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.

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}

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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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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.

Table 1 Outcomes of Pregnancies in Women with Previously Diagnosed Budd–Chiari Syndrome or Portal Vein Thrombosis.

	Budd–Chiari syndrome (24 pregnancies) ³⁴	Portal vein thrombosis (104 pregnancies) ^{50–52}
Miscarriages	29%	14%
Stillbirths	6%	2%
Premature births	76%	14%
Cesarean section	47%	37% ^a
Variceal hemorrhages	0%	5%
Non-variceal hemorrhages	35%	6%
Thrombotic events	15%	3% ^a

^aData obtained from references ^{50,52}.

Anticoagulation therapy was used during 17 of the pregnancies.

As shown in Table 1 and Figure 2, miscarriage, defined as a spontaneous termination of pregnancy before 20 weeks of gestation, occurred in 29% of the pregnancies. After gestation week 20, one stillbirth occurred, but all other infants did well despite a high incidence of preterm birth.

Maternal outcome was good. No death occurred during pregnancy. Yet, three thrombotic events happened, including 2 related to shunt obstruction. Six bleeding events were recorded, including four in the early post-partum period. Prothrombin gene mutation was associated with a poorer outcome of pregnancies.

Although great caution is required when comparing European patients seen after 1985 with Indian patients managed between 1960 and the early nineties, it seems that the current overall management of BCS has allowed

an increasing number of young female patients to achieve an improved condition allowing them to consider pregnancy and go through this pregnancy without jeopardising their lives.^{18,19} Recent Indian data support this view although most women suffered BCS revealed by pregnancy in that report.³⁵

PORTAL VEIN THROMBOSIS AND PREGNANCY

Is Pregnancy a Risk Factor for Portal Vein Thrombosis?

Portal vein thrombosis (PVT) diagnosis during pregnancy or post-partum is uncommon. In the largest recent series, 0–4% of PVT cases were time-related to pregnancy.^{36–41} Thrombosis risk factors have been reported in some cases of PVT revealed by pregnancy, namely protein S deficiency,^{42–44} but not in others.^{45–48} Here again, results of investigation for underlying MPD are seldom mentioned, raising the hypothesis that some cases may have been misdiagnosed as idiopathic, as around 30% of non-cirrhotic PVT occurs in MPD patients.⁴⁹ Altogether, these data suggest that pregnancy alone is not a clear risk factor for PVT. Another precipitating factor, whether local or systemic, must be ruled out in all cases.

Outcome of Pregnant Women with known PVT

Despite differences in the incidence of documented prothrombotic states and in the use of anticoagulation, the best information stems from three series of patients, two Indian and one European, including a total of 104 pregnancies (Table 1 and Figure 2).^{50–52} Maternal and fetal outcomes are summarised in Table 1 and Figure 2. Fetal

Figure 2 Fetal outcome in pregnancies with known and treated portal vein thrombosis (left) or Budd–Chiari syndrome (right).

outcomes were good with low numbers of stillbirths and perinatal deaths despite a slightly higher rate of prematurity than expected in the general population.⁵³ Results for the mothers also described increased morbidity, but no death. Only five episodes of variceal hemorrhage happened, including three in patients without adequate prophylaxis for portal hypertension-related bleeding. Other hemorrhagic events were genital or parietal bleedings and occurred in most cases in the peri-partum period and in patients not on anticoagulation. There were two thrombotic events, one transient ischemic attack and one splenic infarction. No case of mesenteric ischemia or deep-vein thrombosis was reported. The only statistically significant risk factor for unfavorable outcome identified in the European study was a higher platelet count at diagnosis. Similar to BCS, this association points to chronic underlying prothrombotic conditions, and particularly MPD, as a possible cause for an unfavorable pregnancy outcome, due to thrombotic occlusion in the placental circulation.

A previous Indian study dating back to 2001 described the outcome of 23 pregnancies in 12 women with PVT.⁵⁴ However, the interpretation of this study is limited by the fact that PVT was diagnosed during the index pregnancy in 6 out of the 12 patients. This may explain the higher frequency of fetal complications than in the two more recent series mentioned above: there were 4 miscarriages (17%), 3 stillbirths (16%), and only 2 preterm births (11%).

