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

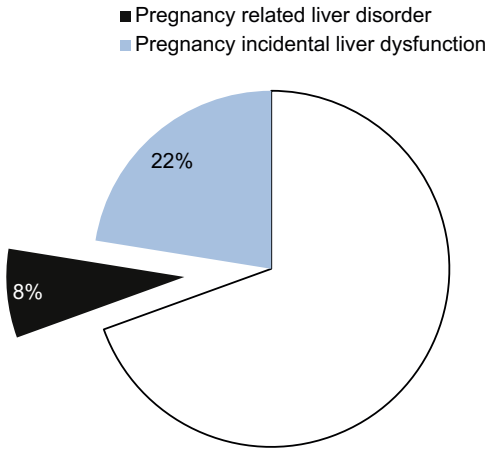


Figure 1 Contribution of pregnancy-related liver disorders to the maternal mortality at Christian Medical College, Vellore between 1999 and 2011.

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

makeup as the fetus and as there is a rapid recovery in most mothers with AFLP after delivery of fetus/placenta, the role of placenta in pathogenesis of AFLP was studied. Figure 2 summarises the proposed central role of placenta in the pathogenesis of AFLP.

A defect in FAO in placental mitochondria of the patients with AFLP, leads to mitochondrial dysfunction and increased oxidative and nitrosative stress in the placenta and the serum. At the same time, defective oxidation of fatty acids, leads to accumulation of toxic intermediates (free fatty acids, e.g. arachidonic acid) in placenta and serum of these patients. These steps were demonstrated in a series of experiments conducted at our laboratories. We could also demonstrate that incubation of a liver cell line with arachidonic acid in the concentrations found in serum of patients with AFLP was enough to cause mitochondrial damage, apoptosis and lipid accumulation in-vitro.[21]

Valproic acid is known to cause liver damage similar to AFLP. In a rat model of valproate-induced microvesicular liver steatosis, we demonstrated that there is co-existent oxidative stress in the sub-cellular organelles of the liver leading to mitochondrial dysfunction.[28] This was shown to be secondary to defective mitochondrial FAO, leading to increased channelling towards peroxisomal and microsomal oxidation.[28]

Clinical Features and Investigations (Table 2)

AFLP is a disease of late pregnancy and usually presents with vomiting, abdominal pain and jaundice. Polydipsia and polyuria can be present. Though it is more common in primiparous women, it is known to occur in multigravida females with history of prior uneventful pregnancies. The clinical course may be varied. Patients may become very ill with features of encephalopathy, hypoglycaemia and/or ascites.

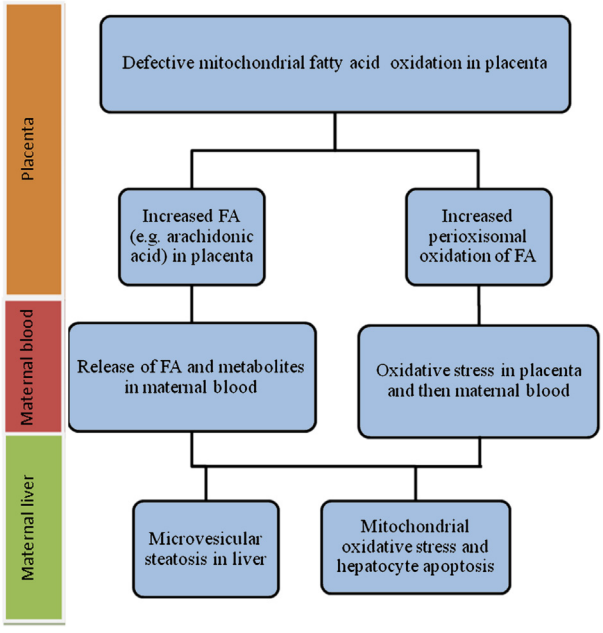


Figure 2 Role of placenta in the pathogenesis of acute fatty liver of pregnancy. (adapted from ref. 21); FA : Fatty acids.

Table 2 Clinical Features and Laboratory Investigations in 17 Patients of AFLP (Diagnosed by Liver Histology and 'Swansea' Diagnostic Criteria) Seen at our Center During 2001–2006.

