Pregnancy outcomes in women with Budd-Chiari syndrome or portal vein thrombosis

A multicentre retrospective cohort study

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Abstract

Objective: to evaluate current practice and outcomes of pregnancy in women previously diagnosed with Budd-Chiari syndrome and/or portal vein thrombosis, with and without concomitant portal hypertension.

Design and setting: multicentre retrospective cohort study between 2008-2021

Population: Women who conceived in the predefined period after the diagnosis of Budd-Chiari syndrome and/or portal vein thrombosis

Methods and main outcome measures: We collected data on diagnosis and clinical features. The primary outcomes were maternal mortality and live birth rate. Secondary outcomes included maternal, neonatal and obstetric complications.

Results: Forty-five women (12 Budd-Chiari syndrome, 33 portal vein thrombosis; 76 pregnancies) were included. Underlying prothrombotic disorders were present in 23 of 45 women (51%). Thirty-eight women (84%) received low-molecular-weight heparin during pregnancy. Of 45 first pregnancies, 11 (24%) ended in pregnancy loss and 34 (76%) resulted in live birth of which 27 at term age (79% of live births and 60% of pregnancies). No maternal deaths were observed, one woman developed pulmonary embolism during pregnancy and two women (4%) had variceal bleeding requiring intervention.

Conclusions: The high number of term live births (79%) and lower than expected risk of pregnancy-related maternal and neonatal morbidity in our cohort suggest that Budd-Chiari syndrome and/or portal vein thrombosis should not be considered as an absolute contra-indication for pregnancy. Individualized, nuanced counselling and a multidisciplinary pregnancy surveillance approach are essential in this patient population.

Tweetable abstract:

Budd-Chiari syndrome and/or portal vein thrombosis should not be considered as an absolute contra-indication for pregnancy.

Key Points

- Budd-Chiari syndrome and portal vein thrombosis are associated with adverse pregnancy outcomes.
- High number of term live births in this multicentre retrospective cohort study.
- No maternal mortality, lower than expected risk of pregnancy-related maternal and neonatal morbidity.
- Individualized, nuanced counselling prior to pregnancy and a multidisciplinary pregnancy surveillance approach are essential in this patient population.

Introduction

Budd-Chiari syndrome and portal vein thrombosis are unusual manifestations of venous thromboembolism. Budd-Chiari syndrome is a rare disorder and current knowledge on its epidemiology, aetiology and prognosis stems mainly from small observational studies [1,2]. It is defined as obstruction of the hepatic venous outflow predominantly caused by thrombosis of the hepatic veins or proximal inferior vena cava. Presence of portal hypertension and comorbidity form the major determinants of patient outcome [3-5]. Underlying prothrombotic disorders, such as myeloproliferative neoplasms, antiphospholipid syndrome and inherited thrombophilia are common in Budd-Chiari syndrome [1,2]. Regardless of underlying disorder, there is an indication for long-term anticoagulant therapy [6-8]. Concurrently, liver-dysfunction-associated coagulopathy, portal hypertension and gastrointestinal varices contribute to an increased bleeding risk in these patients [8].

The prevalence of sex-specific transient risk factors, in particular use of oral contraceptives, is present in up to 40% of patients with Budd-Chiari syndrome [1,4]. Pregnancy as a risk factor could be identified in approximately 13% of Budd-Chiari syndrome patients in the few studies investigating this [9,10]. Women with Budd-Chiari syndrome have a higher incidence of primary infertility and adverse pregnancy outcomes compared with the general population [11]. Treatment of Budd-Chiari syndrome, including a portosystemic shunt or stent placement, may increase the probability of successful conception and pregnancy outcome [11-13]. Oesophageal variceal bleeding is the most feared complication during pregnancy in women with concomitant portal hypertension [14,15].

