Pregnancy-Related Liver Disorders

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Pregnancy-related liver disorders accounted for 8% of all maternal deaths at our center from 1999 to 2011. Of the three pregnancy-related liver disorders (acute fatty liver of pregnancy (AFLP), HELLP (Hemolysis, elevated liver enzymes, low platelets) syndrome and pre-eclamptic liver dysfunction, which can lead to adverse maternal and fetal outcome, AFLP is most typically under - diagnosed. Risk of maternal death can be minimised by timely recognition and early/aggressive multi-specialty management of these conditions. Urgent termination of pregnancy remains the cornerstone of therapy for some of these life threatening disorders, but recent advancements in our understanding help us in better overall management of these patients. This review focuses on various aspects of pregnancy-related liver disorders. (J Clin Exp Hepatol 2014;4:151–162)

Any liver disorder can occur co-incidentally in pregnancy. Pregnancy can also occur in a patient with pre-existent chronic liver disorder/portal hypertension. In addition, liver dysfunction in pregnancy can also be secondary to pregnancy (i.e. pregnancy-related liver disorders). The 5 pregnancy-related liver disorders—acute fatty liver of pregnancy (AFLP), HELLP syndrome (hemolysis, elevated liver enzymes and low platelets), pre-eclamptic liver dysfunction, intrahepatic cholestasis of pregnancy (ICP) and hyperemesis gravidarum—occur in different gestational time periods.[1] This review focuses on these pregnancy-related liver disorders.

PREGNANCY-RELATED LIVER DISORDERS: A PREVENTABLE CAUSE OF MATERNAL DEATH

Maternal mortality, defined as death on account of pregnancy occurring during pregnancy or within 42 days of childbirth/abortion, forms an important part of vital governmental statistics.[2] In India, maternal mortality ratio has declined from 254 per 100,000 live births in 2004–2006 to 212 per 100,000 live births in 2007–09, however it still falls way short of the United Nation's millennium development goal for 2015 of 109 per 100,000 live births.[3] With an estimated birth rate of 22 per 1000 population,[4] and total population of 1.21×10^9,[5] there is a maternal death approximately for every 9 min in India. India accounts for 19% of global maternal deaths.[6] Pregnancy-related liver disorders are uncommon; however these are important as some of these disorders can lead to death which can be prevented with timely recognition and management. The verbal autopsy method adopted to ascertain the etiology of maternal death in census of India does not include jaundice as the potential cause of death, thus contribution of pregnancy-related liver disorders to maternal mortality cannot be discerned in the current census data from India. On an audit of maternal deaths at our center from 1999 to 2006 (183 maternal deaths and 61,277 deliveries), jaundice complicated up to 25% of all maternal deaths and pregnancy-related disorders were responsible for 9%[7]; Figure 1. Similarly, from 2007 to 2011 (102 maternal deaths and 52,478 deliveries), pregnancy-related liver disorders accounted for 6% of maternal deaths (Unpublished data from our center).

INTERPRETATION OF LIVER FUNCTION TESTS DURING PREGNANCY

In pregnancy, interpretation of liver function tests remains similar to that in the non-pregnant state. In an uncomplicated pregnancy, serum bilirubin and serum alanine and aspartate aminotransferase remain in the normal range.[8] A mild increase in serum alkaline phosphatase (attributed to increase in placental isoenzyme) and a mild decrease in serum albumin levels (secondary to hemodilution due to increased plasma volume) are noted during normal pregnancy (Table 1).[8,9]

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Abbreviations: AFLP: acute fatty liver of pregnancy; CS: Caesarean; FAO: fatty acid oxidation; HbsAg: hepatitis B surface antigen; HELLP: hemolysis elevated liver enzymes and low platelets; HG: hyperemesis gravidarum; ICP: intrahepatic cholestasis of pregnancy; LCHAD: long chain hydroxyacyl coA dehydrogenase; LDH: lactate dehydrogenase; LFT: liver function tests; MP: malarial parasite; MTP: mitochondrial tri-functional protein; PFIC: progressive familial intra-hepatic cholestasis; PRLD: pregnancy-related liver disorders; PT: prothrombin time; UDCA: ursodeoxycholic acid
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Pregnancy and Liver

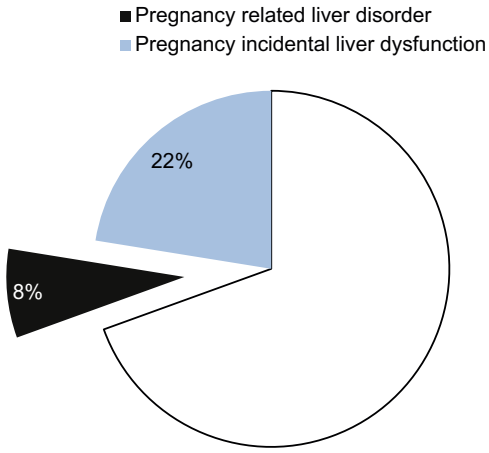

Figure 1 Contribution of pregnancy-related liver disorders to the maternal mortality at Christian Medical College, Vellore between 1999 and 2011.