OTHER VASCULAR DISORDERS OF THE LIVER AND PREGNANCY

Hereditary hemorrhagic telangiectasia is a rare genetically transmitted vascular disease affecting the brain, heart, lungs and liver circulation through the formation of vascular malformations. When symptomatic, liver involvement can manifest as high-output cardiac failure, ischemic cholangiopathy, porto-systemic encephalopathy or portal hypertension.⁵⁵ The hyperdynamic state of pregnancy places patients at risk for decompensation of cardiac disease. There have been a few reported cases of heart failure during pregnancy in patients with hepatic arteriovenous malformations. Most had standard management of heart failure and recovered in the first postpartum months.^{56–59} One had recurrent bacterial cholangitis after delivery and required liver transplantation.⁶⁰

In patients with the sinusoidal obstruction syndrome, blood flow in the sinusoids is impaired, leading to liver dysfunction. Patients present with ascites, right upper quadrant pain and jaundice. Pregnancy in women with prior sinusoidal obstruction syndrome has not been reported.

A total of 150 pregnancies in 62 women with **non-cirrhotic portal hypertension** has been reported thus

far by independent groups.^{2,54,61} Conclusions are unclear to draw as patient populations were heterogeneous, including women with liver disease either known before conception or revealed during pregnancy, and also some women with associated extra-hepatic portal vein obstruction. The largest series described the outcome of 27 pregnancies in 15 patients with non-cirrhotic portal fibrosis.⁵⁴ The rate of variceal bleeding during pregnancy was 26%, occurring mostly in patients with newly diagnosed disease. Variceal hemorrhage was associated with a poorer obstetrical outcome. There was a significant overall rate of stillbirths of 14%.

Pregnancy in patients with rarer vascular diseases of the liver has been seldom reported. In **peliosis hepatis**, blood-filled cavities of various sizes are found in the liver parenchyma. While the use of oral contraceptives has been associated to its development,^{62,63} pregnancy has not been linked to its appearance. Fatal outcome of pregnancy has only been reported in one woman with massive postpartum hemorrhage, multi-organ failure in whom a peliotic liver was incidentally found at laparotomy.⁶⁴ Concerning **hepatic artery anomalies** in pregnancy, there has been a single case report about a woman with fatal intra-peritoneal hemorrhage caused by a ruptured aneurysm of the common hepatic artery at 32 gestation weeks.⁶⁵ These reports being exceptional, no conclusion can be drawn concerning pregnancy in women with peliosis or hepatic artery anomalies. Pregnancy has not been reported in other rare vascular disorders of the liver, such as **congenital porto-systemic shunts** (Abernethy malformation).

Pregnancy can be anticipated as safe if the disease is stable and if varices have been screened and adequately managed if portal hypertension is present (see below).

MANAGEMENT OF PREGNANT WOMEN WITH VASCULAR DISEASES OF THE LIVER

Management of Anticoagulation during Pregnancy and Postpartum

The management of anticoagulation during pregnancy has been discussed in details elsewhere and can be guided by the American College of Chest Physicians (ACCP) guidelines.^{66,67} A proposed approach is illustrated in Figure 4.

Briefly, low-molecular-weight heparins (LMWH) are the preferred agent for anticoagulation during pregnancy. Their advantages include not crossing the placenta, considerable experience in pregnancy and weight-based dosing. Anticoagulation with unfractionated heparin during pregnancy is also considered safe for the fetus, but necessitates dose adjustment with activated partial thromboplastin time. Vitamin K antagonists (VKA) are generally avoided because they cross the placental barrier and carry a teratogenic risk, especially between the 6th and 12th week of gestation. All women on long-term

Figure 3 Management of women with vascular liver disease of child-bearing age. Abbreviation: VLD: vascular liver disease.

Figure 4 Management of anticoagulation in women with vascular liver disease and a desire for pregnancy. Abbreviation: LMWH: Low molecular weight heparin.

anticoagulation with VKA attempting to become pregnant need counseling regarding avoidance of the potential teratogenic effects of VKA and should have a clear plan to switch to LMWH. Current guidelines recommend, based on weak evidence, to perform frequent pregnancy tests and to substitute LMWH once pregnancy is confirmed. Preconception substitution is also an option for women concerned with VKA embryopathy risk and accepting the costs and injections that LMWH imply. Concerning heparin-induced thrombocytopenia (HIT), ACCP guidelines recommend no monitoring of platelet count in pregnancy because the risk in this group of patients is considered to be low.⁶⁸ However, HIT has been reported to occur more frequently in BCS patients upon initiation of anticoagulation with unfractionated heparin.⁶⁹ Other anticoagulants should thus be preferred.