Parameters		
Demographics	Maternal age (years)	22 (20–28)
	Gestational age at presentation (weeks)	37 (33–40)
	Primi-gravida (%)	65%
Laboratory parameters at admission	S. bilirubin (mg%)	13.0 (6.4–20.4)
	S. albumin (g%)	2.1 (1.5–2.6)
	Aspartate aminotransferase (U/L)	146 (43–376)
	Alanine aminotransferase (U/L)	129 (32–282)
	Prothrombin time (s)	39 (15–120)
	S. creatinine (mg%)	1.7 (0.6–3.5)
	MELD score	32 (22–46)
	Prolonged prothrombin time[a] (% of patients)	100%
	Hypoglycemia[b](% of patients)	24%
	Encephalopathy (% of patients)	35%

MELD: Model for end stage liver disease.
[a]Prothrombin time > 16 s.
[b]Random blood sugar < 60 mg/dl.

Liver function tests usually show mild to moderate increase in aminotransferases with jaundice. Coagulopathy, renal failure, hyperuricemia and leukocytosis are commonly observed. Ultrasound scan may show fatty infiltration of the liver, but this is neither sensitive nor specific. Liver biopsy demonstrating diffuse/peri-venular microvesicular steatosis remains the diagnostic gold standard.[29,30] Various parameters in 17 AFLP patients; diagnosed by histology and 'Swansea' diagnostic criteria (see below), are depicted in Table 3.[31]

Diagnosis

Based on multiple retrospective studies, Ch'ng et al,[12] proposed the Swansea diagnostic criteria for AFLP. Accordingly, a patient is diagnosed to have AFLP, if there is no alternate explanation for the liver dysfunction in pregnancy and 6 of the 14 criteria are satisfied; Table 3.

These criteria were later prospectively validated against a clinical diagnosis by Knight et al[11] We have validated these criteria against the gold standard for diagnosis, i.e. diffuse/peri-venular microvesicular hepatic steatosis on biopsy, Table 4.[31] High negative predictive value (100%) for these criteria in predicting microvesicular steatosis, justifies the use of 'Swansea' criteria for the presumptive diagnosis of AFLP. As coagulopathy delays the possibility of

Table 3 'Swansea' Diagnostic Criteria for Acute Fatty Liver of Pregnancy.

In a patient in late pregnancy; presence of 6 of the 14 criteria in absence of alternate explanation

Symptoms
- Abdominal pain
- Vomiting
- Polydipsia/polyuria
- Encephalopathy

Laboratory parameters
- Hyperbilirubinemia
- Raised aminotransferase
- Hypoglycaemia
- Coagulopathy
- Deranged renal function
- Hyperuricemia
- Hyperammonemia
- Leucocytosis

Radiology and histology
- Ascites/bright liver on ultrasound
- Diffuse/perivenular microvesicular steatosis on liver biopsy.

(Adapted from ref. 12).

liver biopsy in most of these patients, it is not advisable to wait for histology confirmation before swiftly embarking on management.[31] We have noted a rapid resolution of liver histology after delivery and thus the timing of liver biopsy, if undertaken, is also important.[31]

To simplify and facilitate early suspicion of AFLP, we proposed 'simplified' criteria for diagnosis of AFLP.[32] According to this, we should consider AFLP in all women presenting in late pregnancy (i.e. late 2nd or 3rd trimester) with unexplained acute liver failure (i.e. jaundice with coagulopathy and/or encephalopathy and/or hypoglycaemia). The time required to evaluate other etiologies of liver failure has to be balanced against the urgency of delivery. We usually rule out other causes like history of ingestion of potentially hepatotoxic drugs, malaria and acute viral hepatitis B, before a diagnosis of AFLP is entertained, Table 5. As depicted in Table 2, of the features defining the syndrome, presence of coagulopathy is a sine qua non, and encephalopathy/hypoglycaemia are noted in a few patients.

As the management is delivery, we endeavour to urgently deliver these patients based on clinical suspicion.

Table 4 Diagnostic Utility of 'Swansea' Criteria for Predicting Hepatic Microvesicular Steatosis in Patients with Pregnancy Related Liver Disorder. 'Swansea' Criteria had a 100% Negative Predictive Value for Detecting Diffuse/Peri-venular Hepatic Microvesicular Steatosis.

		Liver histology showing diffuse/ peri-venular microvesicular steatosis	
		Yes	No
AFLP (based on Swansea criteria)	Yes	17	3
	No	0	4

AFLP: Acute fatty liver of pregnancy.(Adapted from ref. 31).

Table 5 'Simplified' Criteria for Diagnosis of Acute Fatty Liver of Pregnancy (AFLP).

