Hemostatic issues in pregnancy-induced liver disease

Ton Lismana,*, William Bernalb

aSurgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

bLiver Intensive Care Unit, Institute of Liver Studies, Kings College Hospital, Denmark Hill, London, United Kingdom

ARTICLE INFO

Keywords:
Thrombosis
Bleeding
Post-partum
Pregnancy
Liver disease
Delivery
Cesarean section

ABSTRACT

Liver diseases may be accompanied by profound changes in the hemostatic system including thrombocytopenia, decreased plasma levels of pro- and anticoagulants, and alterations in plasma levels of fibrinolysis. The net effect of the hemostatic changes in chronic and acute liver diseases is a hemostatic system that is in relative balance due to the simultaneous decline in pro- and antihemostatic drivers. A unique category of liver diseases are those induced by pregnancy. In acute fatty liver of pregnancy, profound hemostatic changes occur, which may be caused by a combination of liver failure and disseminated intravascular coagulation. Hemostatic changes in preeclampsia and HELLP syndrome are dominated by thrombocytopenia, although alterations in plasmatic coagulation may also occur. Post-partum bleeds, bleeding from cesarean section wounds, and hepatobiliary bleeds may occur in both patient groups. Patients with intrahepatic cholestasis of pregnancy do not show clinically relevant hemostatic alterations, despite biochemical evidence of liver injury.

© 2017 Elsevier Ltd. All rights reserved.

1. Rebalanced hemostasis in liver diseases

The liver is a central organ in the hemostatic system as it is the site of synthesis of many proteins involved in hemostasis. In addition, the liver is involved in clearance of activated coagulation factors and factor-inhibitor complexes. Patients with advancing liver disease therefore frequently acquire alterations in their hemostatic system [1]. Decreased plasma levels of proteins involved in coagulation and fibrinolysis that are synthesized in the hepatocyte are frequently present in these patients. Although it is commonly assumed that decreased hepatic synthesis is directly responsible for these decreased levels, a consumptive coagulopathy of systemic or intrahepatic origin may also contribute [2,3]. In addition, thrombocytopenia is common and is likely related to decreased synthesis of thrombopoietin, a decreased platelet half-life, splenomegaly, direct bone marrow suppression by toxins such as ethanol, and increased consumption [4]. Endothelial-derived plasma proteins are increased in patients with liver disease as a result of chronic endothelial activation with a multifactorial background which includes changes in systemic and intrahepatic blood flow, endotoxemia, and reduced clearance [5–7].

Historically, the hemostatic changes of patients with cirrhosis were thought to result in a hypocoagulable state, as evidenced by abnormal laboratory indices of hemostasis (such as thrombocytopenia and a prolonged prothrombin time) and clinical bleeding events. It was therefore common practice to try to correct these abnormal laboratory indices by transfusion of platelets or fresh frozen plasma (FFP) prior to invasive procedures. In recent years, it has become clear that these historical concepts on the coagulopathy of liver disease are incorrect [8–10]. Patients with liver disease have concomitant changes in pro- and antihemostatic pathways, and show intact hemostatic capacity when tested with more advanced laboratory tests. Specifically, the thrombocytopenia of liver disease appears compensated by highly elevated levels of von Willebrand factor [7], thrombin generation is preserved by a commensurate decline in pro- and anticoagulants [11], and low fibrinogen levels appear compensated by prothrombotic changes in fibrin structure [12]. Clinically, the preserved hemostatic status of patients with liver disease is evident from extensive experience in liver transplant surgery, which can be performed without the requirement for any blood product transfusion in a significant proportion of patients [13]. Many centers performing liver transplant surgery have abandoned the policy to prophylactically transfuse blood products prior to surgery, and paradoxically, the abstinence of prophylactic administration of blood products has likely contributed to a reduction in perioperative blood loss. Besides awareness that prophylactic prohemostatic therapy in patients with liver diseases may not be useful, and may even do harm, it is increasingly recognized that patients with liver disease are not protected from thrombotic disease [14]. Patients with liver disease may experience systemic or local thrombotic events for which prophylaxis or treatment with anticoagulant drugs is indicated [15].

We and others have coined the hemostatic status of patients with liver disease ‘rebalanced hemostasis’ [8]. However, although the ‘average’ patient with liver disease appears approximately normocoagulable, it should be realized that the rebalanced hemostatic system is fragile and susceptible to alterations that may tip the bal-
ance toward either a bleeding diathesis or a thrombotic tendency. It is at present not possible to predict which patients are at risk for bleeding and which for thrombotic complications.

