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Review Article

Liver Disease Associated to Pregnancy in the Critically Ill Obstetric Patient: Pregnancy Associated Liver Dysfunction

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Abstract

During pregnancy, hepatobiliary disease may present with subtle findings, with symptoms that often are nonspecific and liver function tests that are rarely diagnostic. The clinical outcomes range from self-limiting to rapidly fatal. 5 distinct liver diseases unique to pregnancy, which includes Hyperemesis Gravidarum (HG) Intrahepatic Cholestasis of Pregnancy (ICP) preeclampsia hemolysis, elevated liver enzymes, and low platelets with or without preeclampsia (HELLP syndrome) and Acute Fatty Liver of Pregnancy (AFLP). Recent advancements in our understanding help us in better overall management of these patients. This first part of a two parts article focuses on the causes of pregnancy-induced liver diseases.

Keywords: Liver injury; Pregnancy acute fatty liver of pregnancy; Haemolysis elevated liver enzymes; Hyperemesis gravidarum; Intrahepatic cholestasis of pregnancy

Introduction

During pregnancy, hepatobiliary disease may present with subtle findings, with symptoms that often are nonspecific and liver function tests that are rarely diagnostic. Minor elevations in aminotransferases may mask the early state of life-threatening processes. Abnormal liver test results are obtained in 3% to 5% of pregnancies because of many potential causes that need to be recognized. Failure to do so may result in higher morbidity and mortality rates in mothers and fetuses. The clinical outcomes range from self-limiting to rapidly fatal.

There are 5 distinct liver diseases unique to pregnancy which includes Hyperemesis Gravidarum (HG) Intrahepatic Cholestasis of Pregnancy (ICP) preeclampsia; hemolysis, elevated liver enzymes, and low platelets with or without preeclampsia (HELLP syndrome) and Acute Fatty Liver of Pregnancy (AFLP). This first part of a two parts article focuses on the causes of pregnancy-induced liver diseases.

Physiological Changes in Liver Physiology in Pregnancy

The alterations during pregnancy mimic physiological changes in patients with decompensated chronic liver disease. Blood volume increases by about 50%, peaking in the second trimester, there´s a rise in maternal heart rate, cardiac output, a fall in blood pressure and in systemic vascular resistance, but the difference with chronic liver disease and pregnancy is that the blood flow to the liver remains constant and the liver usually remains impalpable. Telangiectasia or spider angiomas and palmarerythema are normal findings in pregnancy and are caused by the hyperoestrogenic state. Gall bladder motility is decreased, which increases the lithogenicity of the bile. There is also a fall in serum albumin concentration, due to the expansion in plasma volume, and the alkaline phosphatase activity increases due to added placental secretion [1]. Aminotransferase concentrations (alanine amino transferase and aspartate aminotransferase), bilirubin, and gamma-glutamyltranspeptidase all remain normal throughout pregnancy [2].

Pregnancy-Related Liver Diseases

Hyperemesis gravidum

About 50% - 90% of all pregnancies are accompanied by nausea and vomiting, however, in up to 20% of cases, nausea and vomiting may continue until delivery [3]. There are two condition related, Nausea and Vomiting During Pregnancy (NVP) and Hyperemesis Gravidarum (HG), the most severe grade of NVP [4]. HG has an estimated incidence of 0.5% - 2% of all live births [5]. A standard definition of HG is the occurrence of more than three episodes of vomiting per day with ketonuria and more than 3kg or 5% weight loss, the diagnosis is usually made clinically following the exclusion of other causes [6,7]. Clinical findings include dehydration, acidosis due to inadequate nutrition, alkalosis due to loss of hydrochloride and hypokalemia. There are two degrees of severity: grade 1, nausea and vomiting without metabolic imbalance; and grade 2, pronounced feelings of sickness with metabolic imbalance.

Etiology

The cause of HG is not well understood but appears to have both physiologic and psychologic components. Estrogen, progesterone, adrenal, and pituitary hormones have been proposed as causes but currently there is no conclusive evidence implicating any of them [8,9].

Recently, Helicobacter pylori infection has been implicated as a possible cause of HG [10,11]. Positive IgG concentrations have been found in hyperemesis patients compared with controls [12].

Li [13]. reported in a meta-analysis that of the HG cases, 1289 (69.6%) were H. pylori-positive and 1045 (46.2%) were H. pylori-

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positive in control group. Compared to the non-HG normal pregnant controls, infection rate of H. pylori was significantly higher in pregnant women with HG and it should be considered as one of the risk factors of HG.

Molecular mechanisms involved in HG have been a target of study recently, linking gut hormones and inflammation peptides in the pathogenesis, but there still the need of more studies to link these mediators to the pathogenesis of the disease.