Portal vein thrombosis, in absence of hepatobiliary malignancy or cirrhosis, may be caused by an underlying prothrombotic state and/or a local inflammatory factor, and can lead to portal hypertension [2,5,7,8]. Conversely, portal vein thrombosis is one of the main complications in patients with non-cirrhotic portal hypertension [15-17]. In a recent multicentre European study, 45 pregnancies in 24 women with portal vein thrombosis were evaluated retrospectively [16]. The risk of pregnancy loss and preterm birth appeared to be increased, but favourable foetal and maternal outcomes were reported in 33 of 36 pregnancies reaching 20 weeks of gestation.

Because uncertainty exists regarding neonatal outcome and maternal morbidity, such as recurrent thrombosis and bleeding, there is no consensus on optimal management strategies throughout pregnancy for women with Budd-Chiari syndrome or portal vein thrombosis. Clinical practice with regard to preconceptional counselling is heterogeneous and some physicians still advise against pregnancy. We evaluated current practice and outcomes of pregnancy in women previously diagnosed with Budd-Chiari syndrome and/or portal vein thrombosis, with and without concomitant portal hypertension.

Methods

Study population and design

We performed a multicentre retrospective cohort study in four academic hospitals (Amsterdam UMC – location Academic Medical Center, Amsterdam; Erasmus University Medical Center, Rotterdam; University Medical Center Groningen, Groningen; Radboud University Medical Center, Nijmegen). The study protocol was approved by the medical ethics committee of the Amsterdam UMC - Academic Medical Center in Amsterdam. Data were extracted from the electronic medical records from January 1st 2008 to January 1st 2021. Cases were identified using CTcue, a search engine designed for unstructured medical data. The search included the *International Classification of Diseases, Tenth Revision* codes as well as text words "Budd-Chiari syndrome", "Budd" or "portal vein thrombosis" or "portal vein" present anywhere in the medical records. Additionally, existing cohorts of known Budd-Chiari syndrome and/or portal vein thrombosis patients in each centre were checked and used to cross-reference cases identified in the search. We manually reviewed the electronic medical record for each case to ensure eligibility. The search was limited to women who were considering to become pregnant, who were counselled regarding pregnancy or who had been pregnant after the diagnosis of Budd-Chiari syndrome and/or portal vein thrombosis. Concomitant presence of portal hypertension (defined as hepatic venous pressure gradient ≥6 mmHg or radiological findings suggesting portal hypertension, defined as splenomegaly, ascites, varices, portosystemic collaterals) was additionally assessed.

All data were retrieved from the electronic patient files. Women with a diagnosis of Budd-Chiari syndrome and/or portal vein thrombosis who were pregnant (confirmed by urine pregnancy test or ultrasound) after this diagnosis in the observational period, were included for analysis in the study. Exclusion criteria were ectopic pregnancy, a history of hepatobiliary malignancy or liver transplantation and pregnancies terminated for non-medical reasons. Approval for study conduct was obtained and eligible patients were contacted. Study outcomes were assessed from conception up to 12 weeks after delivery or 6 weeks after pregnancy loss.

Outcomes

The primary outcomes were pregnancy-related maternal mortality and live birth rate. Secondary maternal outcomes included hypertensive disorders of pregnancy (preeclampsia and pregnancy-induced hypertension [18]), arterial and venous thrombotic events, antepartum and postpartum bleeding events, and complications of pre-existent portal hypertension (oesophageal variceal bleeding, ascites). Secondary neonatal outcomes included gestational age at delivery, birth weight, small for gestational age (birth weight below 10th percentile and subgroup analysis below 3rd percentile [19,20]), Apgar score <7 at 5 minutes, venous pH <7.21, asphyxia and admission to the neonatal intensive care unit (NICU).

Data on anticoagulant therapy and data on obstetric outcomes and complications, such as type and onset of delivery and postpartum haemorrhage were also collected.

Statistical analyses

Descriptive statistics were used to summarize demographic and clinical characteristics. Primary and secondary outcomes were reported for all patients and separately for patients with Budd-Chiari syndrome (including those with concomitant portal vein thrombosis) and portal vein thrombosis. Additionally, we presented the outcomes for all pregnancies and for all first pregnancies, stratified per patient group.

