CASE REPORT

Portal Vein Thrombosis in Pregnancy with Protein S Deficiency: a Case Report with Literature Review.

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Abstract

Portal vein thrombosis is uncommon in general population and rare in pregnancy. Inherited thrombophilia is a genetic condition that increase the risk of thromboembolic disease especially during pregnancy. The usage of hormone therapy in a thrombophilic patient in pregnancy may further potentiate the occurrence of thromboembolism. We report a case of a pregnant woman who developed an acute portal vein thrombosis due to protein S deficiency and aggravated by the usage hormone therapy during pregnancy. The patient was successfully treated with low molecular weight heparin therapy.

Keywords: *Portal vein thrombosis, pregnancy, protein S deficiency, hormone therapy, low molecular weight heparin.*

Introduction

Pregnancy increases the risk of venous thromboembolism (VTE) 4-5 fold over that in the non-pregnant state.[1,2] Approximately 80% of VTE events during pregnancy are deep vein thrombosis (DVT) and 20% are pulmonary embolism.[3] The prevalence of portal vein thrombosis (PVT) in general population according to the population-based necropsy studies is reported to be 1%, often secondary to cirrhosis or malignancy.[4,5,6] The occurrence of non-cirrhotic PVT is extremely rare.[4] Although pregnancy is a hypercoagulable state and at risk for portal hypertension,[7,8] PVT is still considered rare complication during pregnancy and postpartum period.[9]

Recurrent thromboembolic events occur in 15-25% of pregnancy.[3] Other most important risk factor for VTE in pregnancy is presence of thrombophilia. Thrombophilia defects can be inherited, acquired or complex as a result of environmental influence interacting with the genetic background. The inherited thrombophilia is factor V Leiden, prothrombin G20210A (also called the prothrombin gene mutation) [10], protein S deficiency, protein C deficiency and antithrombin (AT) deficiency.[11] The acquired thrombophilia defects are broadly grouped together as 'antiphospholipid', including lupus anticoagulant (LAC), anti-cardiolipin antibody (ACL) and anti beta2-glycoprotein I. (12)

The use of combined oral contraceptive increases the rate of VTE to 3-5 folds, with an even higher rate in the presence of thrombophilia. [13] Despite evidence that progestin may influence the risk of venous thromboembolism, there are only limited data evaluating the association between progestin-only contraception and thrombosis. Nevertheless, previous meta-analysis and systematic review on the use of progestin-only contraception found that it was not associated with an increased risk of VTE. [14, 15] We report the case of a young woman with previous two miscarriages, developed life-threatening PVT, was found to have protein S deficiency, and was given injections progesterone and dydrogesterone injections at very early in pregnancy without evidence of threatened abortion.

Case report

A 30-year-old Malay lady, gravida 4 with 2 miscarriages, at 12 weeks period of gestation, presented with progressive abdominal pain and vomiting. The symptoms started three days prior to admission to private medical center in February 2021, which started from the right hypochondrium and radiated to the back. Otherwise, there was no fever or per-vaginal bleeding. Her antenatal screening was performed at a private obstetrics and gynaecology outpatient clinic, about eight weeks prior to the referral, at about four weeks of her period of amenorrhoea. She had no vaginal bleeding. Due to history of 2 previous miscarriages, at this juncture, she was started with intramuscular (IM) progesterone weekly, oral dydrogesterone 10 mg daily and oral cardiprin 100 mg daily.

Her first pregnancy in 2018 was uneventful. She had two miscarriages on subsequent pregnancies (2019 and 2020) during the first trimester. There was no symptom related to autoimmune or connective tissue disease. Antiphospholipid antibody screening was negative. Further history revealed that her mother passed away due to bowel ischaemia with history of recurrent miscarriages. It was postulated that the patient's current problem might be related. However, further information on her mother's ailments was not available.

She was afebrile, with mild tachycardia and normal blood pressure. Intravenous pain relief was frequently administered as the pain was intractable. There was tenderness over the epigastric and periumbilical regions with mild ascites. Other systemic examinations were unremarkable.