Although hospitalization for hyperemesis occurs in less than 1% of pregnant women, this translates to a large number of hospital admissions. The factors associated with hyperemesis are primarily medical and fetal factors that are not easily modifiable, but identification of these factors may be useful in determining those women at high risk for developing hyperemesis [14].

Liver association

The liver injury occurs in half of HG patients and it has been reported that the severity of clinical symptoms correlate well with the degree of liver enzyme elevation. The clinical presentation of HG with liver disease can range from mild aminotransferase elevation to serum aminotransferases raised by as much as 20 times the upper limit of normal, but jaundice is rare. HG can start as early as week 4 of gestation and typically resolves by week 18. Biochemical abnormalities resolve on resolution of vomiting. Persistent abnormalities of the liver should alert the physician to alternative diagnoses. Liver biopsy is not indicated, but when done, it shows non-specific changes including mild steatosis and cholestasis [15]. Persistent symptoms beyond week 18 should warrant consideration of a gastroscopy to exclude mechanical obstruction [15].

Treatment

The management of HG is supportive that includes bowel rest, intravenous fluid replacement, and possible parenteral nutrition. Hospitalization In patients with more severe dehydration or ketonuria, inpatient admission is required. Most patients will need 5–8 days of hospital admission, but relapse is common. Normally, this patients won't require management inside an ICU, except for complication in electrolyte disorders, when hemodynamic monitoring is needed, presence of acute kidney injury and starvation that need treatment of a refeeding syndrome. A pregnant woman needs about 2,200 – 2,500 kcal/day and protein consumption following depleted fat stores is seen unless this is supplied. Protein consumption will eventually have an adverse effect on fetal growth [16,17]. Thiamine supplementation is an important step, especially in total parenteral nutrition. Nasogastric feeding, percutaneous endoscopic gastrostomy and feeding jejunostomy have been reported in severe patients [18,20]. Maternal complications such as infection and thromboembolism were higher when compared with women without such interventions [21]. Electrolyte imbalance should be corrected immediately.

Total Parenteral Nutrition (TPN) may be useful in highly refractory cases in order to ensure a sufficient calorie intake [22]. However, there is no evidence to support the use of TPN and it should only be used as a last resort when all other treatments have failed, as it can be as sociated with severe complications such as thrombosis, metabolic disturbances and infection [23].

Pharmacologic therapy

Antihistamines are usually the first-line drugs for treatment of both NVP and HG with no increase on teratogen risk [24]. Promethazine and chlorpromazine are among safe drugs which can be used during pregnancy [25,26]. A combination of metoclopramide and diphenhydramine has been reported to be more effective than droperidol and diphenhydramine combination with less adverse effects [27]. Diazepam has been used on HG patients, [28] a combination of antiemetic therapy and diazepam reduced the need for hospitalization and improved patient satisfaction. However diazepam is a category D drug in pregnancy so its use should be considered in refractory severe cases only [29]. No benefit in outcomes is seen with the use of steroids [30].

Intrahepatic Cholestasis of Pregnancy

Intrahepatic Cholestasis of Pregnancy (ICP) is a relatively benign cholestatic pathology of the liver and characterized by itchy skin and enhanced serum bile acid levels. ICP first manifests itself on week's 28-30 of pregnancy in the form of pruritus especially pronounced at nighttime. Almost half of the patients develop jaundice. The enhanced serum bile acid level is sometimes the first or the sole laboratory sign of the disease [31].

The incidence of ICP is reported to be between 0.2% and 2%; it is most common in South America and northern Europe. There is a higher incidence of in trahepatic cholestasis of pregnancy in women with a multiple pregnancy (up to 22%), [32,33]. in women who have conceived after *in vitro* fertilization treatment (2.7% compared with 2%), [34]. and in older obstetric patients (35 years) [35]. In a large, Swedish epidemiologic study that included 10,067 cholestasis cases and 94,863 women with uncomplicated pregnancy, there was a higher incidence of cholelithiasis and seropositivity for hepatitis C in women with ICP

Etiology

The cause of ICP remains unclear but is related to abnormal biliary transport across the canalicular membrane. Direct effects of female sex hormones induce cholestasis and inhibit the bile salt export pump. Mutations in the bile salt export pump have been implicated in the pathogenesis of intrahepatic cholestasis [37,38]. The multidrug resistance protein 3(MDR3) is the key transporter for phospholipids across the canalicular membrane. Mutations in this gene lead to loss of function and thus increased serum bile acids [40]. The MDR3 mutation is located on chromo some 7q 21.1 and has been identified in 15% of cases of ICP [39]. Overall, ten different mutations have been identified [40,41]. Floreani [41]. found that only heterozygous mutations cause transporter dysfunction, whereas complete absence of transport function is associated with severe liver disease. Evidence for genetic susceptibility to ICP includes familial clustering of the disorder, and there are reported pedigrees in which the mode of inheritance has a sex-limited, dominant pattern [42]. Several studies have identified genetic variation in genes encoding biliary transport proteins and in the principal bile acid receptor, farnesoid X receptor. Evidence fora role for the reproductive hormones in the etiology of natural history of the disease and also from studies in which oral progesterone was administered to prevent preterm labor. Murine studies demonstrated that estrogen contributes to the development of cholestasis by causing reduced expression of hepatic biliary transport