The association between baseline characteristics and first pregnancy outcome, defined as pregnancy loss and any maternal adverse event, was assessed by means of a univariate logistic regression analysis and was expressed as odds ratios with corresponding 95% confidence intervals (95% CI). All statistical analyses were carried out using the *SPSS* package (version 27.0, April 2020).

Results

We identified 134 potentially eligible women with Budd-Chiari syndrome and/or portal vein thrombosis in the predefined study period. Eleven women (8%) were advised against pregnancy and 5 (4%) failed to conceive. One woman unintendedly became pregnant and was advised to terminate the pregnancy as potential risks were considered too high. **Figure 1** provides an overview of the study screening process and reasons for exclusion.

Forty-five included women conceived 76 times after the diagnosis of Budd-Chiari syndrome and/or portal vein thrombosis; 21 patients (46%) conceived only once and 24 patients (53%) conceived twice or more. Patient characteristics were similar in women with Budd-Chiari syndrome and portal vein thrombosis (**Table 1**). Two women had a history of venous thrombosis prior to the diagnosis of Budd-Chiari syndrome or portal vein thrombosis, none of the women had prior arterial thrombosis.

Budd-Chiari syndrome

Twelve women had a previous diagnosis of Budd-Chiari syndrome of whom five (42%) also had portal vein thrombosis. The mean (standard deviation [SD]) age at diagnosis was 23 (4.6) years, while the mean (SD) age at first conception was 31 (4.9) years (**Table 1**). An underlying prothrombotic disorder or oral contraceptive use were the most common risk factors for thrombosis, with more than one risk factor being present in 6 of 12 women. None of the women with Budd-Chiari Syndrome had oesophageal varices at time of pregnancy. Imaging studies were not repeated upon pregnancy confirmation. Three women had received a transjugular intrahepatic portosystemic shunt (TIPS) at time of diagnosis of Budd-Chiari syndrome.

Portal vein thrombosis

Thirty-three women had a previous diagnosis of portal vein thrombosis. The mean (SD) age was 31 (5.0) years with a mean (SD) body mass index (BMI) of 24.8 (4.4) kg/m^2 at first conception (**Table 1**). Antiphospholipid syndrome was present in two women (6%) and secondary to systemic lupus erythematosus in one woman. Seven women (21%) had an inherited thrombophilia and six women (18%) had a myeloproliferative neoplasm. Twenty-six women (77%) had portal hypertension prior to the first conception and nine women (27%) underwent oesophageal variceal ligation prior to pregnancy of whom two were on beta-blockade during pregnancy. Seven women (21%) had a previous pregnancy loss in their medical history, mostly early pregnancy loss.

Anticoagulant therapy

Prior to pregnancy, 19 (42%) women used anticoagulant treatment with vitamin K antagonists (17 of 19) or direct oral anticoagulants (2 of 19). During pregnancy, all 12 women with Budd-Chiari syndrome used anticoagulant treatment and 73% of women with portal vein thrombosis (24 of 33). None of the women used antiplatelet medication prior to pregnancy. At first pregnancy confirmation, 38 of 45 women (84%) either switched to or started on low-molecular-weight heparin; 17 on therapeutic, 17 on prophylactic dose, and in 4 women the dose was unknown. In 7 of 45 (16%) women no anticoagulation was given during pregnancy. Low-molecular-weight heparin was continued throughout pregnancy and in most (30 of 38; 79%) women also in the postpartum period. Standard peripartum management was to stop anticoagulant medication at start of contractions or last dose 24 hours before induction of labour. Anticoagulant therapy was restarted 12-24 hours after birth if postpartum haemostasis was achieved.

Maternal outcome

One woman with Budd-Chiari syndrome was diagnosed with ectopic pregnancy and this pregnancy was excluded from the analyses. No maternal mortality was observed in the 12 women with Budd-Chiari syndrome and none experienced portal hypertension related complications. One woman with pre-existent portal hypertension was diagnosed with oesophageal varices during pregnancy but she did not experience a bleeding event during the first pregnancy. No thrombotic events occurred during the first pregnancy and one woman (9%) experienced antepartum vaginal bleeding (**Table 2**). TIPS remained patent in all three patients.

