



## Hemostatic issues in pregnancy-induced liver disease

Ton Lisman<sup>a,\*</sup>, William Bernal<sup>b</sup>

<sup>a</sup>Surgical Research Laboratory, Department of Surgery, University of Groningen, University Medical Center Groningen, Groningen, The Netherlands

<sup>b</sup>Liver Intensive Care Unit, Institute of Liver Studies, Kings College Hospital, Denmark Hill, London, United Kingdom

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### 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.

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### 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-

\* Corresponding author: Ton Lisman, University Medical Center Groningen, Department of Surgery, BA33, Hanzplein 1, 9713 GZ Groningen, The Netherlands. Tel.: +31 50-3619028; Fax: +31 50-3632796.

E-mail address: [j.a.lisman@umcg.nl](mailto:j.a.lisman@umcg.nl) (T. Lisman).

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 diseases 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 hepatobiliary 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 advice 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

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