proteins and through internalization of the bile acid transporter bile salt export pump. More recent studies have established that sulphated progesterone metabolites are partial agonists of farnesoid X receptor, thereby impairing hepatic bile acid homeostasis by reducing the function of the main hepatic bile acid receptor [43]. Several environmental factors are also reported to play a role in the etiology of ICP, including dietary selenium levels [44]. Deficiency of this vitamin has been reported in women with ICP [45]. The etiology of the fetal complications is likely to relate to the deleterious effects of toxic bile acids, which accumulate in the fetal compartment [46].

The interaction between steroid levels, selenium, and seleno-enzyme glutathione peroxidase at the molecular level of the hepatocyte is complex. As estrogen levels increase during pregnancy, the oxidative stress on the liver also increases. In patients with low levels of selenium and glutathione peroxidase, the oxidative damage of estrogens cannot be properly counterbalanced. This leads to damage of the hepatocytes and decreases their ability to excrete bile [47].

Immunologic deregulation also plays an important role in the pathogenesis of ICP [48], where the increase in serum bile acid causes a change in the immune system from a TH2-mediated response to TH1. As pregnancies that have a shift to a TH1 immune response have more adverse outcomes, many of the risks of ICP are mediated by the immune system. The evidence of the immunologic pathway in the genesis of ICP has been proposed because of the significant increases in the levels of TH1- and TH17-associated cytokines, TNF-α IL-6, IL-12, IL-17A, IL-18 and IFN-γ, while TH2-associated cytokines, IL-4, IL-10, TGF-β1 and TGF- β2 and suppressor of cytokine signaling-3 (SOCS3), are reduced. Increases in nuclear factor-κ B (NF-κ B) further shift to a TH1 response [49,52]. Chemokines pro-inflammatory mediators are induced by cytokines such as IL-1 or TNF [53]. In ICP patients, CXCL6, CXCL14, IL-7R, CCL3 and CCL25 are up regulated along with CXCL1, CXCL4 and CXCL7 [54]. Increases in CXCL cytokines stimulate neutrophil chemotaxis while the CCL chemokines stimulate monocyte migration along with lymphocytes [53]. This recruitment of lymphocytes leads to cellular damage as will be seen in the future discussion concerning neutrophils. The pathways by which the immune cells take this effect and how exactly they are involved require further research. Decreased levels of placental ADAMTS-12 were found to be associated with ICP, suggesting a possible role of inflammation in the pathogenesis.

Liver association

An elevation in maternal-fetal bile acid flow and a reduced fetal capacity to eliminate bile acids through the immature fetal liver, in addition to altered placental function; appear to be responsible for impaired fetal-maternal bile acid transport in ICP [57]. Those phenomena contribute to an excess accumulation of hydrophobic bile acids that are hepatotoxic in the fetal compartment. Impaired fetal-maternal transport of bile acids across the placenta and the inability of the fetus to excrete cholic acid leads to an accumulation of bile acids and fetal cardiotoxicity, thus causing fetal dysrhythmia and sudden intrauterine fetal demise [58]. Total bile acid levels of up to 10- to 25-fold, which may be the first, laboratory abnormality [59]. A significant rise in cholic acid and a decline in chenodeoxycholic acid levels leading to a marked elevation in the cholic/chenodeoxycholic acid ratio may be detected. A reduced glycine/taurine ratio may also be present [60]. A mild elevation in liver enzymes may be detected in up to 60% of the subjects [61]. Alanine Aminotransferase (ALT) and Aspartate Aminotransferase (AST) levels rarely exceed two times the upper limits of normal pregnancy [62]. GGT levels are found to be increased in less than 1/3 of the cases, indicating a greater impairment of hepatic function. Hyperbilirubinemia, which rarely reaches 6mg/dL, may be another laboratory finding with an incidence of 25% [61]. Serum Alkaline Phosphatase (AP) levels may be elevated up to 4-fold, but does not contribute much to the diagnosis, as AP increase in pregnancy is already expected physiologically. A liver biopsy, although not recommended for the diagnosis, would just show a normal hepatic parenchyma with widening of the bile canaliculi, pure centrilobular cholestasis without inflammation, bile plugs in the hepatocytes, and canaliculi predominantly present in ZONE 3 [60,61]. Liver biopsy is indicated in cases of jaundice with no pruritus, the beginning of symptoms before 20 weeks of gestation, and sustained abnormal laboratory findings beyond 8 weeks after delivery [61].

