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Acute Liver Injury During Pregnancy in ICU

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Abstract:
Liver disease that occurs during pregnancy can present a challenge for health care providers. Certain liver diseases are uniquely associated with pregnancy, whereas others are unrelated. The liver diseases unique to pregnancy include acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, Hemolysis and Elevated Liver enzymes and Low Platelets (HELLP) syndrome and hyperemesis gravidarum,. Liver disease such as acute viral hepatitis can occur in pregnancy, and pregnancy may occur in a patient with underlying chronic liver disease, including patients with cirrhosis

Keywords : ***Pregnancy , Liver Injury , preeclamspia***

Introduction

The pregnant woman experiences physiological changes to support fetal growth and development. During the pregnancy serum estrogens and progesterone levels increase progressively and reach a maximum during the third trimester. These sex steroids have effectson metabolic, synthetic and excretory hepatic function. Pregnancy has little effect on a normal liver. There are no significant changes in liver function during pregnancy, but some markers of liver function may alter slightly. For example, alkaline phosphatase may go up modestly as the pregnancy advances, due toLiver disease that occurs during pregnancy can present a challenge for health care providers. Certain liver diseases are uniquely associated with pregnancy, whereas others are unrelated. The liver diseases unique to pregnancy include acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, Hemolysis and Elevated Liver enzymes and Low Platelets (HELLP) syndrome and hyperemesis gravidarum,. Liver disease such as acute viral hepatitis can occur in pregnancy, and pregnancy may occur in a patient
With underlying chronic liver disease, including patients with cirrhosis its production by a normal placenta. Blood levels of albumin will decrease because of the dilution of an expectant mother's blood.
However, any abnormalities in standard tests (bilirubin, aminotransferase, or prothrombin time) should be considered an indication of possible liver problems. Liver disease that occurs during pregnancy can present a challenge for health care providers. Certain liver diseases areuniquely associated with pregnancy, whereas others are unrelated. The liver diseases unique to pregnancy include acute fatty liver of pregnancy, intrahepatic cholestasis of pregnancy, Hemolysis and Elevated Liver enzymes and Low Platelets (HELLP) syndrome and hyperemesis gravidarum,. Liver disease such as acute viral hepatitis can occur in pregnancy, and pregnancy may occur in a patient with underlying chronic liver disease, including patients with cirrhosis

Pregnancy Associated Liver Disease

Hyperemesis Gravidarum

HG is the most severe form of illness within the spectrum of nausea and vomiting of pregnancy. It 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 9weeks gestation (6,7). The exact aetiology of HG is unclear. Human chorionic gonadotropin (HCG) hormone, which peaks in the first trimester has been shown to correlate with the severity of HG. HG is more common in molar and twin pregnancies where HCG levels are significantly elevated. HCG can physiologically activate the thyroid stimulating hormone (TSH) receptor resulting in supressed TSH and elevated T4. A positive correlation between HCG, T4 and the severity of HG has been demonstrated (8,9). Other theories have been suggested including genetic, psychological, cultural

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and hormonal however none have been definitively proven (10).

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. 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,
thromboprophylaxis, thiamine supplementation and antiemetic treatment to enable slow reintroduction of oral fluids and diet. Treatment of nausea and vomiting of pregnancy with vitamin B6 or vitamin B6 plus doxylamine is safe and effective and should be considered the first line pharmacotherapy
in countries where available (11,12). Second line therapies including dopamine antagonists (metoclopramide) (13), phenothiazines (chlorpromazine, prochlorperazine) and anticholinergics (dicycloverine) have reasonable safety data (12,14). Refractory cases that don't improve with these drugs may respond to ondansetron or glucocorticoids (15,17)