In 33 women with portal vein thrombosis (first pregnancies), no maternal deaths were observed. Two women (6%) with pre-existent oesophageal varices had a variceal bleeding during pregnancy requiring intervention; one woman, without adequate beta-blocker prophylaxis prior to pregnancy, had a variceal bleeding at 22 weeks' gestation and was temporarily admitted to the

intensive care unit with good maternal and neonatal outcome. The second woman had received adequate band ligation prior to pregnancy but nonetheless experienced variceal bleeding during pregnancy which was quickly controlled by emergent band ligation on the ward (**Table 2**). Four women (12%) were diagnosed with preeclampsia during the first pregnancy.

Presence of portal hypertension (N= 3) or oesophageal varices (N = 2) prior to pregnancy was not significantly associated with adverse maternal outcome in the first pregnancy; OR 0.22 (95% CI 0.03 to 1.66) and OR 1.19 (0.18 to 8.00), respectively *(Table S1*). Three subsequent pregnancies were complicated by placental abruption (10%), all leading to emergency caesarean sections with live birth as outcome. Two women had a thrombotic event during a subsequent pregnancy while on prophylactic dose low-molecular-weight heparin; one woman developed pulmonary embolism and one woman suffered from a transient ischemic attack.

Live birth

The live birth rate in the first pregnancy was 55% (6 of 11) in women with Budd-Chiari syndrome; 66% (4 of 6) in women with Budd-Chiari syndrome only and 40% (2 of 5) in women with both Budd-Chiari syndrome and portal vein thrombosis. Three (60%) pregnancy losses in the first pregnancy occurred before 10 weeks of gestation (3 of 5; 60%); excluding all first trimester losses demonstrated a live birth rate of 75% (6 of 8). We observed one foetal death at 21 weeks gestational age due to an intrauterine infection. One neonate died 12 weeks after a very premature delivery at 24 weeks gestational age. Three of six (50%) neonates had a birth weight below the 10th percentile; none below the 3rd percentile (**Table 3**).

In women with portal vein thrombosis, the live birth rate in the first pregnancy was 82% (28 of 34). Three of six pregnancy losses occurred before 10 weeks of gestation and three were late pregnancy losses (all at 11 gestational weeks); if the first trimester losses were excluded the live birth rate was 90% (28 of 31). Six of thirty-four neonates had a birth weight below the 10th percentile (21%) of whom 2 had a birth weight below the 3rd percentile (2 of 6; 33%) (**Table 3**).

An analysis based on the association between live birth rate and number of pregnancies (one versus two or more pregnancies), did not demonstrate a significant difference in live birth rate between women with one pregnancy and women with two or more pregnancies; 81% versus 71% (OR 0.57; 95% CI 0.14 to 2.31). Maternal factors including age and BMI at conception, underlying prothrombotic disorders or use of anticoagulation in pregnancy were not statistically significant associated with pregnancy loss in the first pregnancy (*Table S2*).

Obstetric outcome

Seventeen women delivered vaginally and 14 women had a caesarean section of which 11 were planned (79%) and three unplanned or emergency caesarean sections (21%). In the majority of planned caesarean sections, the indication was maternal, as the bleeding risk was considered too high to deliver vaginally. Most women with Budd-Chiari syndrome had uncomplicated vaginal deliveries in the first pregnancy (73%). Half of the women with portal vein thrombosis (13 of 26) had vaginal deliveries. The other half (13 of 26) had planned caesarean sections (85%). Twelve neonates were born small for gestational age (24%) of whom three (6%) had a birth weight below the 3rd percentile (**Table 4**).