1. Setting: late pregnancy (late 2nd or 3rd trimester)
2. Acute liver failure: jaundice with coagulopathy and/or hypoglycaemia and/or encephalopathy
3. No other explanation for liver failure[a]

Presence of all three criteria is required for the presumptive diagnosis of AFLP.

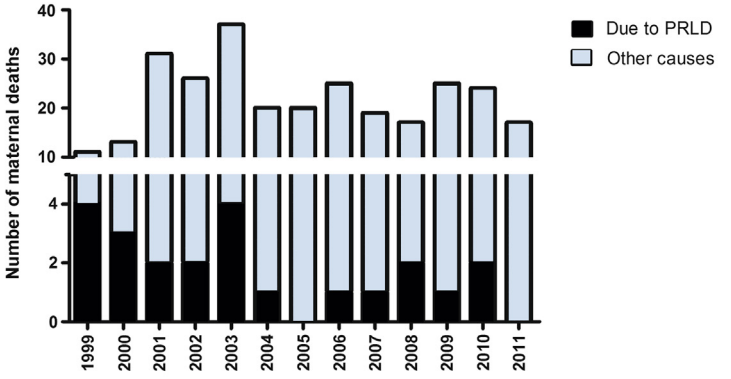
[a]No history of ingestion of hepatotoxic drugs, negative hepatitis viral serology, peripheral smear negative for malarial parasite, etc.(Adapted from ref. 32).

With implementation of this 'simplified' diagnostic criteria, we have observed a steady decline in contribution of AFLP, and other pregnancy related liver disorders, to maternal mortality at our center (decreased from 13% during 1999–2003 to 5% during 2004–2011), Figure 3.[7] However, fetal outcomes have remained unchanged over the years (33% adverse fetal outcome amongst 24 biopsied patients with AFLP and other pregnancy related liver disorders during 2001–2006,[31] as compared to 32% in 28 patients during ongoing prospective study spanning 2010–2012; unpublished data).

Management (Figure 4)

Early recognition and emergent delivery of the fetus is the cornerstone of management. A patient with acute liver failure in pregnancy should be recognised and categorised as a high risk/seriously ill patient. Maternal survival is the priority and any delay in recognition and delivery can be deleterious for the maternal outcome. Multi-disciplinary input (Obstetrician/Hepatologist/Physician/Intensivist/Hematologist/Transfusion medicine/Nephrologist/Anaesthetist and Neonatologist) is needed for this patient. Caesarean section is usually the preferred mode of delivery, though vaginal delivery may be attempted. Vaginal delivery may decrease the risk of intra-abdominal bleeding which has to be balanced against the potential delay in delivery (compared to urgent Caesarean section) and worsening of liver failure. However, in view of hepatic and probably systemic acute mitochondrial dysfunction, the mother is already in a state of energy deficiency and putting her through a stress of vaginal delivery has the potential for worsening liver failure by straining the already depleted energy resources. Vaginal delivery and Caesarean section have not been compared in studies, and it is appropriate that the Obstetrician decides on the mode of delivery on a case-to-case basis. Coagulopathy needs to be addressed prior to delivery with adequate blood product replacement. Continuous watch against hypoglycaemia is needed. At our center, we administer prophylactic broad-spectrum antibiotics, especially against gram negative bacteria. The choice of antibiotics can vary from center to center.

The patient requires close monitoring and care in either an Intensive care unit or a High dependency unit after



	1999	2000	2001	2002	2003	2004	2005	2006	2007	2008	2009	2010	2011
Total no. of pregnancies	7693	7655	7381	7499	7752	7928	7623	7746	8941	9581	10393	11406	12427
Due to PRLD	4	3	2	2	4	1	0	1	1	2	1	2	0
Other causes	7	10	29	24	33	19	20	24	18	15	24	22	17

Figure 3 Contribution of AFLP and other pregnancy-related liver disorders (PRLD) to maternal mortality over 13 years at Christian Medical College, Vellore; PRLD: Pregnancy-related liver disorders.

delivery. Complications like encephalopathy, renal failure and bleeding can delay recovery and require close monitoring and intense supportive care. There are no specific trials in AFLP patients, but we follow standard therapy for liver failure and all the attendant complications (details beyond the scope of the article). Most patients improve within days of the delivery, provided delivery was timely. Occasionally a patient requires prolonged supportive management and only rarely is liver transplant warranted. The need to shift to a liver transplant center has to be decided by treating team on a case-to-case basis. In a large prospective series from UK, of the 55 patients with AFLP, 1 patient required liver transplant and the same patient died, making a case fatality ratio of 1.8%.[11]