Treatment

The most effective medical treatment of ICP is Ursodeoxycholic Acid (UDCA). 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 [63]. Bile acid levels in maternal blood may predict perinatal complications [64]. But the role of UDCA in ameliorating these complications is unclear [65,67]. Fewer instances of fetal distress/asphyxial events were seen in the UDCA groups when compared with placebo but the difference was not statistically significant. Large trials of UDCA to determine fetal benefits or risks are needed.

UDCA has this effect by increasing the activity of the canalicular BSEP and MDR3, used for exporting phospholipids, along with basolateral MRP4 which exports bile salt conjugates and placental ABCG2 protein, an export of bile acids and sulfated progesterone in the placenta. With BSEP, UDCA seems to be doubling the half-life of the protein by slowing down the endocytosis of the pump. This decreased degradation is most likely occurring with ABCG2 as well because it's mRNA was not found to be increased with UDCA treatment. Along with increasing the activity of these pumps, UDCA has many other effects. It decreases the toxicity of the bile pool, prevents oxidative stress and apoptosis, and upregulates serum expression of the vasodilator, corticotropin-releasing hormone, which is downregulated in ICP [48].

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.

There is insufficient evidence to indicate that same, guar gum, activated charcoal, dexamethasone, cholestyramine, Salvia, Yin Cheng Hao Decoction (YCHD), Danxioling and Yiganling, or Yiganling alone or in combination are effective in treating women with cholestasis of pregnancy [66].

Intrahepatic cholestasis of pregnancy normally resolves after delivery but, in rare cases of familial forms, the condition can persist

after, leading to fibrosis and even cirrhosis. In these cases, an increased risk of cholestatic liver disease exists, irrespective of pregnancy. Intrahepatic cholestasis of pregnancy might therefore be a predictor for the development of liver and biliary disease in the future.

Preeclampsia-eclampsia

Preeclampsia is a multisystemic disorder that affects 5 to 10% of all pregnancies and can evolve to MODS causing kidney, central nervous system, Hematologic and liver dysfunction [68,71]. The disease can progress to widespread microangiopathy that mainly affects the kidney, liver, and brain. Thrombocytopenia, liver dysfunction, microangiopathic hemolytic anemia, acute renal failure, placental abruption, visual disturbances, stroke, seizures, and maternal death are serious consequences of preeclampsia [71,72].

Etiology

The pathophysiology of preeclampsia is thought to involve procoagulant and proinflammatory states that create glomerular endotheliosis, increased vascular permeability, and a systemic inflammatory response that results in end organ damage and hypoperfusion [72].

Hypertension it's the result of vasospasm, but the triggering factor its unknown, however the most acceptable hypothesis describes that women with preeclampsia have an increased responsiveness to all presser hormones including angiotensin II, norepinephrine and vasopressin [73,74]. Preeclampsia is considered a endothelial disorder with two stages: the first stage occurs when there is an abnormal placental implantation secondary to a deficient invasion of the uterine spiral arteries by trophoblast cells, this causes an altered placental development and an impaired placental blood flow which gives as a result hypoxic remodeling features to the placenta. Inadequate placentation, owing to deficient trophoblast invasion of uterine spiral arteries, a characteristic of preeclampsia, can lead to placental hypoxia that can lead to abnormal expression of angiogenic factors. Persistent placental hypoxia promotes hypoxia-inducible factor-1 alpha (HIF-1a) release, which fosters a proliferative noninvasive trophoblast phenotype further aggravating hypoxia [75,76].

The second stage consist in the ischemic and reperfusion phenomena associated to an hypoxic placenta which release inflammatory cytokines, interleukin 6 and angiogenic molecules such as soluble endogolin (sEng) and soluble fms-like tyrosine kinase 1 receptor (sFlt-1) [74]. An increase in the concentration of sFlt-1 decreases free, and thus bioactive, PlGF and VEGF. Another splicing variant of VEGFR-1, sFlt1-14, generated primarily in non endothelial cells, functions similarly to sFlt-1 as a potent VEGF inhibitor. Interestingly, conversion of VEGFR-1 mRNA to sFlt1-14 prevents VEGFR-1-mediated signal transmission, in contrast to sFlt-1, whose production in endothelial cells is accompanied by a large excess of the transmembrane receptor. Expression of sFlt1-14 has been shown to be significantly increased in preeclampsia.