ACUTE FATTY LIVER OF PREGNANCY (AFLP)

AFLP was first described in 1934 and was termed as 'acute yellow atrophy of the liver'. AFLP still remains an important obstetric emergency with significant maternal and peri-natal mortality. It is a catastrophic illness, characterised by microvesicular fatty infiltration of the liver cells in late (2nd or 3rd trimester) pregnancy.[10]

Epidemiology

AFLP is a rare disease occurring in late pregnancy. A recent prospective population based study spanning 229 hospitals and 1,132,964 pregnancies in UK, estimated an incidence of 5 cases per 100,000 pregnancies (95%C.I: 3.8–6.5/100,000 pregnancies).[11] Another prospective hospital based study from UK reported 5 cases of AFLP per 4377 pregnancies.[12] A prospective study from a tertiary care center in India estimated an incidence of 30 cases of AFLP per 100,000 pregnancies.[13]

On analysing the published data regarding liver dysfunction in pregnancy in India,[13–18] it appears that pregnancy-related liver disorders contribute to maternal mortality all over India, but are under-recognised.[19] As mentioned earlier, at our center from 1999 to 2011 we had 285 maternal deaths and 113,755 pregnancies; of these of maternal deaths 8% were due to pregnancy related liver disorders (i.e 23 patients) and 6%; 17of whom (7 had histological confirmation) had AFLP.[7]

Table 1 Liver Function Tests in Normal Pregnant Females from Southern India.

Parameters	Values in pregnant mothers mean (SD)		
	1st trimester	2nd trimester	3rd trimester
Serum bilirubin (mg/dl)	0.4 (0.2)	0.37 (0.1)	0.44 (0.2)
Serum albumin (g/dl)	4.2 (0.2)	3.7 (0.3)	3.4 (0.2)
Aspartate aminotransferase (IU/L)	22 (6)	20 (7)	20 (8)
Alanine aminotransferase (IU/L)	18 (14)	15 (7)	13 (5)
Alkaline phosphatase (IU/L)	70 (22)	90 (41)	171 (75)

(Adapted from ref. 8).

Pathogenesis[20,21]

AFLP is an example of mitochondrial hepatopathy (similar to Reye's syndrome and toxicity due to drugs like valproic acid) and is attributed to a defect in mitochondrial beta oxidation of fatty acids.

Why does AFLP Occur in Late Pregnancy?

It is thought that the mother has a compensated defect in fatty acid utilisation which manifests in late pregnancy when the mother is more dependent on fatty acid metabolism for energy. An association between fetal fatty acid oxidation disorders and maternal liver disease has been proposed (as described in the next section). As the pregnant mother is increasingly dependent on fats as the primary energy source in late pregnancy, the stage is set for phenotypic manifestation of liver disease to become overt in late pregnancy, in a hitherto asymptomatic and otherwise healthy individual.

Association of Fetal Fatty Acid Oxidation Defects with Maternal Liver Disease

AFLP and other pregnancy-related liver disorders occur more commonly if the fetus is homozygous or compound heterozygous for a defect in any of the enzymes involved in fatty acid oxidation (FAO).[22,23] These defects are autosomal recessive and the most commonly described FAO defect in AFLP patients is a mutation in the long chain hydroxyacyl coA dehydrogenase (LCHAD) part of the mitochondrial tri-functional protein (MTP). Defects in other enzymes involved in the FAO pathway have also rarely been reported in AFLP patients e.g. carnitine palmitoyl transferase.[24] Presence of FAO defects in the fetus is estimated to increase by 18 fold the risk of AFLP and other pregnancy related disorders in the mother.[25] However, not all mothers with AFLP have these described mutations,[26,27] and not all mothers carrying fetus homozygous for these defects develop AFLP.[25] Thus, the pathogenetic mechanism of AFLP is heterogenous.

Why does Maternal Health Dramatically Improve after Termination of Pregnancy? Possible Role of Placenta

As the placenta which serves as a selective barrier and an interface between fetus and mother, has the same genetic