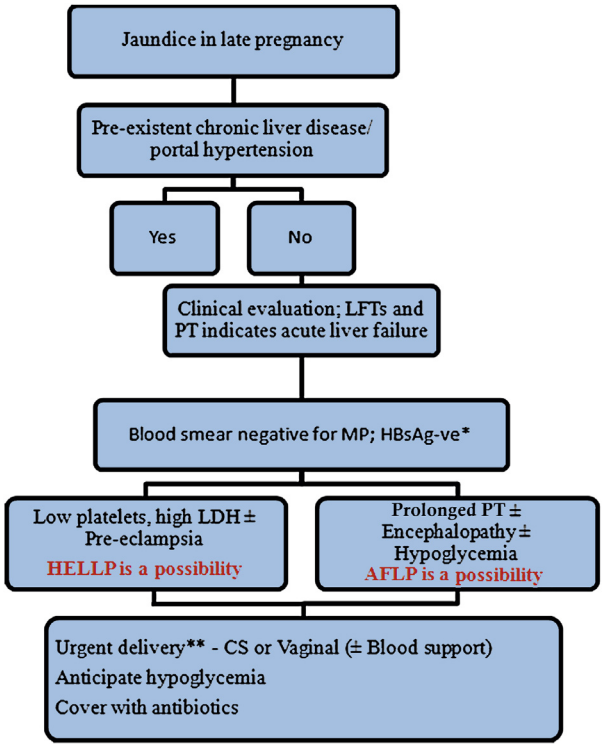


Figure 4 Management protocol for pregnancy related liver disorders complicating late pregnancy (late 2nd, and 3rd trimesters) in labour room. *Reports of other hepatitis viral serology may not be available immediately, **patient to be shifted to Intensive care unit after delivery for monitoring and management. LFT: liver function tests; PT: prothrombin time; MP: malarial parasite, HBsAg: hepatitis B surface antigen; LDH: lactate dehydrogenase; HELLP: hemolysis, elevated liver enzymes, low platelets; AFLP: acute fatty liver of pregnancy; CS: Caesarean section.

Intravenous Oxytocin should be considered in all patients post-delivery. An occasional patient may benefit from bilateral uterine artery ligation in case of postpartum hemorrhage. In an event of uncontrolled bleeding complication, we have found use of bolus injection of recombinant activated factor VII (rFVIIa) helpful in a few patients. In our series of 6 patients of AFLP with uncontrolled bleeding and severe coagulopathy, a single (only 1 patient required 2 doses) intravenous bolus dose of rFVIIa (2.4 mg) was successful in immediate normalisation of bleeding parameters, and also achieved control of bleed in all patients. The blood (6 ± 5 to 0.1 ± 0.2 units/day per patient; *P*-value:0.05) and blood products (34 ± 18 to 1 ± 1 units/day per patient; *P*-value:0.006) requirements decreased significantly after the administration of rFVIIa. There were no thrombo-embolic complications.[33]

As managing these patients demands a team approach, early recognition and referral to an equipped center is essential. The maternal mortality and morbidity, hospital and ICU stay, and requirement of blood products is considerably less if delay in delivery can be avoided. With early aggressive management, maternal mortality has decreased from nearly 100% to <10% in most recent series.[1]

Care of the Baby

Peri-natal mortality remains high, and the child has to be monitored for features of fatty acid oxidation defects.[23,29] Specific FAO defects (e.g. E474Q mutation in LCHAD

component of MTP protein as seen in some populations[23,34]), are yet to be studied in Indian population and further studies in this area are needed before a protocol for screening the newborns can be advocated for our population.[35]

These FAO defects can be clinically heterogeneous and the symptoms are exacerbated by metabolic stress. The patients with FAO defect may be asymptomatic or may have variety of symptoms–hepatic encephalopathy, sudden infant death, myopathy, cardiomyopathy, arrhythmias, etc.

Some studies suggest screening for LCHAD deficiency in all babies born to mothers with a diagnosis of AFLP.[36] The screening is usually by acylcarnitine assay of dried blood sample. Confirmation of diagnosis and picking up a specific fatty acid oxidation defect remains cumbersome and depends on pattern of organic acidurias, plasma fatty acid profile and acylcarnitine profile, enzyme activity analysis and genetic mutation analysis.[37]

Avoidance and early management of catabolic stress, e.g. fasting, intercurrent infection etc.; is of prime importance. These babies should also be managed with high carbohydrate and low fat diets while providing all the essential fatty acids in adequate amount. Regular clinical assessment is also necessary. The management remains complex with continuous care from Paediatrician, Neonatologist, Dietician and Geneticist.