Due to the complex pathophysiology and aetiology of PE, a wide range of potential biomarkers have been investigated [77]. These biomarkers can be classified under different categories and many novel biomolecules have been identified. In addition to the predictive value of biomarkers, the identification of these entities (e.g., metabolomics or proteomic molecules) may elucidate the underlying mechanism for the pathogenesis of PE. Although no single biomarker has been deemed suitable for clinical application at present [78]. various novel biomarkers or combinations of biomarkers with other well recognized clinical parameters are promising. Single biomarkers in research conducted with different study cohorts, i.e., Early Onset Preeclampsia (EOPE), Late Onset Preeclampsia (LOPE) or Preeclampsia in general. Five biomarkers were highlighted: ADAM-12, in hibin-A, PAPP-A, PlGF and PP-13. ADAM12 is part of the ADAM protein family, which are involved in cell-to-cell and cell-to-matrix interactions in neural and muscle development as well as fertilization. [79,80]. PAPP-A is part of the first trimester Down's syndrome screening test and is a large zinc glycoprotein produced by placental trophoblasts [80]. PlGF and sFLT are both angiogenic factors. PlGF is a polypeptide growth factor mainly expressed in placental trophoblasts and regulate the early development of placental villi [81]. While sFLT induces endothelial cell dysfunction [82]. Prediction models utilizing a combination of biomarkers and clinical parameters improved the predictive value in studies examining preeclampsia (without distinction of EOPE and LOPE) with an area under the SROC of 0.893. However, the majority of combined models include evaluation of clinical history or assessment of uterine artery Doppler waveforms. This limits the potential of solely using laboratory-based biomarkers [83].

Liver association

Liver involvement it's uncommon and the pathogenesis of the injury is caused a combination of hepatic arterial vasospasm of the hepatic vasculature and precipitation of fibrin within the portal and periportal areas of the liver lobule. This results in lobular ischemia and hepatocyte necrosis [84], as a result of genetic predisposition and imbalance of prostacyclin and thromboxane. The presence of endothelial dysfunction and coagulation activation, leaded by the placental ischemia [85]. The hepatic lesions can be microscopes and macroscopic: the characteristic of microscopic changes in volvesperiportal areas with identifiable sinusoidal fibrin thrombi, hemorrhage, and hepatocellular necrosis. Portal and periportal thrombosis, hemorrhage, fibrin deposition ischemic lesions and micro vascular fat deposits can also be present histologically [85].

Micro vesicular fatty infiltration has also been observed in some cases of preeclampsia, suggesting a possible overlap with acute fatty liver of pregnancy [72].

The macroscopic changes involve intrahepatic hematoma, infarction and in liver capsular rupture [86]. All these changes can causes an altered hemodynamic pattern. Doppler ultrasound shows the share of debit portal increases total hepatic blood in the 3rd trimester of pregnancy during the preeclampsia the arterial resistances was found increased, this could be present or not in HELLP syndrome [86].The presence of a decreased hepatic blood flow was only found among women with preeclampsia that developed HELLP syndrome [87].

Aminotransferase activity could be as high as ten times the upper limit of normal, whereas bilirub in concentrations are rarely increased, usually is normal, but mild increases to 5mg/dL may be observed [86]. All these biochemical changes usually resolve within 2 weeks of delivery [86].

Treatment

The only effective treatment for preeclampsia is delivery of the fetus and placenta. However, if mild preeclampsia is evident before fetal lung maturity at 36 weeks of gestation, one may consider expectant management with intensive monitoring. Pharmacological agents used in preeclampsia include antihypertensive such as Beta blockers, calcium channel blockers and low-dose aspirin.

No specific therapy is required for the hepatic involvement of PE and its only significance is as an indicator of severe disease with a need for immediate delivery to avoid complications. The tight control of blood pressure is essential for eclampsia and HELLP syndrome [88] and immediate delivery is necessary in some cases with multi-organ dysfunction, liver infarction or hemorrhage, disseminated intravascular coagulation (DIC), fetal compromise, and others [89,91].

In travenous administration of magnesium sulfate, and fetal monitoring should be performed to prevent or predict seizures. Lower-dose and loading dose-only regimens could be as safe and efficacious as standard regimens; however, this evidence comes from low to very low quality studies and further high quality studies are needed [93].

Effect of corticosteroids is unclear and remains controversial for the patients [92]. The number of platelet and biochemical abnormalities return to normal levels within 2 weeks of delivery however subsequent pregnancies in patients with HELLP syndrome carry a high risk of complications [92].

Low Molecular Weight Heparin (LMWH) has emerged as a potential pharmacological therapy option for preventing the development of placental-mediated complications of pregnancy in women at high risk of recurrence in subsequent pregnancies. Several randomized trials have been conducted to assess the effectiveness of LMWH in the prevention of PE and other placental disorders [94].

