of HELLP syndrome or eclampsia. Complete HELLP syndrome was found in 6 out of 11 women, while incomplete HELLP syndrome was diagnosed in the remaining five. The cases of chronic liver diseases were not included in the study.

Amongst various abnormalities of LFT, the majority (45 %) women had AST elevation of less than 100 IU/L and

47.5 % had ALT elevated in 100–500 IU/L range. The commonest value of bilirubin level was between 1 and 2.5 mg/dL found in 47.5 % cases. Only 7–10 % women exhibited bilirubin values of[10 mg/dL and/or AST/ALT values [500 IU/L. LDH of more than 600 IU/L was elevated in 66.25 % women. Alkaline phosphatase between 141 and 564 IU/L was found in 40 % women and more than 1000 IU/L in one woman only.

The mean values of all LFT abnormalities are shown in **Table 1**. The mean value for bilirubin in hypertensive disorders of pregnancy ranged from 1.64 to 3.8, whereas it was between 5 and 10 for ICP and AFLP and went to very high levels of [10 in cases of infective hepatitis only. Transaminases were highest in infective hepatitis, whereas alkaline phosphate was highest in ICP.

Table 1: Mean LFT levels for pregnant women with various diseases

Sn.	Disease	Serum	Bilirubin	AST	ALT	Alkaline phosphatase	Serum LDH
		Total	Direct				
1.	Pre-eclampsia	1.64	1.43	124.04	125.21	249.63	725.56
2.	Eclampsia	1.75	1.45	121.70	107.67	230.83	645.00
3.	HELLP syndrome	3.99	3.80	175.00	166.00	307.46	990.36
4.	Viral hepatitis	12.25	9.50	741.40	814.00	663.10	163.10
5.	ICP	3.80	3.40	100.00	114.00	1750.00	380.00
6.	Miscellaneous	4.03	90.67	101.70	92.33	317.67	770.00
7.	AFLP	6.00	7.00	670.00	778.00	500.00	900.00

Out of three women in second trimester pregnancy, two had intrauterine foetal death and the third was terminated because of severity of PE. All aborted after induction. Majority of women, i.e. 53 (66.26 %), delivered vaginally out of whom 29 (36.25) had spontaneous onset. Labour was induced in 30 (37.5 %) women because of obstetric indications and 24 (30 %) delivered, whereas 06/30 of this group underwent caesarean section needing delivery urgently due to worsening foetomaternal condition in severe pre-eclampsia. Eighteen additional women delivered by caesarean section due to various obstetric indications making a total of 24 (30 %).

Overall, 27 (33.75 %) women suffered from adverse outcome. Disseminated intravascular coagulopathy complicated four cases and was managed by transfusion of blood components in two, whereas the other two succumbed: one with AFLP and another with abruption of placentae. There were total four maternal deaths in the group including these two. The remaining two died of multi-organ failure: one in a case of hepatitis E and another in HELLP syndrome. The major maternal morbidity was observed in 23 (28.75 %) women. Commonest complication was post-partum haemorrhage which could be arrested by medical methods. 33/80 (41.25 %) women had intrauterine death including two cases of second trimester with severe early onset pre-eclampsia. Out of 47 live births, 21 (26.25 % of total 80 cases) were small for date infants.

Discussion

The incidence of abnormal LFT in pregnancy is higher in younger age group. In our study, majority of women were of low socio-economic status, not booked for antenatal care and generally got admitted in the hospital

only as emergency. Similar facts are observed in other Indian studies too [4, 6–9]. Most common gestational period of abnormal liver function test was third trimester, and pregnancy-related causes were the commonest cause, particularly the pre-eclampsia-related disorder. This explains the oedema to be the leading presenting symptom although it is no more a diagnostic criterion but remains an important clinical feature of pre-eclampsia.

In most studies, the cause of abnormal LFT is reported to be pregnancy-specific disorder and varies from 67 to 89 % [10–12]. Our finding of 83.25 % is in agreement with others. Liver diseases had a very peculiar pattern of association with the gestational age, and most cases in first trimester are of hyperemesis gravidarum. In the second trimester, it is often due to the causes that are coincidental and are nonspecific to the pregnancy, whereas the pregnancy-specific causes such as ICP, AFLP or more commonly pre-eclampsia-related disorder are the etiopathological factor in the third trimester. Although we did not have any case of hyperemesis gravidarum with abnormal LFT in the first trimester, our second and third trimester cases followed the pattern described above. Thus, the gestational age seems to be the best guide for further evaluation of abnormal LFT in pregnancy

Although many women were tested positive for Australia antigen, only one was found to have abnormal LFT and was included in the study. Viral hepatitis is reported to be commoner in developing countries, and the fulminant hepatitis especially in relation to hepatitis E is higher in pregnancy [13]. Malnutrition superimposed on the normal demand of pregnancy and inversion of T and B lymphocytes in early pregnancy have been postulated to be the contributing factor. We had five cases of hepatitis E

In our study, out of the 80 women, only one (1.25 %) woman had intrahepatic cholestasis of pregnancy. The incidence of ICP varies from 0.1 to 1.5 % of pregnancies [14]. Our case presented with 38-week gestation, and her laboratory investigation shows marked elevation in alkaline phosphatase level with moderate increase in serum bilirubin level. Many women with pre-eclampsia-related liver function abnormalities do not have symptoms, and only awareness of associated possibility of liver problem can make the clinician to ask for liver function tests leading to timely detection and proper timely management in these cases. This can avoid life-threatening complications.

