Pregnancy and Vascular Liver Disease

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Vascular disorders of the liver frequently affect women of childbearing age. Pregnancy and the postpartum are prothrombotic states. Pregnancy seems to be a trigger for Budd–Chiari syndrome in patients with an underlying prothrombotic disorder. Whether pregnancy is a risk factor for other vascular liver disorders is unknown.

In women with a known vascular liver disorder and a desire for pregnancy, stabilisation of the liver disease, including the use of a portal decompressive procedure when indicated, should be reached prior to conception. The presence of esophageal varices should be screened and adequate prophylaxis of bleeding applied in a manner similar to what is recommended for patients with cirrhosis. Most women likely benefit from anticoagulation during pregnancy and the postpartum. Labor and delivery are best managed by a multidisciplinary team with experience in this situation. Assisted vaginal delivery is the preferred mode of delivery. Although the risk of miscarriage and premature birth is heightened, current management of these diseases makes it very likely to see the birth of a live baby when pregnancy reaches 20 weeks of gestation. (J Clin Exp Hepatol 2015;5:41–50)

Vascular disorders of the liver include a spectrum of conditions involving the portal venous system, the intrahepatic vessels, the hepatic veins and the terminal portion of the inferior vena cava. Although rare, they frequently affect women of childbearing age.[1] Fertility rates have been reported to be unchanged in women with non-cirrhotic portal hypertension of various etiologies before and after onset of liver disease when compared with healthy controls.[2] This contrasts with cirrhosis, known to be associated with decreased fertility.[3] Issues raised by pregnancy in patients with vascular liver disease include the following: (a) is pregnancy a risk factor for vascular liver disease? (b) what are the outcomes of pregnancy in women with established vascular diseases of the liver? and (c) how to manage pregnancy and delivery?

The objective of this review article is to address these issues.

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Abbreviations: BCS: Budd–Chiari syndrome; LMWH: low-molecular-weight heparin; MPD: myeloproliferative disorders; PVT: portal vein thrombosis; VKA: vitamin K antagonists
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PHYSIOLOGIC CHANGES ASSOCIATED WITH PREGNANCY

Hemodynamic Changes Associated with Pregnancy

Pregnancy is associated with several systemic hemodynamic changes. A rise in blood volume and cardiac output by 30–50% occurs during the second and third trimesters. Arterial blood pressure decreases by 10% during mid-pregnancy and returns to pre-pregnancy levels at term.[4] These features are due to a drop in systemic vascular resistance. Red blood cell total mass increases, but to a lower extent than total blood volume which results in a slight decrease in hematocrit levels. The gravid uterus obstructs the venous return in the inferior vena cava so that, at term, much of the blood flow from the lower part of the body is redirected to the azygos system.[5,6]

A limited number of studies have evaluated the changes in splanchnic blood flow during normal pregnancy. Studies dating back to the seventies and using bromsulfalein clearance rate have yielded inconsistent results, suggesting increased or unchanged splanchnic blood flow.[7,8] Subsequent estimates of hepatic blood flow in normal pregnancy using ultrasonography with Doppler have demonstrated a significant rise in portal blood flow as compared to pre-pregnancy values during recumbency and standing rest.[9] This occurs via an increase in the diameter of the intra- and extra-hepatic branches of the portal vein, despite a reduction in mean blood velocity.[10,11] Blood flow in the hepatic artery is unchanged even though resistance indexes are reduced.[10,11]

There are no data on hemodynamic changes occurring during pregnancy in women with chronic liver disease. Yet, if the above-mentioned changes also occur in patients with vascular liver disease, pregnancy may exacerbate portal hypertension. Indeed, the hypervolemic and systemic hyperdynamic state associated with pregnancy is reminiscent of the circulatory changes classically associated with portal hypertension and may thus further augment them.[12]

Hemostatic Changes Associated with Pregnancy

Presumed to take place for the hemostatic challenge of delivery, various coagulation changes occur during pregnancy, as reviewed elsewhere in detail.[13] These changes are summarised in Figure 1. Briefly, there is an increased activity of procoagulant factors, a decrease in certain natural anticoagulant factors and in fibrinolysis. For many of these changes, close correlations have been established with the hormonal changes of pregnancy, and in particular with increased serum estradiol levels.[14] This procoagulant state is illustrated by the elevated levels of fibrin degradation products, including D-dimers, during pregnancy.[13]

Accordingly, a decrease in commonly used coagulation tests, such as prothrombin time (PT), thrombin time (TT) and the activated partial thromboplastin time (aPTT) has been described in studies comparing pregnant patients to healthy controls.[15,16] A practical consequence of that feature is that levels of coagulation parameters classically used to evaluate liver function, such as INR, should be interpreted with caution in pregnant patients with underlying liver disease.

