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ANTEPARTUM CEREBRAL VENOUS THROMBOSIS (APCVT): OUTCOMES IN A HOSPITAL-BASED COHORT FROM INDIA

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ABSTRACT

Background: Cerebral venous sinus thrombosis (CVST) is an uncommon but important cause of stroke in young women due to acquired or inherited hypercoagulable state. CVST occurring during antenatal period can affect foeto-maternal outcome. Data focusing specifically on antepartum CVST remain limited.

Objectives: To evaluate clinical profile, radiological pattern, treatment, and long-term outcome of antepartum CVST.

Methods: Pregnant women with radiologically confirmed antepartum CVST were included from the teaching hospital based CVST registry. Information collected included demographic profile, gravida status, duration of pregnancy, hospital stay, clinical and laboratory data, neuroimaging findings, treatment details, outcome at discharge and follow-up.

Results: Fifteen women with antepartum CVST (mean 25.87; SD 3.7 years) were included from the CVST registry. CVST onset was during first trimester in majority (86.67%). Presenting symptoms included headache (93.33%), seizures (73.33%) focal neurological deficits (66.66%), and impaired consciousness (40.0%). Fourteen patients had venous infarction (superficial venous territory 12, deep venous territory 1, combined 1). Five patients including the two women who required decompressive craniectomy successfully continued the pregnancy on heparin therapy followed by warfarin. Eight women opted for medical termination of pregnancy. Two patients succumbed and excellent outcome was observed in 6 patients at discharge, 10 patients at three months and 11 patients at last follow-up.

Conclusion: Antepartum CVST was most common during first trimester in our cohort with excellent long-term outcome in most. Majority of the women opted for termination of pregnancy due to concerns of disease outcome, need for prolonged parenteral anticoagulation. Decompressive craniectomy had beneficial effect.

KEYWORDS: Cerebral venous sinus thrombosis, Antepartum, Anticoagulation, Decompressive craniectomy

INTRODUCTION

Physiological changes during pregnancy resulting in increased levels of procoagulant factors, reduced fibrinolytic activity and acquired resistance to activated protein C can result in hypercoagulable state predisposing them for cerebral venous sinus thrombosis.[1,2,3,4] Pregnancy related cerebral venous thrombosis can be associated with underlying inherited or acquired thrombophilia. Other predisposing factors are hyperhomocysteinemia, dehydration, infections, anaemia, suboptimal peripartum care especially in developing countries.[5] The incidence of pregnancy related CVST ranges from 1 to 4 / 10,000 deliveries in developed countries and 40 to 50/10,000 in developing countries[6] constituting approximately 9.8 to 20% of CVST cases globally.[7,8,9,10,11] Pregnancy related CVST is more frequent during third trimester and early postpartum period.[2] Existing literature on pregnancy-related CVST include both the antepartum and postpartum states.[6,12,13] Antepartum CVST is a high-risk pregnancy posing major therapeutic challenge due to occurrence of raised intracranial pressure, focal neurological deficits, seizures, antiseizure medications and need for prolonged parenteral anticoagulation.[2] Studies solely focussing on antepartum CVST are sparse. Given the potential for maternal morbidity and adverse foetal outcome early recognition and timely management of CVST is crucial. This study aims to evaluate the clinical profile, management strategies, and fetomaternal outcome of antepartum CVST.

MATERIALS AND METHODS

Women with antepartum CVST were included after institutional ethical clearance from the teaching hospital-based CVST registry maintained from 2001. The diagnosis of CVST was confirmed using cerebral magnetic resonance imaging (MRI) and magnetic resonance venography (MRV).[2] Demographic data, gravida status, duration of pregnancy at onset of CVST, clinical symptomatology including features of raised intracranial pressure, seizures, focal neurological deficits and level of sensorium were collected. Venous sinus involvement, cerebral oedema, location and pattern of venous infarction were gathered.