Future Pregnancies

There is a small risk of recurrence in subsequent pregnancies and more so if there is a demonstrable defect in fatty acid oxidation.[38,39] Therefore, it is prudent to inform the mothers of the small risk of recurrence in subsequent pregnancies. Need for regular monitoring and institutional delivery has to be stressed if the patient opts for another pregnancy.

PRE-ECLAMPTIC LIVER DYSFUNCTION

Pre-eclampsia is usually reported as the most common cause of liver dysfunction related to pregnancy.[12,13] It occurs after 20 weeks of pregnancy and is characterised by hypertension (blood pressure >140/90 mm Hg), proteinuria with or without pedal edema.[12]

Epidemiology (Table 6)[29,40]

Liver dysfunction portends poor prognosis and is noted in upto 50% of patients with pre-eclampsia.[41,42] A minority of patients with pre-eclampsia have HELLP syndrome.[43–47] Not all patients with HELLP have pre-eclampsia, but pre-eclampsia increases the risk for HELLP syndrome.

Pathogenesis

Pre-eclampsia remains a 'disease of theories',[48] but recent work suggests a two stage process—Stage 1 : abnormal placentation leading to placental hypoperfusion progressing in some patients to Stage 2: endothelial dysfunction leading to multi-systemic involvement characteristic of pre-eclampsia.[49,50] Imbalance between angiogenic and anti-angiogenic factors might play a role in transition from stage 1 to 2.[49,51] The role of various maternal genetic factors,[52] behavioural and environmental factors in pathogenesis of pre-eclampsia are under study.[53,54]

Table 6 Epidemiology of Pre-eclampsia and Complications Thereof.

		Incidence	Reference
Among all pregnancies	Pre-eclampsia	~ 5%	29,40
	HELLP syndrome	1–6%	43,45
Among patients with pre-eclampsia	At least single abnormal liver function test	Up to 50%	41
	Eclampsia	11%	46
	HELLP syndrome	11–35%	46,47

Clinical Presentation

Patient may be asymptomatic or present with abdominal pain, nausea or vomiting. Although some form of liver dysfunction is noted in upto 50% of these patients, it signifies severe disease.[41,42] As in involvement of other organs, endothelial dysfunction leads to hepatic microcirculatory disturbances and subsequent hepatocellular necrosis. Prothrombin time is usually normal except in patients with disseminated intravascular coagulation. HELLP syndrome is considered as a severe form of pre-eclampsia.

Management

Control of blood pressure and urgent delivery are the cornerstones of management of severe pre-eclamptic liver dysfunction and are essential in preventing further complications—acute renal failure, seizures, hepatic rupture or hepatic infarct. Even in mild pre-eclampsia beyond 36 weeks of gestation, early induction of labour has been shown to reduce the incidence of serious complications.[55] Prophylactic administration of magnesium sulphate to patients with pre-eclampsia decreases the risk of eclampsia (convulsions associated with pre-eclampsia) and may reduce risk of maternal death.[56] Parenteral magnesium sulphate remains the mainstay of therapy in case of convulsions.[57] The exact mechanism of action of magnesium sulphate in eclampsia remains elusive, but vasodilation and decreased disruption of blood brain barrier secondary to calcium antagonism may play a role.[58] Steroids, for fetal lung maturity, may be considered prior to pre-term delivery.[59] Liver dysfunction usually shows immediate trend to improvement after delivery. Low dose aspirin, initiated at ≤16 weeks of

gestation may prevent severe pre-eclampsia in future pregnancies.[60]

HELLP SYNDROME (HEMOLYSIS, ELEVATED LIVER ENZYMES AND LOW PLATELETS)

Although the association of hemolysis, low platelets and liver dysfunction with hypertensive disorders of pregnancy was known since 1954,[61] the term HELLP syndrome was first coined in 1982 by Weinstein et al[62] HELLP syndrome is thought to be a severe form of pre-eclamptic liver dysfunction, but it can occur in normotensive patients as well. Table 6 illustrates the overall incidence of HELLP in all pregnancies and also in patients with pre-eclampsia. Abdominal pain, nausea and vomiting with or without jaundice are the usual presenting symptoms.