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 6weeks of delivery (20). 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 (21). ICP typically presents in the third trimester but it can present as early as 7weeks 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 (22) and progesterone metabolites (23) in pregnancy unmask the disease in genetically susceptible women. The presenting symptom of ICP is usually pruritus, typically worse on the palms and soles, but this may be generalised or affect any part of the body. The only associated rash is secondary to excoriations from scratching. Some women also complain of dark urine and pale faeces. The characteristic biochemical features . It is noteworthy that the bilirubin concentration is rarely raised. The European Association for the Study of the Liver and the Royal College of Obstetrics and Gynaecology guidelines recommend that ICP should be diagnosed in pregnant women with pruritus and serum bile acids elevated above the reference range [11,24]. 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) (25,26). 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 (25,26). Although most women with ICP have elevated liver transaminases in conjunction with
hypercholanaemia, it is noteworthy that both prospective cohort studies did not report an association between the ALT/AST concentration and adverse perinatal outcomes (25,26). Serum bile acid levels can fluctuate and rise with advancing gestation, so weekly checks should be performed in women with ICP (24) The diagnosis of ICP is based on a combination of pruritus and elevated serum bile acid concentrations above the normal reference range both reversible within 4–6weeks after pregnancy and after exclusion of other potential aetiologies. Approximately 15% of cases have genetic variation in one of the hepatocanalicular transport proteins; ABCB11 (bile salt export pump) or ABCB4 (phosphatidylcholine flippase). Smaller studies have reported genetic variation and/or heterozygous mutations in ABCC2 (conjugated organic anion transporter) (27), ATP8B1 (FIC1) (28,29) and the nuclear bile acid receptor (farnesoid X receptors) (28,30). Of clinical interest, ABCB4 mutations are typically associated with elevated serum gamma-glutamyl transferase levels (GGT), whereas ABCB11, ATP8B1 and farnesoid X receptor mutations with low GGT levels. The first line treatment for ICP is ursodeoxycholic acid (UDCA), which results in improved maternal

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symptoms and biochemistry in approximately 75% of cases (20, 30 , 31) . UDCA has several functional effects that are likely to contribute to improvement in maternal and fetal consequences of ICP. It enhances biliary transport of bile acids, is anti-apoptotic and is likely to improve excretion of pruritogens, e.g. progesterone sulphates (23,25). *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 (21). ICP has a high recurrence rate in subsequent pregnancies. 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 (44,46). A high prevalence of hepatitis C infection in women with ICP has been reported (44). Whether this reflects an enhanced susceptibility to hepatitis C infection in women with ICP or vice versa remains unclear.

It is important to advise women that they have an increased risk of hepatic impairment when taking the combined oral contraceptive pill, but most progesterone containing contraception is not associated with hepatic impairment. If women have ongoing symptoms or biochemical hepatic impairment for more than 3months postpartum an alternative/additional diagnosis should be sought.

Pre-eclampsia, Eclampsia and Haemolysis, Elevated Liver Enzymes, Low Platelets (HELLP) Syndrome

Pre-eclampsia is a multisystem disorder defined by the international society for the study of hypertension in pregnancy as *de novo* hypertension after the 20th week of pregnancy (blood pressure (BP) 140/90) combined with proteinuria (>300mg/day), other maternal organ dysfunction, such as renal insufficiency, liver involvement, neurological orhaematological complications, uteroplacental dysfunction, or fetal growth restriction (47).

In a patient with pre-existing essential hypertension, superimposed pre-eclampsia diagnosed if at least one of the above features are present (47). Pre-eclampsia affects between 3–5% of all pregnancies and can present from 20weeks gestation, to as late as 4weeks postpartum (48). The presence of seizures differentiates pre-eclampsia from eclampsia. HELLP syndrome is considered as a severe form of pre-eclampsia. Risk factors for pre-eclampsia are: previous pre-eclampsia or hypertension in pregnancy, chronic kidney disease, hypertension, diabetes, and autoimmune disorders (49).The aetiology of pre-eclampsia is incompletely understood. It is postulated that abnormal placentation leads to placental hypoperfusion, which in some patients progresses to endothelial dysfunction, leading to the multi-systemic involvement characteristic of pre-eclampsia (50). 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 (51). 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 subcapsular haematomas, parenchymal haemorrhage and ultimately hepatic rupture (52)

Clinical features of pre-eclampsia may be absent with the diagnosis made during routine antenatal care; if present they include right upper quadrant pain, headache, visual changes, nausea and vomiting. Many women are hyperreflexic and oedema is common (48). Elevated serum transaminases occur in 30% of cases. At the severe end of the spectrum of pre-eclampsia, HELLP syndrome may manifest. The derangement of liver function tests in patients with pre-eclampsia and eclampsia should highlight the presence of severe disease. 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.