Laboratory investigations revealed leukocytosis (14.9 x 10^9/L) with neutrophilia (87%), mild anaemia (haemoglobin- 10.9 g/dL) and normal platelet count. C-reactive protein was high (127.2 mg/L, normal < 5 mg/L). Total serum protein (50 g/L) and albumin (27 g/L) were low, other liver enzymes (transaminases and alkaline phosphatase), and renal function were normal. Her coagulation profiles were normal.

Doppler ultrasound abdomen and pelvis at 13 weeks gestation (Figure 1 A and B; Figure 2) revealed presence of extensive echogenic thrombus seen in the right and left portal veins, extending into the main portal vein, portal confluence and distal splenic veins. The superior mesenteric and hepatic veins were patent. The liver and spleen appear normal. Fetal heart was normal. The chest radiograph with abdominal shield and echocardiography were unremarkable. Upper endoscopy showed no evidence of gastro-oesophageal varices.

Anti-phospholipid antibody screening including anti-cardiolipin (aCL) antibody and lupus anticoagulant (LaG) were negative. Protein S level was 46% (normal, 60-124%). Protein C, 91% (normal, 50-136%) and antithrombin III, 80% (normal, 75-125%). Factor V Leiden was not detected. The antinuclear antibody (ANA), anti-double-stranded DNA (dsDNA) and extracted nuclear antigen (ENA) were negative.

Patient was treated as acute PVT in pregnancy precipitated by protein S deficiency and usage of hormone therapy. Subcutaneous injection of low molecular weight heparin (LMWH), Enoxaparin, 60 mg (1mg/kg) twice daily was started with continuation of aspirin 100 mg daily. She was also covered for secondary infection with intravenous (IV) ceftriaxone. She showed a marked response after 24 hours with significant resolution of abdominal symptoms.

Repeat doppler ultrasound (Figure 3) after one month on LMWH treatment showed resolving of portal venous thrombosis, with only strands of residual thrombus seen in main portal vein. Her pregnancy progressed well, and she remained symptom free with subcutaneous enoxaparin. She was referred to an obstetrician in another tertiary hospital for continue care for her pregnancy and delivery. She was successfully delivered via lower section caesarean section (LSCS) without complications.

Discussion

Pregnancy is a pro-thrombotic state, which increases the risk of venous thromboembolism (VTE) 4-5-fold over that in the non-pregnant state. [1,2] During pregnancy, the concentrations of the clotting factors are increased, resulting in hypercoagulable state, which may increase the risk of thrombosis. Moreover, pregnancy combined with either heritable or acquired forms of thrombophilia constitutes a cumulative risk of thrombosis [3]. The usage of hormonal therapy further increases the risk of thrombosis in this patient.

Protein S is a vitamin K dependent glycoprotein that is synthesized within the liver and endothelial cells. In circulation, it exists in two forms of which approximately 60% is bound to C4b-binding protein (C4bBP) and 40% in free form. It acts as a cofactor to facilitate the action of activated protein C on factors Va and VIIa. Only free protein S has anticoagulant function. Results from MEGA case-control study by Pintao *et al*. found that only very low level of free protein S (ie: < 0.10^{th} percentile or <33 U/dL), but not the total protein S were associated with increased risk for venous thrombosis. Very low level of total protein S were not able to identify subject at risk for venous thrombosis in population-based study. This concurred with other studies, in which free protein S level was a better indicator of venous thrombosis than total protein S. [16]

Protein S deficiency is a rare inherited thrombophilia that is caused by a variation in the PROS1 gene with autosomal dominant inheritance. Its prevalence is unknown, and the diagnosis is difficult. Protein S deficiency may be acquired, and its concentration is reduced in pregnancy, kidney disease, and in women using contraceptive pills. Around 3% of patient presenting with VTE are found to be protein S deficient. [17]) Studies suggest that the risk of pregnancy associated VTE in asymptomatic patients with protein S deficiency is low. Gerhardt et al. reported, in the absence of other major risk factors for VTE, the risk of thromboembolism in protein S deficiency is around 0.7% at age of less than 35 years and 1% for those more than 35 years. [18] The risk is higher in women with inherited thrombophilia plus a positive personal or family history of thrombosis.