Anticoagulation should be continued in patients for whom long-term treatment was judged indicated. For those without long-term anticoagulation, the decision to initiate it must take into account the severity of previous thrombotic episodes, complications of previous pregnancies, the perceived risk of bleeding and the identified prothrombotic risk factors. This can warrant the use of thrombosis prophylaxis during pregnancy and even more during the postpartum. This topic is addressed by ACCP guidelines.⁶⁷

Peripartum management of anticoagulants should be planned with a multi-disciplinary approach. Practically, it is preferable to avoid therapeutic injection of LMWH 24 h before induction of labor or cesarean delivery.³⁴ Reintroducing anticoagulation is recommended 24 h after the procedure if the obstetrical or surgical risk of bleeding is considered low.⁷⁰ Anticoagulation can usually be resumed earlier after an uneventful vaginal delivery if the thrombotic risk is judged to be very high. Overall, it should be taken into account that on the one hand the risk for venous thromboembolism is highest during the first postpartum weeks, but that on the other hand most reported bleeding events take place in the early postpartum period.^{34,50}

Warfarin use in the postpartum is safe as is not excreted in breast milk.⁶⁶

Prevention of Variceal Bleeding

The most dreaded complication of portal hypertension during pregnancy is variceal hemorrhage. Incidence rates ranging from 0 to 43% have been reported in series of patients with vascular diseases of the liver. This large interval may be explained by various degrees of primary and secondary prophylaxis for variceal bleeding over time. Furthermore, these studies included both patients with disease discovered during pregnancy—and thus not receiving prophylaxis, as well as patients with previously known liver disease—receiving adequate prophylaxis. The

mortality related to variceal hemorrhage reported in pregnant patients with non-cirrhotic portal hypertension (4–13%) was much lower than in pregnant patients with cirrhosis (15–33%).⁷¹ Liver dysfunction in patients with cirrhosis probably accounts for this difference. Concerning fetal outcomes, a series of 50 pregnancies in patients with non-cirrhotic portal hypertension or PVT reported a significant association between variceal hemorrhage and a higher incidence of miscarriages, stillbirths and perinatal deaths.⁵⁴

The eradication of varices prior to conception has a major influence on the occurrence of variceal bleeding. The largest published series described only 3 episodes of variceal hemorrhage out of 95 pregnancies, all in patients without adequate prophylaxis.^{34,50,51} In another series, most hemorrhagic episodes took place in patients in whom diagnosis of liver disease was made during pregnancy, whereas those with preconception screening for esophageal varices had low rates of bleeding.⁵⁴ In women with known vascular liver disorder who want to be pregnant, routine screening for esophageal varices should thus be undertaken. Extrapolating the recommendations for patients with cirrhosis, we propose that the patients at risk for bleeding should receive primary prophylaxis, either with beta-blockers or with endoscopic band ligation.⁷² Beta-blockers are generally considered safe in pregnancy, with the exception of atenolol, which has been associated with fetal growth restriction.⁷³ Nonselective beta-blockers used in portal hypertension, propranolol and nadolol, both carry an FDA category C warning (risk cannot be ruled out),⁷⁴ and have been associated in some reports with hypoglycemia in the newborn.⁷⁵ Their use is however widely accepted and seems safe provided awareness of caregivers and an adapted surveillance of the newborn.

If the vascular liver disorder is diagnosed during pregnancy, authors generally agree on recommending screening for esophageal varices during the second trimester.^{74,76,77} During this period, the expansion of maternal blood volume becomes maximal and the perceived risk of bleeding increases. Some authors propose such a second trimester endoscopic screening in all women with liver disease, including those who have undergone preconception eradication of varices.⁷⁸ This strategy is illustrated in Figure 3.

Management of Variceal Bleeding

It is reasonable to recommend that variceal hemorrhage occurring during pregnancy be managed as in the non-pregnant patient. Decisions are probably best guided by current practice guidelines with some remarks.^{72,79}

Sclerotherapy and variceal banding have both been proven safe in pregnancy.^{80,81} Banding probably remains the preferred technique because of its proven safety in pregnancy, proven superiority and avoidance of injection of sclerosants.^{74,79,82,83}

Concerning pharmacologic adjuncts to endoscopy, terlipressin is labeled category D (evident risk in human studies) by the Food and Drug Administration because of the risk of inducing vasospasm. Octreotide carries a category B label (no risk in animal studies, risk in human unknown). Although some authors mention risks associated with octreotide use,⁷⁴ considerable experience in pregnancy comes from its use in endocrinological diseases such as acromegaly.⁸⁴ Therefore, the potential benefits seem to outweigh the risks. As fluoroquinolones are contraindicated in pregnancy, third-generation cephalosporines are a good option for bacterial infection prophylaxis.