The mechanism of action of prophylactic LMWH for the possible prevention of severe PE is currently unknown because of the predominantly clinical end points of previous trials, its commonly attributed to an anticoagulant action of heparin within the placenta, although the major trials did not include assessment of the placenta after delivery and improved outcomes are observed in at-risk women without demonstrable thrombophilia disorders [95]. An alternative hypothesis to an anticoagulant action is that LMWH exerts direct vascular actions in the maternal compartment to reverse the placenta-mediated systemic vascular dysfunction characteristic of PE [94,96,97]. Linked to the liberation of detrimental endothelium-bound antiangiogenic molecules. Al though bound to the endothelium; antiangiogenic proteins can interfere with the homeostatic function of the endothelium and reduce NO bioavailability [98]. Because sFlt-1 binds to the cell surface or extracellular matrix via heparan sulfate proteoglycans, LMWH may displace sFlt-1 from these heparin-binding sites via competitive binding, leading to higher levels ofsFlt-1 while yielding an improvement in endothelial function [94,99]. This proposed mechanism would be consistent with previous reports that heparin increases the bioavailability of NO in patients with coronary artery disease, whereas concurrently increasing levels of circulating MPO [100].

Large, high-quality clinical trials are necessary to define the extent of any benefit of LMWH to screen-positive women and should be the focus of future research [94].

Hellp Syndrome

HELLP syndrome, it's an acronym for: hemolysis, elevated liver enzymes, and low platelet count is an unusual complication of pregnancy that is observed in only 10% to 15% of women with preeclampsia, nevertheless of the 100% of women with HELLP syndrome 90% have antepartum preeclampsia. It may present at any time during the second or third trimester of pregnancy. Approximately 20% of patients develop manifestations of HELLP within two days after delivery.

The diagnosis is based on laboratory evidence of microangiopathic hemolytic anemia, hepatic dysfunction, and thrombocytopenia in a patient suspected to have preeclampsia. In such a patient with HELLP syndrome, a peripheral blood smear often will have evidence of schistocytes, burr cells, and helmet cells, which reflect damaged erythrocytes. Increases in Lactic Dehydrogenase (LDH) levels and decreases in serum haptoglobin levels are sensitive early markers of HELLP syndrome that occur before increases in indirect serum bilirubin concentration and decreases in hemoglobin values. The early onset of decreasing haptoglobin values suggests that hemolysis occurs soon after the onset of this disease process.

Etiology

The exact pathophysiology of HELLP syndrome has not been clearly elucidated, yet is thought that results from abnormal or aberrant placental development with altered placental function resulting on ischemia producing oxidative stress and a activation of complement and coagulation cascades, increased vascular tone, platelet aggregation and alterations of the thromboxane-prostacyclin ratio [101]. all these changes induce generalized endothelial and microvascular injury caused by placenta-derived FasL (CD95L) which is toxic to human hepatocytes, this triggering the production of TNF-α which may induce hepatic necrosis and injury, resulting in microangiopathic hemolytic anemia, periportal hepatic necrosis and thrombocytopenia, There are also data suggesting that HELLP represents a vasculophathy mediated by an abnormal concentration of vascular growth factors [102].

The pathogenesis of the maternal HELLP and PE syndromes may be perceived as cascades of reactions. A combination of activated coagulation and complement, with high circulating levels of sEndoglin, sFlt1, TNFa and active von Willebr and factor may cause the thrombotic microangiopathy in HELLP.

The chromosome 12q is coupled with the HELLP syndrome. The STOX1 gene, the ERAP1 and 2 genes, the syncytin envelope gene, and the −670 Fas receptor polymorphisms are involved in the development of preeclampsia. The ACVR2A gene on chromosome 2q22 is also implicated [103]. The toll-like receptor-4 (TLR-4) and factor V Leiden mutation participate both in development of preeclampsia and the HELLP syndrome.(103) Carriers of the TT and the CC genotype of the MTHFR C677T polymorphism seem to have an increased risk of the HELLP syndrome. The placental levels of VEGF mRNA are reduced both in women with preeclampsia and in women with the HELLP syndrome [104]. The BclI polymorphism

is engaged in development of the HELLP syndrome but not in development of severe preeclampsia. The ACE I/D polymorphism affects uteroplacental and umbilical artery blood flows in women with preeclampsia. In women with preeclampsia and the HELLP syndrome several genes in the placenta are deregulated. Preeclampsia and the HELLP syndrome are multiplex genetic diseases [103,104].

Liver involment

The liver involvement in HELLP syndrome is similar to the alterations presented in pre-eclampsia. Hepatic rupture with hemoperitoneum in women with HELLP syndrome has received substantial attention in the literature [105,117]. However, less is known about other hepatic complications that have more subtle presentation and may precede more severe conditions. Because hepatic hematoma occurring in association with preeclampsia and HELLP syndrome is a potentially life- threatening complication, prompt recognition is critical and may help reduce morbidity and mortality [118].