Pathogenesis

The exact pathogenesis is not known, but similar to pre-eclampsia, it is thought to be secondary to endothelial dysfunction and thrombotic microangiopathy. As there is a considerable overlap in presentation and manifestations of HELLP syndrome and AFLP, role of FAO defects have been studied in HELLP syndrome as well, but the association seems to be weak.[63] Role of vascular growth factors and ADAMTS 13 deficiency in HELLP syndrome is under study.[64,65]

Diagnosis

The diagnosis of HELLP syndrome remains controversial,[66] and is based on presence of hemolysis (as evidenced by serum lactate dehydrogenase > 600 U/L, the characteristic peripheral smear and indirect hyperbilirubinemia— usually present, but not necessary for presumptive diagnosis), elevated liver enzymes (serum aspartate aminotransferase > 70 U/L) and low platelets ($<100 \times 10^9$/L).[12,67] Majority of patients with HELLP syndrome present in 3rd trimester, but upto 1/4th of these patients can present only in the immediate post-partum period. Antenatal pre-eclampsia is known to occur in most of these patients with post-partum presentation.[67] Absence of hemolysis; i.e. ELLP syndrome and partial HELLP syndrome are other diagnoses that can be entertained. Partial HELLP syndrome is characterised by elevated liver enzymes (serum aspartate aminotransferase > 40 U/L), low platelets ($<150 \times 10^9$/L) with or without evidence of hemolysis.[12] Severe thrombocytopenia portends poor prognosis and urgent need for management.[68] Abnormally elevated prothrombin time signifies an underlying disseminated intravascular coagulation. Liver biopsy changes of sinusoidal congestion with fibrin plug formation, hemorrhage and hepatocyte necrosis are similar to patients with pre-eclamptic liver dysfunction. Haemolytic uremic syndrome and thrombotic thrombocytopenic purpura, albeit uncommon in pregnancy, are other mimics of HELLP syndrome.

Prognosis

Maternal mortality with HELLP syndrome varies from 0 to 15%. It is also associated with serious maternal morbidity and complications; e.g. acute renal failure, hepatic infarct, hepatic hematoma, hepatic rupture, disseminated intravascular coagulation, post-partum hemorrhage, pulmonary edema and rarely liver cell failure.[68–72] The mortality in patients with any of these severe complications is higher. There are usually no long term maternal complications. Peri-natal complications and mortality is high and ranges from 20 to 30%.[69–71] Most of the perinatal complications, e.g. asphyxia, respiratory disease and others, seem to be related to prematurity rather than an inherited defect of metabolism.[67,70]

Management

The patients need close monitoring with optimisation of blood pressure and seizure prophylaxis. Delivery is the only definitive management. The decision to deliver is to be balanced with fetal maturity and it is generally recommended to effect urgent delivery especially if it is near term (>34 weeks), if there is fetal distress or if there are systemic complications as disseminated intravascular coagulation, renal failure etc. Only in a small subset with mild/asymptomatic HELLP syndrome in early pregnancy can the delivery be delayed with careful monitoring. Steroids should be considered only for fetal lung maturity.[73] The route of delivery is usually by Caesarean section but is decided by the Obstetricians on a case-to-case basis. The other precautions, e.g. correction of bleeding problems and administration of prophylactic antibiotics are similar to patients with AFLP (Figure 4). As the pathogenetic mechanism is thought to be platelet plug formation, it may be prudent to refrain from transfusing platelets unless the patient has an active bleed or requires an invasive procedure.

Overwhelming majority will show improvement immediately after delivery. In our experience, patients with renal failure may need longer time to recover and may require prolonged dialysis. Hepatic rupture is a rare but life threatening complication and needs to be managed by a multispecialty team comprising Obstetrician, Hepatologist, Intensivist, Neonatologist, Interventional radiologist and Surgeon.

There is a small but definite risk of recurrence in subsequent pregnancies, and the same needs to be informed to the patient and watched for in subsequent pregnancies.[74]

OVERLAP IN DIAGNOSTIC CRITERIA OF AFLP, HELLP SYNDROME AND PRE-ECLAMPTIC LIVER DYSFUNCTION

In a given patient it is often difficult to differentiate AFLP, HELLP syndrome and pre-eclamptic liver dysfunction

clinically as the diagnostic criteria for more than one condition is fulfilled in majority of them.[31] In a study from our center, some of the 20 patients who met the 'Swansea' criteria for AFLP also fulfilled the criteria for HELLP syndrome (8 patients), partial HELLP syndrome (5 patients) and pre-eclamptic liver dysfunction (2 patients).[31] Though liver biopsy may help differentiate these conditions, it is usually neither needed nor feasible in most cases. Hypoglycemia, prolonged prothrombin time and encephalopathy are more commonly seen in AFLP as compared to HELLP syndrome and severe renal dysfunction and hypertension are more commonly noted in HELLP syndrome. In clinical practice, majority of patients with AFLP fulfil the diagnostic criteria for HELLP or partial HELLP syndrome.[7] At this stage, this differentiation might not be so essential as the treatment for all conditions remain urgent delivery. But with enhanced understanding of the pathogenesis of these conditions in future, newer therapeutic targets might be uncovered and then a rapid diagnosis may prove necessary for specific interventions. This differentiation remains a clinical problem and requires further studies.