Transjugular intrahepatic portosystemic shunt (TIPSS) placement has proved to be a feasible option in three single-patient case reports of pregnant patients with cirrhosis and refractory variceal bleeding.^{85–87} One of these reports estimated the level of fetal irradiation to be acceptable (5.2 mSv).⁸⁷

Management of Labor and Delivery

Vaginal delivery in women with portal hypertension has been widely considered as potentially dangerous if not contraindicated. Increases in intra-abdominal pressure during the active phase of labor have been thought to increase the risk of variceal rupture. The Valsalva maneuver causes a two to threefold increase in portal pressure.^{88,89} No prospective studies exist that help guide the choice of the delivery mode. Nevertheless, the following observations can be made. First, there are very few reported cases of variceal hemorrhage closely linked to delivery. One report described two cases: a woman with non-cirrhotic portal hypertension bleeding from ectopic varices causing massive hemoperitoneum and death in the hours following vaginal delivery and another in a woman with cryptogenic cirrhosis and massive bleeding from abdominal wall varices after emergent cesarean section.⁷⁷ Second, among recent series of pregnancies in women with vascular disorders of the liver, there were three reported cases of variceal hemorrhage during 95 pregnancies, and none occurred around delivery.^{34,50,51} The theoretical risks of vaginal delivery must then be weighed against those associated with cesarean section. Certain are particular to surgery in patients with portal hypertension: bleeding from direct injury to porto-systemic parietal collaterals and post-operative ascitic decompensation. Others are not specific to liver disease patients but particularly relevant to vascular liver disease patients. In particular, cesarean delivery is a known risk factor for post-partum venous thromboembolism when compared to vaginal delivery.⁹⁰ This further increases the already elevated thrombotic risk of many women with vascular diseases of the liver.

While some investigators propose elective cesarean section for patients with esophageal varices known to be large,⁷⁷ vaginal delivery with adequate analgesia and active assistance in the active phase of labor is currently

recommended by most authors.^{5,54,71,91} Analgesia should probably be provided by a peridural approach or, if impossible, by short-acting narcotics. It is also proposed that the second or active phase of labour be assisted by forceps or ventouse to reduce the parturient's straining efforts.⁹¹ Platelet counts considered safe for delivery are generally over 50 000/ μ L for cesarean section, over 20 000/ μ L for vaginal delivery, over 75 000/ μ L for epidural anesthesia and 50 000/ μ L for spinal anesthesia.^{92,93}

Therefore, vaginal delivery with assisted active phase of labour is probably the best option for pregnant patients with vascular disorders of the liver, with cesarean section being reserved for obstetrical indications.

In the post-partum, the use of estrogen-derived oral contraceptives is contra-indicated as they are associated with an increased risk of BCS^{94,95} and likely of PVT.^{37,95}

Elective termination of pregnancy is a delicate issue that might be discussed in women with at a risk perceived to be too high for the mother and/or the fetus, given high-risk thrombophilia and/or previous major complications of pregnancy.

CONCLUSIONS

Although at heightened risk for both mother and fetus, pregnancy is still feasible for women with vascular disorders of the liver if the liver disease is well controlled. These patients should be managed by a multidisciplinary medical team with experience in such diseases. Although the risk of miscarriage is heightened, a pregnancy reaching 20 weeks of gestation is very likely to end with the birth of a live baby. Strong recommendations concerning anticoagulation cannot be formulated. Nevertheless, the benefit of anticoagulation likely outweighs the hazards in women with high-risk thrombophilia and those with a history of thrombosis causing critical ischemia such as mesenteric vein thrombosis. Anticoagulation invariably implies a risk of bleeding, particularly at the time of delivery. Variceal hemorrhage is a rare complication during pregnancy when adequate prophylaxis has been applied.

As for all women of childbearing age with chronic diseases, best outcomes are probably achieved by careful planning of pregnancy before conception and discussion of birth control options in all women of childbearing age.

CONFLICTS OF INTEREST

All authors have none to declare.

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