The hepatocyte injury is caused by placenta-derived FasL (CD95L) which is toxic to human hepatocytes [118]. The content of FasL in villous trophoblast is higher in HELLP than in PE [119]. and FasL concentration in maternal blood is elevated in HELLP [118]. FasL triggers the production of TNFα which may induce hepatocyte apoptosis and necrosis. Staining with TNFα and elastase antibodies in the liver was intense in HELLP [120]. Autopsies have shown hepatocyte necrosis without fatty cell transformation, surrounded by fibrin strands and hemorrhages, more rarely sub capsular bleeding and infarcts [121]. Fibrin and leukostasis were seen in sinusoids [122], probably as manifestations of thrombotic microangiopathy. Hepatocyte damage in HELLP is enhanced by the microangiopathy which impedes portal blood flow. Literature data suggest that it could be due to fibrinoid thrombi inside the hepatic sinusoids, which develops a periportal hematoma and necrosis. These thrombi may be secondary to disseminated intravascular coagulation or toxemic vasculophathy like the pathophysiology discussed in preeclampsia [104].

Liver rupture is a rare but life-threatening complication of HELLP syndrome. It is usually preceded by an intra-parenchymal hemorrhage that progresses to a contained sub-capsular intrahepatic hematoma in the right lobe that over distends the liver capsule resulting in capsular rupture and caused intra-peritoneal hemorrhage. Mortality is worse after episode of hepatic rupture and repeated hypertensive episodes may increase the risk of capsular rupture [104].

Most patients have rapid resolution after delivery. However, persistence of thrombocytopenia or hemolysis for more than 72 hours after delivery, worsening hepatic or renal failure, or life-threatening complications should be treated as medically indicated. The question about why only some women develop severe liver manifestations currently has no answer yet.

Treatment

The Tennessee Classification who requires the presence of microangiopathic hemolytic anemia with abnormal blood smear, low serum haptoglobin and elevated LDH levels with elevation of hepatic enzymes above 70IU/L or bilirubin more than 1.2mg/dL and a platelet count below 100x109 L [116].

The cornerstone of management is delivery. There are three major options for the management of women with severe preeclampsia and HELLP syndrome [123].

1) Immediate delivery which is the primary choice at 34 weeks' gestation or later.

2) Delivery within 48 hours after evaluation, stabilization of the maternal clinical condition and CS treatment. At 27 to 34 weeks of gestation, this option appears appropriate and rational for the majority of cases.

3) Expectant (conservative) management for more than 48–72 hours may be considered in pregnant women before 27 weeks' gestation. In this situation, corticosteroids (CS) treatment is often used, but the regimens vary considerably.

Whereas delivery is the mainstay of treatment for the HELLP syndrome [124], CS treatment, in addition to accelerate maturation of the fetal lungs, evidence of favorable maternal effects has been reported. This includes diminished edema, inhibited endothelial activation and reduced endothelial dysfunction, prevention of thrombotic microangiopathic anaemia, and inhibition of cytokine production and thereby induces anti-inflammatory effects in the HELLP syndrome [125].

1) Standard CS treatment to promote fetal lung maturity

2) high-dose dexamethasone treatment of the mother (10 mg dexamethasone every 12 hours).

3) Treatment with repeated doses to reduce maternal morbidity and hastening recovery.

Available evidence does not support that CS treatment can improve the outcome of pregnancies affected by the HELLP syndrome either antepartum and/or post-partum. Benefits from CS treatment for disease modification in the HELLP syndrome should individually be compared with immediate delivery, the current gold standard [126]. Thus, there is strong evidence for a single course of standard CS treatment in preterm delivery, including severe preeclampsia, but no conclusive evidence supporting CS treatment of the HELLP syndrome [127].

Eser [128]. reviewed the use of plasmapheresis in HELLP syndrome treatment. The mechanism of the effect of plasma exchange in HELLP syndrome is still controversial. HELLP syndrome is a microangiopathic disease and it has similar clinical and laboratory characteristics of thrombotic thrombocytopenic purpura and hemolytic-uremic syndrome. It is possible that plasma exchange removes aggregating and procoagulant factors released from both activated platelets and endothelial cells [129,130,131]. It has been suggested that therapeutic plasma exchange reduces mortality by improving hepatic, renal, respiratory, and cerebral functions and correcting coagulopathy. Plasma exchange may also be considered in patients who are not responding to supportive therapy [129,132 ,133].

Acute Fatty Liver in Pregnancy (AFLP)

With a prevalence of 1/7000–16000 births acute fatty liver of pregnancy is a rare but life-threatening disease [134]. A maternal mortality of 18% and an infant mortality of 23% are mentioned in publications.

AFLP is characterized by accumulation of microvesicular fat that crowds out normal hepatocytes function. Early recognition and prompt termination of pregnancy, has improved the prognosis of these patients. However, AFLP still causes severe maternal morbidity and in some cases mortality, especially in certain critical patients [135]. Acute Liver Failure (ALF) and Acute Renal Failure (ARF) are the most important and life-threatening complications of AFLP [136,137]. These women had moderate to-severe renal insufficiency, and many of them also had profound coagulopathic changes.