The median reported amount of postpartum blood loss was 400 mL, ranging from 100 mL to 4000 mL. Of the six women who experienced postpartum bleeding of more than 1000 mL in the first pregnancy, 50% (3 of 6) occurred after vaginal delivery. Interventions included red blood cell transfusion and administration of tranexamic acid. Four of these six women (67%) were on anticoagulant treatment shortly before delivery.

Discussion

Budd-Chiari syndrome and portal vein thrombosis are rare disorders, particularly in women of reproductive age [4,16]. We here report detailed data on management and maternal, neonatal and obstetrical outcomes of pregnancy in this patient population. In our multicentre retrospective cohort study on pregnancy outcomes in 12 women with Budd-Chiari syndrome and 33 with portal vein thrombosis, we observed live birth in 76% of first pregnancies. No maternal mortality was observed and the risk of maternal thrombotic and bleeding events was lower than expected. Pregnancy outcomes did not differ between women with concomitant portal hypertension and those without. Anticoagulation during pregnancy was not associated with an increased risk of pregnancy loss or maternal adverse events.

Underlying prothrombotic conditions were identified in almost all women with Budd-Chiari syndrome and portal vein thrombosis, in line with up to 90% reported in previous studies [4,11,21,22]. Prophylactic or therapeutic doses low-molecular-weight heparin during pregnancy and the postpartum period were given in all the women with Budd Chiari Syndrome and in the majority of women with portal vein thrombosis. Venous thrombosis, most notably pulmonary embolism, remains one of the leading causes of maternal morbidity during pregnancy in general, with an incidence of pregnancy-related venous thromboembolism ranging from 1 to 2 per 1000 deliveries [23,24]. The risk of recurrent venous thromboembolism is 3-to-4 fold higher during a subsequent pregnancy, with an absolute risk estimated up to 10% without thromboprophylaxis [25,26]. A history of thrombosis and thrombophilia are well-recognized factors contributing to the significantly higher risk of venous thromboembolism during pregnancy [27,28]. However, we observed a very low rate of recurrent

thrombosis and bleeding in our cohort, suggesting that the use of anticoagulation in this specific population with often underlying prothrombotic disease is effective and safe in the prevention of pregnancy-related recurrent venous thromboembolism [29].

Although the observed number of term live births was higher than expected based on previous studies, the risk of pregnancy loss was substantial and five patients could not conceive at all despite trying. Both inherited and acquired thrombophilia have been associated with adverse pregnancy outcomes [30]. Subgroup differences between Budd-Chiari syndrome or portal vein thrombosis likely exist, but whether relevant to course and outcome of pregnancy remains unclear. Considering the relatively small study population, further analysis based on etiological factors was deemed not feasible. Although antithrombotic treatment is given to prevent recurrent thrombosis during pregnancy, there may be additional beneficial effects on pregnancy outcome [31-33].

No perinatal mortality was observed and most neonates were born at term age. A birth weight below the 10th percentile was used as a proxy for foetal growth restriction in the absence of information on functional placental markers such as Doppler measurements. Twelve neonates were born small for gestational age (24%) of whom three (6%) had a birth weight below the 3rd percentile. Other placenta-mediated outcomes, such as placental abruption and pre-eclampsia, occurred in 11% of neonates. Although these numbers are small, it is plausible that Budd-Chiari syndrome and portal vein thrombosis are associated with a higher risk of placental insufficiency and associated adverse neonatal outcomes. Hypothetically, similar to reduced maternal cardiac diastolic function, venous return pressure may be higher resulting in poor placentation and thus affect pregnancy outcome [34].

We observed a relatively low rate of variceal bleeding (3%) during pregnancy and only in women with pre-existent oesophageal varices, particularly given that the vast majority of women used anticoagulation during pregnancy (albeit 17/38 in prophylactic dose). Prior studies have suggested variceal bleeding to occur in up to 15% of pregnancies in this population, but results from these small cohort studies are conflicting [16,34,35]. Approximately half of the women in our cohort delivered vaginally. This is in line with two previous studies on pregnancy outcomes in women with Budd-Chiari syndrome, in which 47-70% of women had a caesarean section [12,13]. The mode of delivery did not affect the risk of postpartum bleeding. This is line with more recent cohort studies which suggest that there is no specific need for a caesarean section and a medically assisted vaginal delivery is still the preferred mode [10,12].