The management of pre-eclampsia is supportive. The only cure is delivery of the placenta and hence the fetus should be delivered as soon as possible by the safest route, especially if the fetus is beyond 34weeks gestation, fetal distress is evident or there

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is evidence of maternal deterioration. Hypertension should be treated; intravenous labetalol, intravenous hydralazine and oral nifedipine are first line agents for acute lowering of BP in pregnant women (53 , 55). If gestation is less than 34weeks, glucocorticoids should be given to promote fetal lung maturity (56). Patients may require coagulation support. Magnesium sulphate should be given to women with HELLPsyndrome and other forms of severe pre-eclampsia. Outcomes at the more severe end of the spectrum are difficult to predict and prognostic information is limited to small series (2,3,57). Women with pre-eclampsia and eclampsia are recognised to have double baselinerisk of heart and cerebral vascular disease later in life and it remains unclear if this association is correlational, causal or a combination (58) HELLP syndrome was first described by Weinstein in 1982 and occurs in approximately 10–20% of women with pre-eclampsia (59,61). Although HELLP is recognised to complicate pre-eclampsia in up to 20% of cases, HELLP syndrome can occur in women with normal blood pressure, reflecting the multisystem nature of pre-eclampsia and related disorders (62). The diagnosis of HELLP syndrome is based mainly on clinical features. 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 (30% of cases) and rarer complaints including bleeding and jaundice (63). A significant number of patients are asymptomatic (63). On examination, hypertension is evident in up to 85% and proteinuria is common. Disseminated intravascular coagulation can occur with evidence of elevated fibrin degradation products, a low fibrinogen and a secondary rise in the prothrombin time. Imaging of the abdomen should be considered in all women with HELLP syndrome and is imperative in those with abdominal pain, shoulder tip pain or hypotension (64),, in order to investigate for the life-threatening complications of hepatic haemorrhage, rupture and infarction, which have been reported to occur in up to 45% of women with HELLP syndrome (63,65). Liver biopsy is not indicated 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 (characteristic periportal changes with haemorrhage, sinusoidal fibril deposition and hepatocyte necrosis) (66). The management is as for pre-eclampsia.

Hepatic Rupture, Infarction and Haematoma

Hepatic haemorrhage and rupture can complicate pre-eclampsia, eclampsia, HELLP syndrome and patients with AFLP and is associated with a 50% mortality(63). Patients can 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 (64). Contained haematomas can be managed conservatively with aggressive coagulation support, prophylactic antibiotics and transfusion as required (76). If there is any evidence of haemodynamic instability, then urgent angiography with hepatic artery embolization and/or surgical intervention iswarranted. Surgical intervention includes packing of the liver, hepatic artery ligation and resection (64,68). 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, but if there are areas of extensive infarct, death from multi-organ failure or hepatic rupture can occur.

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 (69,70). It is a rare complication of pregnancy, usually occurring in the third trimester, and in the UK affects approximately 1 in 20,000 pregnancies (71), 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, and an abnormality in mitochondrial β-oxidation is a recognised cause of AFLP in a subset of cases (70,72) The enzyme, long-chain 3-hydroxyacyl coenzyme A dehydrogenase (LCHAD), is a key part of the mitochondrial

trifunctional protein. Approximately 20% of neonates born to mothers with AFLP have been shown to have defects in β-oxidation and to be deficient in LCHAD due to mutation on one or both alleles of the α-subunit of the trifunctional protein (72). Due to the genetic defect, fetal fatty acids accumulate and return to the mother via the placenta. They are then deposited in the liver and present phenotypically as maternal liver disease. Mothers of neonates with LCHAD deficiency have been shown to have a 79% chance of developing AFLP or HELLP syndrome (72). Other reports have shown a 20-fold increased risk of maternal liver disease in pregnancy in fetuses with fatty acid oxidation defects (73). AFLP and HELLP are both multifactorial disorders that have a requirement to excrete pathologically high concentrations of β fatty acid oxidation metabolites which is likely to unmask susceptibility to both disorders.

The onset is usually between the 30th and 38th gestational week although up to 20% present postnatally (71) 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 (74,73). Pre-eclampsia is common but not invariable. Biochemical changes . include hyperbilirubinaemia and a variable elevation of serum transaminases. In addition, serum ammonia, lactic acid and amino acid levels are increased reflecting mitochondrial failure. Renal dysfunction, leucocytosis and thrombocytopenia are also common. The prothrombin time is prolonged and fibrinogen levels are reduced; disseminated intravascular coagulation is seen in approximately 10%.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 (2,3) Although the definitive diagnosis of AFLP is made histologically , liver biopsy is rarely performed due to the need to stabilise and deliver affected women. Recently clinical diagnostic criteria have been developed and validated for AFL.

CONCLUSION

Liver disease in pregnancy and pregnancy in women with liver disease is rare. However, this is a clinically important group of patients due to the increased morbidity and mortality for both the mother and baby.. Once women with liver disease become pregnant, it is essential that they have rapid referral to specialist physicians with experience of managing hepatic disorders in pregnancy. Maternal and fetal outcomes are improving due to ongoing research, improved guidelines and our better understanding of preconception risk stratification, disease mechanisms and therapeutic options.

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