Combined oral hormone therapy containing oestrogen and progestin is well known to be associated with increased risk of both arterial and venous thrombosis. The prothrombotic effects are mainly related to exposure and the dosage of oestrogen, whereas progestin seems to counter the prothrombotic effect of oestrogen. Effect of hormone therapy will cause increase in marker of activated coagulation, reduction in coagulation inhibitors, and acquired activated protein C resistance. The most important changes occurred with coagulation inhibitors. Antithrombin and protein C decreased by nearly 10%, tissue factor pathway inhibitor (TFPI) activity reduced by 15% and TPFI free antigen reduced by almost 30%. The strong effect of hormone therapy on TFPI has also been demonstrated in women taking oral contraceptive and this effect may be an important mechanism for thrombotic risk in this group. [19]

Dydrogesterone is a progestin-only pill medicine which is used in a variety of indications, including prevention of recurrent miscarriage. Nevertheless, vaginal micronized progesterone has been recommended as per guideline to woman with confirmed intrauterine pregnancy, if presented with vaginal bleeding and have previous miscarriages. [20] Hence, inappropriate use of these OCP may cause untoward complications. The relative risk of thrombosis in combined oral contraceptive pills is 3-5-fold, whereas the absolute risk for healthy individual on this therapy is low. The risk of VTE in a person taking contraceptive pills is even higher in the presence of associated risk such as thrombophilia. [10, 21] Most progestin-only pills do not increase the risk of VTE; however, injection form may contain a higher concentration of progestin and increase the risk of VTE to two to four-fold. Previous studies showed that progestin-only pills are relatively safe. [22]

Two most common sites of VTE in pregnancy are deep vein thrombosis and pulmonary embolism. 15-20% of thromboembolic events in pregnancy are recurrent. The rate of recurrent VTE in women who did not receive anticoagulation therapy has been reported to range from 2.4% to 12% as compared to women who were on anticoagulation therapy (0 to 2.4%). (3)

Portal Vein Thrombosis (PVT) is a rare disorder and PVT complicating pregnancy is rarer. In one of the multicentre studies, the incidence and prevalence of PVT were 0.7 per 100000 inhabitants per year. [5,6] Underlying liver pathology, infection and surgical intervention are the most common predisposing factors. Systemic factors such as an inherited or acquired thrombophilia and primary myeloproliferative disorders also contribute to the occurrence of PVT. Three main group of the causes of PVT are malignant thrombosis, cirrhotic PVT, and non-malignant, non-cirrhotic PVT.[5, 6]

Acute PVT may present with fever, abdominal pain, and new onset of ascites, whereas chronic PVT usually present with hematemesis, splenomegaly, and ascites. Acute and complete thrombosis is usually associated with intestinal congestion and occasionally with non-

sanguineous diarrhoea. One of the complications is intestinal infarction with mortality of 20-60%. Among other complications of PVT are portal hypertension, thrombocytopenia, and variceal bleeding. Pregnant women are at high risk of variceal bleeding which may lead to maternal morbidity and mortality. [9]. Table 1 showed reported cases of PVT in pregnancy and its' clinical manifestation. The main clinical manifestations are right upper quadrant pain, back pain, and fever.

Anticoagulant therapy is still the main treatment for VTE. Table 1 showed few other reported cases of acute and chronic PVT in pregnancy. Most cases showed favourable outcome with treatment with anticoagulant therapy, except for case reported by Savoia F *et al*. pregnancy was electively terminated at week 15. This patient responded well to LMWH. Her symptom and thrombus size documented from repeat doppler ultrasound almost resolved after one-month treatment.[26].