In addition to clinical outcomes, we aimed to evaluate practice regarding (pre)pregnancy counselling women with Budd-Chiari syndrome or portal vein thrombosis prior to pregnancy. Of all women with a diagnosis of Budd-Chiari syndrome potentially eligible for study participation, we identified eleven patients who were advised against pregnancy and one patient who was advised to actively terminate pregnancy as the risk of oesophageal bleeding was considered too high. In general, Budd-Chiari syndrome or portal vein thrombosis is not considered a clear contraindication for pregnancy. Treating physicians at all sites opted for a multidisciplinary approach and the individual

patients were carefully counselled prior to pregnancy. These results reflect current clinical practice in four academic centres in The Netherlands and may differ in other countries.

The small sample size, observational and retrospective nature of our study, and heterogeneity in study population are limitations for interpreting our results. These are, however, in line with other retrospective small studies, studies with similar limitations, on pregnancy outcome in this population [12, 13, 16,35,36]. Additionally, selection bias should be considered as some women may have failed to conceive and women with the highest risk of adverse pregnancy outcome may have been negatively counselled and refrained from pregnancy.

However, as counselling may differ in individual cases, both with respect to the message of the treating physician and the reception by the patient, our cohort likely still includes women considered to be high-risk by some. Provided the sparsity of data on this particular topic, the results from our study are relevant for clinical practice and may provide evidence for guidance, particularly with regard to counselling for pregnancy.

The high number of term live births and lower than expected rate of pregnancy-related maternal and foetal morbidity in our small cohort indicate that there is no absolute contra-indication for pregnancy in patients with Budd-Chiari syndrome and/or portal vein thrombosis. A multidisciplinary approach is indispensable to increase the chances of a favourable pregnancy outcome for both mother and child taking into account comorbidities.

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Authorship contributions

H.M.W., E.N.H., S.E.D., S.M. and W.G. participated in all aspects of the study and authored the manuscript. H.M.W., E.N.H and J.R.D. retrieved patient data. All authors interpreted data, reviewed drafts and approved the final draft of the manuscript.

Conflict-of-interest disclosures

H.M.W., E.N.H., S.E.D., J.R.D., S.D.M., S.G., J.J.D., J.L., B.A.H., and W.G. have nothing to disclose.
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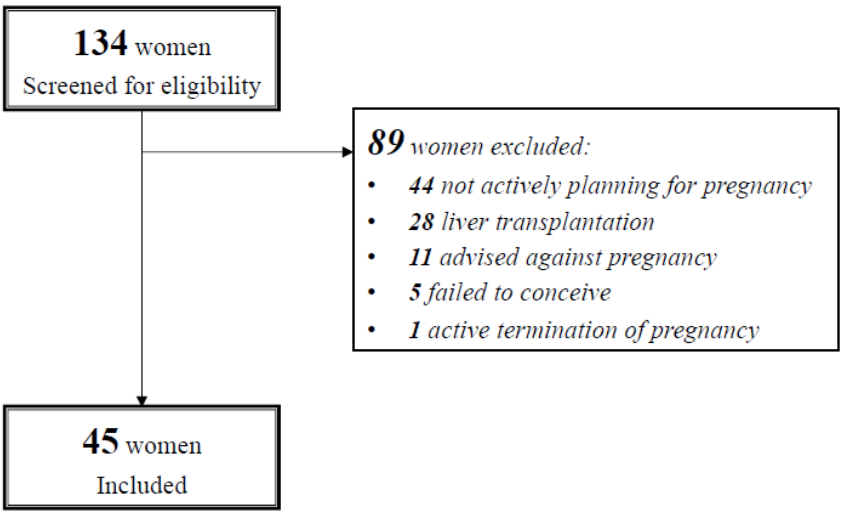

Figure 1. Flowchart of study screening and enrolment

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