The average range of derangement of various liver function tests in pregnancy-associated liver dysfunction are as follows: bilirubin\5 mg % (except for AFLP with value around \10 mg %), transaminases over one and a half times above normal. Aminotransferase elevations are the hallmark of the abnormal liver function. AST elevation in pre-eclampsia-related liver function abnormalities particularly HELLP syndrome may be ranging from 70 to 6000 with a mean of 250 [15]. This is not a true hepatic failure, and most women are not jaundiced.

AST and ALT are the most commonly used markers of hepatocyte injury. AST is present in cytosolic and mitochondrial isoenzymes and is found in the liver as well as many other tissues. It is less sensitive and specific for the liver. ALT is also a cytosolic enzyme is found in its highest concentrations in the liver and is more specific to the liver [16]. Hepatocyte necrosis in acute hepatitis, toxic injury or ischaemic injury results in the leakage of enzymes into the circulation. Various liver

diseases are associated with typical ranges of AST and ALT levels. ALT levels often rise to several thousand units per litre in patients with acute viral hepatitis. Lactate dehydrogenase (LDH) is less specific than AST and ALT as a marker of hepatocyte injury. However, it is markedly elevated after an ischaemic liver injury [14]. In cases of HELLP syndrome, the higher level of LDH also represents a marker of haemolysis specifically in the presence of raised bilirubin (serum, urine), urobilinogen (urine) and fragmentocytes (on peripheral smear) resulting from microangiopathic haemolysis. In cases of viral hepatitis, commonly the transaminases are high reaching [500–1000 IU/L and bilirubin often crosses 10 mg % in acute phase. In our study, the mean values of abnormal LFT were more or less followed the same pattern. It is apparent that after the gestational age, the degree of derangements of LFT can guide the approach to diagnosis further.

In our study, the induction rate was high because of many cases with intrauterine foetal deaths and preeclampsia-related obstetric conditions. The woman with ICP delivered a healthy baby after 6 h of induction. The worst outcome was noted in women with HELLP syndrome. Out of 11 women suffering from it, two died and eight suffered from severe morbidity.

HELLP syndrome is associated with poor maternal and foetal prognosis. Maternal mortality ranges from 3.5 to 24 %. These patients are at greater risk of complications such as liver rupture, disseminated intravascular coagulation, abruptio placentae and acute renal failure. In addition to all these complications, we had a high incidence of ascites and it contributed to eight out of total 23 (28.25 %) of severe morbidities. All eight were having generalized oedema too. Water retention and increased activity of the renin–angiotensin–aldosterone system in these women can lead to the development of ascites [17]. AFLP is the extended spectrum of the same disease process [18]. The other studies reported high mortality ranging from 31 to 100 % [19, 20]. In our study too, the only woman having AFLP died due to multi-organ failure. Hepatitis E is also reported to have highest mortality rate when occurs in pregnancy [21–23]. We had one case of hepatitis E who died out of five.

Pre-eclampsia-related obstetric conditions had poorer prognosis for foetus as well, and reported perinatal mortality rate is 24.6–62 % [11, 12]. In our study, the intrauterine death of the foetus occurred in 41.25 % cases, and out of those born alive, SGA infants were 26.25 %. This may be because majority of our cases had preeclampsia-related obstetric conditions which itself may lead to these adverse outcomes and the women manifesting abnormal LFT represent more severe forms of the disease spectrum.

The factor responsible for the higher maternal and foetal morbidity and mortality appear to be due to lack of facilities, lack of awareness regarding the pregnancy-specific conditions which may lead to worsening of the outcome of pregnancy especially in the presence of abnormal liver function, poor nutrition, prevalence of anaemia, delay in seeking medical advice and delay in referral to the tertiary care hospital. Many of these women when brought to the referral hospital are already in moribund condition and often do not respond to treatment.

Conclusion

Pregnancy-specific disorders are the leading cause of abnormal liver function test during pregnant state particularly in the third trimester. Pre-eclampsia-related disorder is the commonest amongst these. Abnormal LFT may not be noticed in the absence of awareness

particularly when jaundice is not the presenting feature. If a systematic approach is adopted, the cause is often apparent. The gestational age of pregnancy particularly in the presence of relevant clinical features may be the first step. This step when followed by the relative values of various liver function tests in different pregnancy-specific and pregnancy nonspecific disorders appear to be the best guide to clinch the diagnosis. Early and timely joint care by the obstetric and medical team can bring the best results in this so far grim situation in the developing world.

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