A multicentric European study by Hoekstra *et al*. showed favourable outcomes in 64% of pregnancies reaching 20 weeks of gestational period in pregnant women with chronic PVT. Miscarriage and preterm birth happened in 38%. Thrombocytosis appear to increase the risk of unfavourable outcome. The study concluded that pregnancy should not be contraindicated in stable PVT patients. [23]

Duplex or colour doppler ultrasound is a non-invasive procedure which can be used for early recognition of PVT in a setting of unexplained acute abdominal pain, especially in pregnancy. In this case, CT scan was not performed in view of higher risk of radiation exposure to pregnant lady as well diagnosis was already established through ultrasound. This modality is also relatively cheap and proven to be a reliable tool for monitoring the size of thrombus.

Conclusion

Portal vein thrombosis is rare in pregnancy and can lead to life threatening complication. Thrombophilia screening in patient with PVT is important as it help to determine the unpredicted risk of developing complications. The choice of oral contraceptives is daunting and challenging. Nevertheless, the available and accessible guideline may help in managing intricate cases. Detail history, a multidisciplinary approach, and prompt treatment with anticoagulant therapy are the keys to a successful outcome.

Conflict of interest

The authors declare no conflict of interest.

Statement of Informed Consent

Informed consent was obtained from patient.

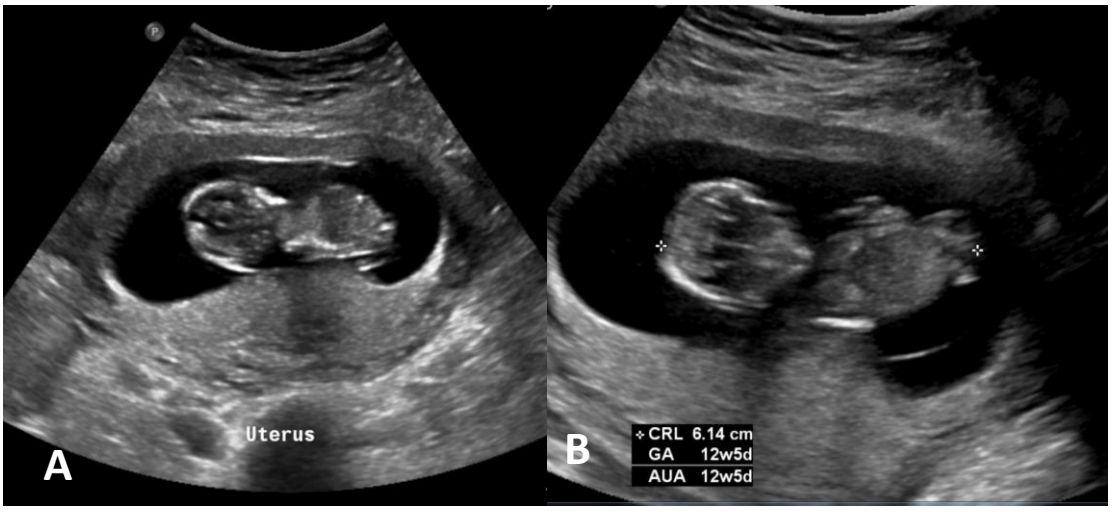

Figure 1 A and B. Ultrasonography showing gravid uterus with singleton. Fetal heart was present.