It must also be kept in mind that the antiphospholipid syndrome, present in some vascular liver disease patients, can cause a prolonged aPTT despite a procoagulant state.

Mild thrombocytopenia related to increased plasma volume is another common feature of pregnancy.[17] Therefore, in pregnant women with vascular liver disease, decreasing platelet counts may not reflect increasing portal hypertension.

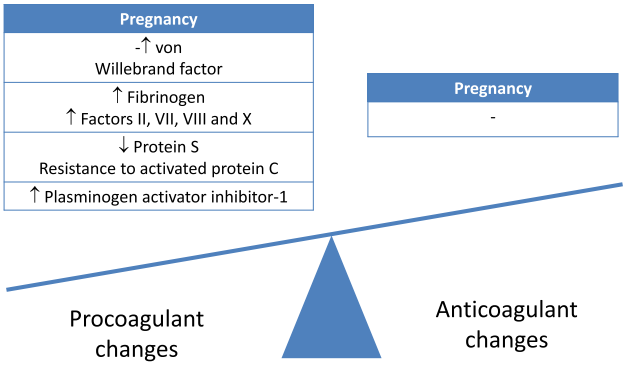

Figure 1 Coagulation changes in pregnancy.

BUDD–CHIARI SYNDROME AND PREGNANCY

Is Pregnancy a Risk Factor for Budd–Chiari Syndrome?

In Indian studies including patients in the seventies and eighties, up to 47% of reported Budd–Chiari syndrome (BCS) cases were encountered in women presenting in pregnancy or postpartum.[18,19] More recently, pregnancy was present within 3 months before BCS diagnosis in about 6% of female patients in an Indian and a large European multicentric study.[20,21] To clarify the relationship between pregnancy and BCS development, the prevalence of pregnancy or post-partum BCS was analysed in women of childbearing age seen consecutively in a reference center over a ten-year period. The proportion of women with a diagnosis of BCS made during pregnancy or postpartum was 16%, i.e. twice higher than the corresponding point prevalence of pregnancy or postpartum among women aged 15–45 years in the general French population.[22] Most BCS cases occurred in patients with other risk factors for thrombosis than pregnancy.[23–29] In particular, women with protein S deficiency seem at higher risk for BCS during pregnancy.[22] This may be due to the previously described decrease in functional levels of this protein during pregnancy.[30,31] Indirect evidence suggests that myeloproliferative disorders (MPD) may also synergise with pregnancy to induce splanchnic vein thrombosis. Work-up for thrombosis risk factors has been incomplete in most studies, in particular regarding the $JAK2^{V617F}$ status. Five percent of 237 pregnancies in women with essential thrombocythemia, were associated with the development of splanchnic vein thrombosis in the weeks or months after delivery.[32] This incidence is higher than expected in essential thrombocythemia patients.[33] Thrombotic events happened more commonly after a complicated (28%) than after an uneventful pregnancy (3%).[32] This suggests that a common determinant may be responsible both for the poor outcome of pregnancy and for thrombosis.

Hence, pregnancy seems to be a trigger for BCS in patients with an underlying prothrombotic disorder. A practical consequence is that presentation of BCS during pregnancy or postpartum should not deter from a comprehensive investigation for other risk factors.

Outcome in Pregnant Women with known BCS

Experience on pregnancy in women with established BCS mainly derives from one retrospective study of 24 pregnancies in 16 patients from 3 European centers.[34] All patients were in a stable condition at the time of conception, 9 of them having been previously treated with a portal decompressive procedure. One or several risk factors for thrombosis had been identified in 14 of these 16 women.