OTHER PREGNANCY RELATED LIVER DISORDERS

AFLP, HELLP syndrome and pre-eclamptic liver dysfunction are life threatening obstetric emergencies. Early suspicion, diagnosis and adequate management are essential for maternal and fetal well being. Intrahepatic cholestasis of pregnancy (ICP) and hyperemesis gravidarum (HG) are other pregnancy related disorders associated with liver dysfunction which cause maternal morbidity. These disorders do not increase risk of maternal death, but ICP can increase the risk of fetal death. The detailed description of these conditions is beyond the scope of the article.

Intrahepatic Cholestasis of Pregnancy (ICP)

ICP is characterised by pruritus and raised serum alkaline phosphatase/bile acids and normal extrahepatic biliary system on imaging. ICP usually occurs in the 2nd half of the pregnancy and usually in late 2nd trimester.[75] It confers only a minimal risk of morbidity/mortality to the mother, but can significantly contribute to peri-natal morbidity.[75,76]

The incidence of ICP varies with geographical region and is most common in South America and Chile in particular.[75] In India, there are only a few studies looking at the epidemiology and incidence is very low at ~0.08%.[13] There is some evidence to suggest that it is more common in winters, in twin pregnancy and pregnancies secondary to in-vitro fertilisation.[75]

The pathogenetic mechanisms remain unclear, but the role of various bile acid and phospholipid transporters is envisaged.[77] Multiple mutations in MDR3 (multidrug resistance protein 3) gene have been demonstrated in a minority of these patients.[78] Increased risk of cholestasis in these patients when exposed to female sex hormones, suggest a hormonal influence to the pathogenesis.[79,80]

Liver dysfunction is usually mild, and typical presentation in 2nd half of pregnancy does not require an extensive evaluation, except USG abdomen to rule out an obstructed biliary system, prior to a presumptive diagnosis.[75]

Ursodeoxycholic acid (UDCA), at a dose of 10–15 mg/kg, is safe for the mother and the fetus, helps in symptomatic relief and is the drug of choice.[81] Bile acid levels in maternal blood may predict peri-natal complications,[82] but the role of UDCA in ameliorating these complications is unclear.[83] Steroids may be considered for fetal lung maturity. The patient has to be referred for monitoring the fetal status in a well-equipped hospital and delivery leads to resolution of the cholestasis, As there is minimal risk to the mother, the decision to deliver has to take in account the fetal maturity, maternal symptoms and fetal complications.

The risk of recurrence in subsequent pregnancies is ~50%. The diagnosis in the 1st pregnancy is usually presumptive and the improvement after delivery confirms the suspicion.[1] In an occasional patient, ICP may predict future liver disorder.[84] Rarely, ICP may be a presentation of an underlying chronic cholestatic disorder like progressive familial intrahepatic cholestasis (PFIC).[85]

Hyperemesis Gravidarum (HG)

Nausea and vomiting is very common in the first trimester, and the definition of hyperemesis gravidarum (HG) is varied. It is usually indicative of severe vomiting with dehydration and dyselectrolytemia necessitating hospitalisation in a proportion of patients.[86] It is a disorder typically of the 1st trimester and usually resolves spontaneously by 16 weeks.[87]

The exact pathogenesis remains unclear, but several factors may play a role in its causation.[88–90] It is more common with molar pregnancy, multiple gestation and especially if the previous pregnancy was complicated by hyperemesis.[86] Diagnosis of HG is that of exclusion and evaluation for other causes is warranted in atypical cases and especially if the vomiting begins or persists into the 2nd trimester. Liver dysfunction, mainly mild-moderate elevation of serum aminotransferases with jaundice only in a minority, is noted in 15–50% of these patients.[91,92] The cause of liver dysfunction is unclear but it usually resolves with improvement in vomiting.