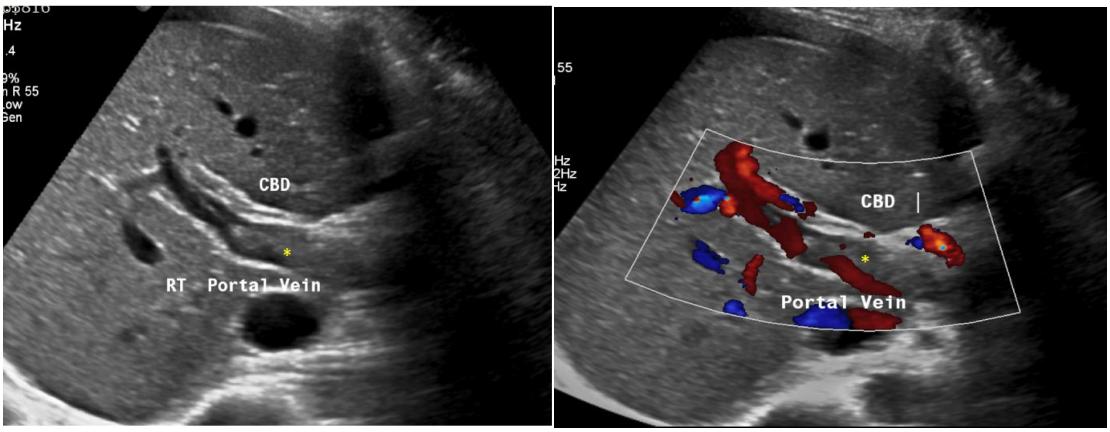

Figure 2. First abdominal ultrasound, showed extensive echogenic thrombus (*) in the right portal vein (left), almost occluded the lumen and causing barely detectable blood flow on colour doppler (right)

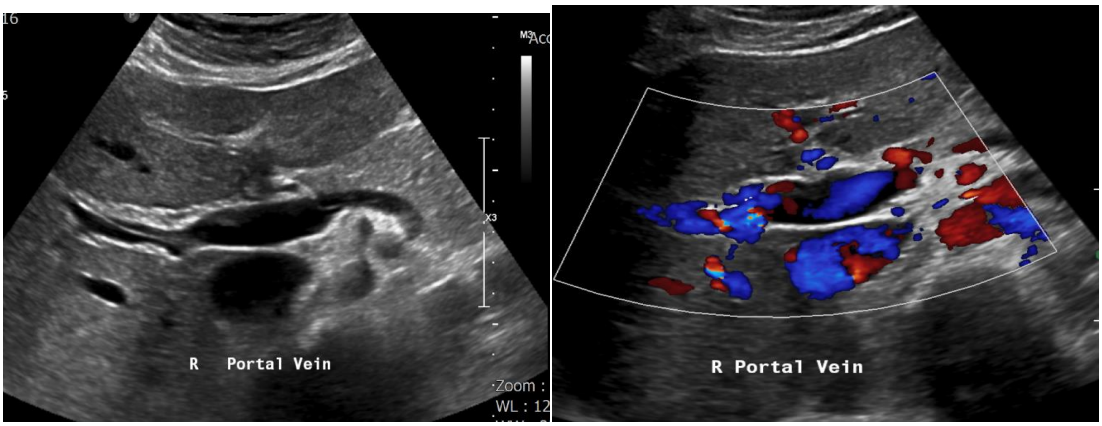

Figure 3. Repeat doppler ultrasound after 1 month of anticoagulant therapy, showed resolving of thrombus in the right portal vein and only seen minimal strands of remaining thrombus. Blood flow to this area improved as shown by colour doppler (left)

References

1. Pomp ER, Lenselink AM, Rosendaal FR, Doggen CJ. Pregnancy, the postpartum period and prothrombotic defects: risk of venous thrombosis in the MEGA study. J Thromb Haemost .2008 Apr; 6(4): 632-7
2. Heit JA, Kobberig CE, James AH, Petterson TM, Bailey KR, Melton LJ 3rd. Trends in the incidence of venous thromboembolism during pregnancy or postpartum a 30-year population-based study. Ann Intern Med. 2005 Nov 15; 143 (10): 697-706