2. Differences in hemostatic status depending on etiology of disease

Clinical and laboratory evidence for both chronic liver diseases and acute liver failure has been provided [8,16]. Although hemostatic changes in chronic and acute liver diseases are similar, there are important differences. For example, thrombocytopenia is usually more severe in advancing chronic liver diseases whereas coagulation abnormalities are more profound in acute liver failure [16]. Also the nature of clinical bleeding and thrombotic events are different between these diseases. Bleeding in chronic liver disease is dominated by variceal bleeding events, which are a consequence of portal hypertension and local vascular abnormalities rather than hemostatic derangement. Variceal bleeding almost never occurs in patients with acute liver failure, whose bleeding episodes are frequently from mucosal lesions [17]. Clinically significant bleeding is rare in patients with acute liver disease in current experience, whereas bleeding is a major cause of concern in patients with cirrhosis. Thrombotic events in both chronic and acute liver disease include venous thrombosis and portal vein thrombosis. In patients with acute liver failure, thrombotic occlusion of dialysis catheters is common.

With the spectra of chronic and acute liver disease, hemostatic changes are not identical, although studies addressing hemostatic changes of a single etiology of liver disease are scarce. Patients with cholestatic cirrhosis appear more hypercoagulable compared to patients with non-cholestatic cirrhosis [18], and clinically this is evident by a decreased requirement for blood product transfusion in cholestatic patients undergoing liver transplant surgery [19]. Another example are differences in clot structure and stability between patients with cirrhosis due to alcohol or due to non-alcoholic fatty liver disease [20].

3. Hemostatic issues and open questions in pregnancy-induced liver diseases

A specific category of liver diseases are those induced by pregnancy. Severe pregnancy-induced liver diseases are associated with a significant risk of morbidity and mortality for both the mother and the baby. Part of this risk relates to bleeding or thrombotic events. The hemostatic changes of pregnancy-induced liver diseases have only scarcely been studied. Such studies are complex as also in normal pregnancy significant changes in the hemostatic system occur [21]. Furthermore, clinically significant bleeding events (i.e., post-partum bleeds) and post-partum venous thrombosis are not uncommon in otherwise normal pregnancies. We will review the literature on clinical and biochemical data on hemostatic disorders in patients with pregnancy-induced liver disease and identify knowledge gaps.

3.1. Acute fatty liver of pregnancy

Acute fatty liver of pregnancy (AFLP) is a rare complication occurring in ~1:20,000 pregnancies, and is a medical and obstetric emergency. Clinical presentation and risk factors have been reviewed elsewhere [21]. Patients with AFLP have accumulation of microvesicular fat droplets within their hepatocytes, with biochemical evidence of liver injury and liver failure. Hemostatic changes include thrombocytopenia, a prolonged prothrombin time, and reduced fibrinogen levels [22]. It has been debated whether hemostatic changes of AFLP are related to liver failure or that disseminated intravascular coagulation (DIC) also contributes. It has recently been reported that according to the DIC scoring system of the International Society of Thrombosis and Haemostasis, the vast majority of patients with AFLP have DIC that persisted after delivery [23]. Nevertheless, it should be noted that the constituents of this score (low platelet count, elevated fibrin split products, elevated prothrombin time, and low fibrinogen) are all compatible with synthetic and clearance defects of the liver. Whether DIC is an important component of liver diseases in general and AFLP in particular thus remains to be established. Importantly, a proportion of patients with AFLP also have preeclampsia (see below).

Whatever the cause, the coagulopathy of AFLP appears to contribute to obstetric bleeding. The bleeding phenotype of AFLP may be further exacerbated by renal failure, which is common in these patients. Post-partum bleeding has been reported in ~50% of patients with AFLP [24]. These bleeds are immediate following vaginal delivery. Following cesarean section, delayed bleeding from surgical wounds may occur. In addition, major intraabdominal bleeding from hepatoiliary sites requiring surgical intervention has been reported [25,26]. Delivery by cesarean section is common in patients with AFLP, and the coagulopathy may be a contraindication for neuraxial anaesthesia, although cases with highly elevated INRs that did not have complications from neuraxial anesthesia have been reported [27].

In patients with liver diseases unrelated to pregnancy, we advise against prophylactic blood product transfusion prior to invasive procedures [28]. Indeed, emerging clinical evidence suggests that lengthy and invasive procedures such as liver transplant surgery can be performed without the requirement for any perioperative blood product transfusion in a proportion of patients, despite substantial pre- and intraoperative abnormalities in the hemostatic system [13]. However, as the bleeding risk of delivery is substantial (even in patients without pregnancy-associated liver disease) [29], and excessive peripartum bleeding can lead to life-threatening situations, our management advise for these patients is more conservative. Although clinical studies on hemostatic management are lacking, we advise a pro-active, individualized approach using transfusion of platelets, fresh frozen plasma, and/or fibrinogen concentrate, guided by functional testing for example using thromboelastography whenever available [30]. In particular in the setting of cesarean delivery, prophylaxis is required, particularly focused on platelets and fibrinogen.