AFLP typically presents between 30 and 38 weeks of pregnancy but sometimes may not be recognized until after the delivery of the child. Cases as early as 26 weeks' gestation have been reported [138]. In a study of cases seen during a 10-year period, the mean gestational age at disease onset was 34.6 weeks, with 8% of women being multiparous, having had more than three prior pregnancies [139]. In 75% of the cases, the child was a boy [140].

Clinical manifestations of AFLP are often nonspecific and include nausea and vomiting (70% of patients), right upper quadrant pain or epigastric pain (50%–80%), or a viral-like syndrome with malaise and anorexia. Pruritus is uncommon, and jaundice commonly occurs in approximately 1 to 2 weeks after the onset of nonspecific symptoms. If untreated, AFLP typically progresses to fulminant hepatic failure with encephalopathy complicated by renal failure, pancreatitis, hypoglycemia, and uncontrollable gastrointestinal or uterine bleeding, DIC, seizures, coma and death.

Etiology

Pathogenesis of AFLP still has not been fully elucidated. Recent molecular advances suggest that AFLP may result from mitochondrial dysfunction, documented a strong association between AFLP and a deficiency of the enzyme Long-Chain 3-Hydroxyacyl-Coa Dehydrogenase (LCHAD) in the fetus, a disorder of mitochondrial fatty acid beta-oxidation [141].

First, the heterozygosity of the mother for a mitochondrial trifunctional protein MTP defect reduces her capacity to oxidize long-chain fatty acids. Second, the stressful nature of pregnancy with its accompanying changes in metabolism, the increased lipolysis, and the decreased β-oxidation [141].

There is published evidence that the presence of the G1528C mutation, potentially hepatotoxic long chain 3-hydroxyacyl fatty acid metabolites, produced by the fetus or placenta, accumulate in the maternal circulation. There is evidence for fatty acid oxidation in a normal human placenta including LCHAD and SCHAD activity [142]. Another study reported significant expression of fatty acid β-oxidation enzymes in human placenta as assessed by immunohistochemically and immunoblot analyses [143]. A recent study also showed high activity of fatty acid oxidation enzymes in human term placenta and chorionic villus samples [144].

Liver involment

With this condition, the hepatic architecture is intact and lobules are swollen. Centrilobular microvesicular fatty infiltration of hepatocytes is diagnostic, and the histology is distinctive from that of HELLP syndrome [145]. Around 25% of patients have significant inflammation of the lobules and portal tracts. Widespread necrosis is usually absent. The characteristic microscopic change is microvescicular steatosis, which can be in the form of minute cytoplasmic vacuoles or diffuse cytoplasmic ballooning that might spare the periportal hepatocytes [68]. There is no correlation between the degree of laboratory abnormalities and the severity of the histologic changes seen in the liver. This latter change might simulate hepatocyte ballooning of other causes. Canalicular cholestasis is also present. Necrosis of individual or groups of hepatocytes replaced by ceroid-laden macrophages might be present. Extra-medullary haemopoesis might also be present. These changes disappear within days to weeks after delivery without persistent injury.

The Swansea diagnostic criteria are an alternative to liver biopsy. Laboratory findings include serum aminotransferase levels varying from normal to 1000U/L, but are usually about 300 to 500 U/L. The total bilirubin concentration is typically less than 5mg/dL. Other laboratory abnormalities include anemia, leukocytosis, normal or low platelet counts, coagulopathy with or without DIC, hypoalbuminemia, hypoglycemia, and acute kidney injury.

Treatment

AFLP usually does not resolve before delivery, and if delivery is delayed, complications such as hemorrhage, acute liver failure with encephalopathy, and intrauterine death may develop. Consequently, the primary therapy for AFLP is early delivery. The choice of the route of delivery remains the decision of the obstetrician and must be appropriate for the individual's clinical situation. If the patients are at high risk for multisystem organ failure and death, admission to the intensive care unit is generally recommended. Before delivery, maternal stabilization should be taken. Before delivery maternal stabilization should be achieved [146]. This includes airway management, fluids and electrolytes reposition, coagulopathy reanimation, metabolic and hypertensive control, and in some cases renal replacement therapy. Once the mother is stabilized, delivery of the fetus, by vaginal birth which is considered the best approach, however in the presence of deterioration of maternal – fetal status a caesarean birth is indicated.

Closed monitoring should be maintained in perioperative settings and support treatment once delivery is performed.

Some cases develop acute liver failure; the role of liver transplantation is limited in AFLP but has been used with success. Although plasmapheresis has been used in some cases, its benefit is unproven. Corticosteroids have not been shown to be effective in management [68].

Complications such as pancreatitis, renal dysfunction and nosocomial infection could develop and early recognition is imperative to reduce morbidity and mortality in this settings.

Conclusion

There is an urgent need to increase awareness about this preventable cause of maternal death, Pregnancy-related liver disorders accounted for 8% of all maternal deaths. 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.

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