3. James AH. Venous thromboembolism in pregnancy. Arterioscler Thromb Vasc Biol. 2009 Mar; 29 (3): 326-331
4. Yogesh KC, Vijay B. Portal vein thrombosis. J Clin Exp Hepatol. 2015 Mar; 5(1):22-40
5. Ogren M, Bergqvist D, Bjorck M, Acosta S, Eriksson H, Sternby NH. Portal vein thrombosis: Prevalence, patient characteristics and lifetime risk: A population study based on 23796 consecutive autopsies. World J Gastroenterol. 2006 April 7; 12 (13): 2115-2119
6. Rajani R, Bjornsson E, Bergquist A, Danielsson A, Gustavsson A, Grip O, et al. The epidemiology and clinical features of portal vein thrombosis: a multicentre study. Aliment Pharmacol Ther. 2010 Nov; 32(9): 1154–1162
7. Battinelli EM, Marshall A, Connors JM. The role of thrombophilia in pregnancy. Thrombosis. 2013 Dec 18; 2013(10): 1-9. doi.org/10.1155/2013/516420
8. Aggarwal N, Negi N, Aggarwal A, Bodh V, Dhiman RK. Pregnancy with portal hypertension. J Clin Exp Hepatol. 2014 Jun; 4(2): 163–171
9. Dasari P, Balusamy S. Portal vein thrombosis during pregnancy. BMJ Case Rep. 2013 May 27; 2013: bcr2012008325. Available from: doi:10.1136/bcr-2012-008325
10. Padda J, Khalid K, Mohan A, Pokhriyal S, Batra N, Hitawala G, Cooper AC, Jean-Charles G. Factor V Leiden G1691A and Prothrombin Gene G20210A Mutations on Pregnancy Outcome. Cureus. 2021 Aug 15;13(8): e17185. doi: 10.7759/cureus.17185
11. De Stefano V, Finazzi G, Mannucci PM. Inherited thrombophilia: Pathogenesis, clinical syndromes, and management [see comments]. Blood. 1996;87(9):3531–44.
12. Armstrong EM, Bellone JM, Hornsby LB, Treadway S, Phillippe HM. Acquired Thrombophilia. J Pharm Pract. 2014 Jun;27(3):234-42. doi: 10.1177/0897190014530424.
13. Solymoss S. Risk of venous thromboembolism with oral contraceptives. CMAJ. 2011 Dec 13; 183(18): E1278-E1279
14. Mantha S, Karp R, Raghavan V, Terrin N, Bauer KA, Zwicker JI et at. Assessing the risk of thromboembolic events in women taking progestin-only contraception: a meta-analysis BMJ 2012; 345: e4944 doi:10.1136/bmj. e4944
15. Glisic M, Shahzad S, Tsoli S, et al. Association between progestin-only contraceptive use and cardiometabolic outcomes: A systematic review and meta-analysis. European Journal of Preventive Cardiology. 2018;25(10):1042-1052. doi:10.1177/2047487318774847
16. Pintao MC, Ribeiro DD, Bezemer ID, Garcia AA, de Visser MCH, Doggen CJM, et al. Protein S levels and the risk of venous thrombosis: results from the MEGA case-control study. Blood. 2013; 122(18): 3210-3219
17. Walker ID. Thrombophilia in pregnancy. J Clin Pathol. 2000 Aug; 53(8): 573-580
18. Gerhardt A, Scharf RE, Greer IA, Zotz RB. Hereditary risk factors of probability of venous thromboembolism during pregnancy and puerperium. Blood. 2016 Nov 10; 128(19): 2343-2349
19. Sandset PM, Høibraaten E, Eilertsen AL, Dahm A. Mechanisms of thrombosis related to hormone therapy. Thromb Res. 2009;123 Suppl 2: S70-3. doi: 10.1016/S0049-3848(09)70015-5.
20. Ectopic pregnancy and miscarriage: diagnosis and initial management. National Institute for Health and Care Excellence (NICE) – 2019. http://www.nice.org.uk/guidance/ng126
21. Trenor CC, Chung RJ, Michelson AD, Neufeld EJ, Gordon CM, Laufer MR, et al. Hormonal contraception and thrombosis risk: A multidisciplinary approach. Pediatrics. 2011 Feb; 127(2): 347-357
22. James AH. Pregnancy, Contraception and Venous Thromboembolism (deep vein thrombosis and pulmonary embolism). Vasc Med. 2017 Apr; 22 (2): 166-169