3.2. Intrahepatic cholestasis of pregnancy

Intrahepatic cholestasis of pregnancy (ICP) is the most common pregnancy-induced liver disease, and a detailed description of the disease is provided elsewhere [21]. Its presenting symptom is pruritus, and biochemical abnormalities include increased serum bile acid and transaminase levels. Bilirubin levels are generally within normal ranges. Vitamin K malabsorption may occur and induce a coagulopathy. Vitamin K supplementation is therefore advocated by some to reduce the risk of post-partum or neonatal bleeding. A recent study, however, found no abnormalities in prothrombin time or platelet count in 223 women with ICP, suggesting that despite biochemical evidence of liver injury and a risk of vitamin K malabsorption no clinically relevant hemostatic alterations occur [31]. Indeed, the same study reported an incidence of post-partum bleeding in 319 patients with ICP that was comparable to that of the general obstetric population. Those patients that received neuraxial anesthesia had no complications such as neuraxial hematomas.

3.3. Preeclampsia and HELLP syndrome

Preeclampsia, eclampsia, and hemolysis, elevated liver enzymes, low platelets (HELLP) syndrome form a spectrum of diseases that are characterized by pregnancy-induced hypertension combined with proteinuria and organ dysfunction [21]. Eclampsia refers to the
onset of seizures in a patient with preeclampsia, while the HELLP syndrome is considered to be a severe form of preeclampsia.

Although the etiology of preeclampsia is incompletely understood, abnormal placental development and a generalized inflammatory response resulting in endothelial cell activation are thought to be important contributors. Generalized activation of endothelial cells results in activation of the hemostatic system, resulting in a thrombotic microangiopathy. An increase in plasma levels of highly reactive von Willebrand factor multimers have been suggested to be responsible for the consumptive thrombocytopenia [32].

Histopathologic findings in the liver include intravascular fibrin deposits that are thought to lead to hepatic sinusoidal obstruction, intrahepatic vascular congestion, and increased intrahepatic pressure. This process contributes to liver failure, but also may lead to intraparenchymal and subcapsular hemorrhage, and eventually hepatic rupture [21].

The hemostatic alterations in preeclampsia and HELLP thus are driven by at least 2 mechanisms – an endothelial-driven thrombotic microangiopathy, and a liver disease-induced coagulopathy although the latter may be mild as the prothrombin time may be normal in patients with HELLP syndrome. In those patients that develop coagulation abnormalities, it is generally assumed that DIC has developed, although it cannot be excluded that those patients that have a positive DIC score, the primary factor driving coagulation abnormalities is liver failure as also outlined in the section on AFLP. It has also been argued that the vast majority of women with preeclampsia and HELLP have liver injury, but do not have overt liver failure and no evidence of clinically relevant DIC [24], and that the prime hemostatic abnormality in these patients thus is a profound thrombocytopenia.

Although preeclampsia and HELLP have a clear thrombotic phenotype, post-partum bleeding complications following either vaginal or cesarean delivery are frequent, also in patients with preeclampsia that do not develop HELLP syndrome [33]. As in AFLP, we advise a pro-active, individualized approach using blood product transfusion guided by functional hemostasis testing. Nevertheless, post-delivery thrombotic events are more frequent in patients with preeclampsia, also in multivariate analysis in which confounders such as infection, and delivery by cesarean section have been taken into account [34]. These data suggest that prohemostatic therapy should be used with caution and that thromboprophylaxis should be initiated as soon as possible.

4. Conclusion

Severe pregnancy-induced liver diseases may be associated with unique and poorly defined hemostatic changes. These changes may be driven by liver disease, but a consumptive coagulopathy may also contribute. In case of HELLP syndrome, the thrombocytopenia is largely, if not fully, independent of liver failure, and relates to the microangiopathy that is part of the HELLP syndrome. Pregnancy-induced liver diseases also are unique in terms of bleeding complications, which are primarily gynecological, and hepatobiliary (related to intrahepatic fibrin deposition in HELLP syndrome, for example). Bleeding may be exacerbated by renal failure and sepsis. Even though laboratory data are lacking, it appears that the hemostatic system may turn to a hypocoagulable state in pregnancy-induced liver disease, although patients are not protected from post-partum thrombotic events. In patients with cirrhosis and acute liver failure unrelated to pregnancy, prophylactic transfusion of blood products is discouraged, but prophylactic correction of hemostasis is advised in pregnancy-induced liver diseases prior to delivery.

Conflict of interest statement

The authors have no conflicts to declare.

References

[28] Lisman T, Porte RJ. Value of Preoperative Hemostasis Testing in Patients with