If managed timely, HG is usually not associated with any major adverse maternal or fetal outcome.[93] Few studies have shown an increased incidence of low birth-weight and prematurity in the babies of these patients.[94,95] The aim of treatment is to ameliorate symptoms, correct dyselectrolytemia and prevent any complications. Various anti-emetic agents have been used safely in HG with uncertain benefit.[96–99] Thiamine replacement to prevent

Wernicke's encephalopathy is to be considered in all patients with HG.[100] No specific treatment is required for liver dysfunction and liver failure is only rarely reported.[87]

Does AFLP occur all over India?

To explore this question, we conducted a search of reports from India of jaundice complicating pregnancy from 2001–2011.[13–15,17,18] We classified these patients with jaundice as either secondary to infective cause (based on viral serology for hepatitis A, B and E and other relevant tests) or non-infective/probably pregnancy related (if hepatitis viral serology was negative), Table 7.[19] During 2001–2011, of reports of jaundice complicating pregnancy from all over India, 84 maternal deaths could be attributable to pregnancy-related liver disorders. Of these, only 58 patients were labelled as pregnancy-related liver disorders by the authors. This study suggests that AFLP and other pregnancy-related liver disorders occur all over India. There is a need to increase awareness about these disorders. Systematic collation of data on maternal mortality from all over India is urgently needed and this should include deaths from jaundice complicating pregnancy.

REDUCING MATERNAL DEATHS FROM PREGNANCY RELATED LIVER DISORDERS IN INDIA—LESSONS FROM THE VELLORE EXPERIENCE

While Obstetricians are clear about the management of patient with pre-eclamptic liver dysfunction and HELLP syndrome; there is considerable degree of uncertainty about the management of AFLP.

Our experience spanning 16 years (1996 to date) at Vellore teaches few key learning points. Firstly; there is confusion in making the diagnosis of AFLP. In the early part of our series, we performed post-mortem liver biopsies to document hepatic microvesicular steatosis in patients who died of suspected AFLP. Once we recognised this disorder and started early delivery of the baby, the maternal survival improved and we performed transjugular liver biopsies post-natally to confirm the diagnosis. With our analysis of clinical criteria (Swansea criteria) to diagnose AFLP, we no longer rely on liver biopsy to diagnose AFLP.

Secondly; should we advocate vaginal delivery or Caesarean section in women with AFLP? In the early part of our series, most women with AFLP at our center had vaginal delivery. With increasing experience and increased input from the multi-disciplinary team, most patients with suspected AFLP now are managed by Caesarean section at our center.

With increasing awareness, early suspicion of pregnancy-related liver disorder and immediate termination of pregnancy; maternal mortality due to these disorders has reduced at our center. Most of the deaths in recent years have occurred in women who delivered at another hospital and were subsequently referred to our center. It is possible that delay of even hours/days in terminating pregnancy may explain the later deaths.

FUTURE WORK

There is an urgent need to increase awareness about this preventable cause of maternal death all over India. Maternal deaths due to liver disease should be included in maternal mortality statistics in India. Though we have made some progress in reducing maternal deaths due to AFLP at our center, fetal outcome remains dismal. Further research is needed to unravel the pathogenesis of this intriguing group of disorders.

Table 7 Burden of Jaundice Complicating Pregnancy Possibly Attributable to Non-infectious Causes in India; an Analysis of Published Literature from 2001 to –2011.

Study	Total patients with jaundice complicating pregnancy	Patients with non-infective etiology	
		Total	Expired
Jaiswal et al,[101] Indore, 2001	127	28	11
Tank et al,[14] Mumbai, 2003	26	23	8
Beniwal et al,[18] Delhi, 2003	97	39	6
Kumar et al,[102] Delhi, 2004	62	30	2
Nagaria et al,[103] Raipur, 2005	41	7	4
Devarbhavi et al,[15] B'lore, 2007	87	46	19
Rathi et al,[13] Mumbai, 2007	96	54	12
Bhatia et al,[17] Delhi, 2008	249	74	19
Yi et al,[104] Mumbai, 2011	48	14	3
Total	833	322	84

(Adapted from ref. 19).

CONCLUSIONS

Pregnancy-related liver disorders are rare but they are important causes of maternal/fetal morbidity and mortality. The inclusion of jaundice as a cause of maternal mortality in the census of India will help in better documenting the extent of the problem all over India. Better understanding of pathogenetic mechanisms will help us in managing these disorders effectively. Early recognition, timely referral and aggressive management can lead to better maternal and fetal outcome in these patients.

CONFLICTS OF INTEREST

All authors have none to declare.

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