23. Hoekstra J, Seijo S, Rautou PE, Ducarme G, Boudaoud L, Luton D, et al. Pregnancy in women with portal vein thrombosis: Results of a multicentric European study on maternal and fetal management and outcome. JHepatol. 2012; 57:1214–1219.
24. Anbazhagan A, Harper A, Bailie C. Portal vein thrombosis in pregnancy-a case series. ADC Fetal & Neonatal. 2010 Nov 16: 95: Fa60
25. Jouini S, Fakunle YM, Azazy A. Portal vein thrombosis in pregnancy: a case report and review of the literature. Ann Saudi Med. 2002 May; Vol 22 (3-4): 227-9
26. Savoia F, Ferrara C, Sansone A, Bifulco G, Nappi C, Di Carlo C. Portal cavernoma during pregnancy. Case Rep Obstet Gynaecol. 2013; 2013: 396083. doi.org/10.1155/2013/396083
27. Ustuner I, Akdogan RA, Guvendag Guvon ES, Sahin KS, Senturk S, Akdogan E, et al. Pregnancy in the setting of asymptomatic non-cirrhotic chronic portal vein thrombosis complicated by pre-eclamsia. Case Rep Obstet Gynaecol. 2013; 2013: 984271. doi.org/10.1155/2013/984271

Table 1. Portal vein thrombosis in pregnancy case reports.

Study	Country	age	No. of pregnancy/ies	Gestational week	Clinical features/complications	Aetiology	Imaging	Treatment
Anbazhagan A *et al.*(24)	UK	ND	ND	38 32 31	Portal hypertension Hypersplenism Thrombocytopenia Esophageal varices Ascites	-Idiopathic -Protein S deficiency & Factor V Leiden mutation -Chronic PVT	ND	Bethamethasone, Propranolol, Spironolactone, LMWH Esophageal banding Uneventful outcome
Dasari P *et al.* (9)	India	22	Primigravida	20	Hypersplenism	Idiopathic	Portal vein showed increased periportal echogenicity and multiple tubular hypoechoic to anechoic structures noted in portal lumen and portal vein cavernoma	Unfractionated heparin warfarin
Jouini S *et al.* (25)	Saudi Arabia	26	G9P5+ 3 abortions	7	RUQ pain, fever of 38ºC	Idiopathic	Well-defined homogenous hyperechoic oval-shaped formation in the splenomesenteric confluence and right branch of the portal vein	IV and SC heparin Warfarin, dydrogesterone (Dydrogesterone^{R}) Uneventful outcome
Savoia F *et al.* (26)	Italy	32	G3P2	11	Back pain, fever	Idiopathic	Cavernomatous transformation of the portal venous system in the hilar region of the liver extended to the intrahepatic system.	LMWH Termination of pregnancy at week 15
Üstüner I *et al.* (27)	Turkey	36	G4P1	38	RUQ pain, uterine cramps, headache, high BP. *Post CS*: thrombocytopenia, anemia, lymphopenia, abdominal pain, ascites, fever, esophageal varices, portal gastropathy	Idiopathic	Chronic portal vein thrombosis and cavernous transformation	LMWH Propranolol Uneventful pregnancy
Ainon MM *et al*	Malaysia	30	G4P1+2	12	RUQ pain, back pain	-Protein S deficiency -Hormone therapy	Thrombus in the right and left portal veins, extending into the main portal vein, portal confluence and distal splenic veins. Patent superior mesenteric and hepatic veins.	LMWH

Abbreviation: UK, United Kingdom; ND, no data; PVT, portal vein thrombosis; G, gravida; P, parity; LMWH, low molecular weight heparin; RUQ, right upper quadrant; BP, blood pressure; CS, caesarian section; IV, intravenous; SC, subcutaneous.