These women received standard of care along with parenteral anticoagulation, antiedema therapy and antiseizure medications. Continuation of pregnancy was at the discretion of the patient and/or caregivers. Patients opting for continuation of pregnancy

were treated with parenteral anticoagulation till delivery and subsequently switched to oral anticoagulation. Patients opting for termination of pregnancy underwent medical termination with subsequent oral anticoagulation. Two patients with large venous infarctions resulting in altered consciousness or impending herniation underwent emergency decompressive craniectomy. Outcome was measured at discharge, one month, three months and last follow-up using modified Rankin score (mRS) categorised as excellent (mRS 0 to 1), good (mRS $\leq$2) or poor (mRS 3 or higher). Statistical analysis was performed using Statistical Package for Social Sciences (SPSS) 16.0 window software (SPSS Inc Chicago, Illinois (IL) 60606 USA). Continuous variables were presented in titre of mean and ± SD.

RESULTS

Among 1012 patients with radiologically confirmed CVST, 346 were women, of whom 132 (13.04%) had pregnancy related CVST. Antepartum CVST occurred in 17 patients, of whom two were excluded due to inadequate data. In the final evaluation, 15 antepartum CVST patients were included.(Figure 1) Eleven of these 15 antepartum CVST patients were primigravida, second pregnancy in three patients, and third pregnancy in two patient. The maternal age ranged from 21 to 34 years (25.87 ± 3.7; median 26). The symptom duration ranged from one to 30 days (11± 7.69 days) and the mean hospital stay was 10.4 days (SD 5.49; range 5 to 23).

Symptoms of raised intracranial pressure with headache and vomiting was the most common presentation (n=14, 93.33%), followed by seizures (n=11, 73.33%) and focal neurological deficits (n=10, 66.66%). One patient presented with status epilepticus and four with serial seizures. At admission 40% of patients had impaired consciousness (three with GCS 9 - 12 and three with GCS $\leq$ 8). Mean haemoglobin level was 10.84 gm/dl (SD 2.31) and six women had anaemia (severe in one, moderate in three and mild in two patients). Serum homocysteine levels were normal in the nine patients tested and one patient had vitamin B12 deficiency.

All 15 patients had superficial venous sinus thrombosis, and two women had additional deep venous sinus thrombosis. Eleven patients (73.33%) had multiple sinus involvement and four had single sinus involvement. Superior sagittal sinus was the most frequently involved (n=11, 73.33%), followed by the transverse and sigmoid sinuses (n=9, 60.00%), cortical veins (n=4; 26.6%) and internal cerebral veins (n=2; 13.33%). Fourteen patients had infarctions in superficial venous territory (93.33%) and two of them had additional thalamic infarction. Left sided venous infarction was present in eight patients, and right side in four and bilateral in one. Eight patients had unilobar infarctions and five had multilobar infarction

Patients with cortical venous infarctions (n=14, 93.33%) received antiseizure medications (ASMs), including prophylactic therapy in three patients. Eleven women received single ASM therapy (78.57%), while the remaining three women (21.43%) required multiple ASMs due to seizure recurrence. Levetiracetam was the most frequently used ASM.

All 15 patients received parenteral anticoagulation with dose adjusted unfractionated heparin infusions or low molecular weight heparin. Eight patients opted medical termination of pregnancy due to apprehensions of prolonged parenteral anticoagulation, bleeding manifestations and effects on foeto-maternal outcomes. These 8 patients were transitioned to vitamin K antagonist therapy after bridging with parenteral anticoagulation. Five patients who continued their pregnancies till delivery received subcutaneous unfractionated heparin therapy (n=3) or low-molecular-weight heparin (n=2). Decompressive craniectomy was required in two patients with large haemorrhagic venous infarction (13.33%) for impending herniation with decline in consciousness who subsequently continued pregnancy with heparin therapy. Four patients underwent caesarean section, and one had normal delivery. Subsequently, these five women were switched over to warfarin and none had any foetal abnormalities.

Two patients with large infarctions succumbed to the illness, one during admission and another soon after discharge. Outcome data was not available for two patients who were lost for follow-up after discharge. Follow-up for the remaining 11 patients ranged from 26 to 216 months (102.9 ± 54.5 months). Excellent outcome (mRS $\leq$ 1) was observed in 6 patients at discharge, 10 patients at three months and 11 patients at last follow-up. Good outcome (mRS $\leq$ 2) was seen in nine patients at discharge, and in 10 patients at three months, and in 11 patients at last follow-up.(Table 1)

Antiseizure medication could be gradually withdrawn in seven patients. Three required continuation of single ASM and one patient required two ASM in view of recurrent focal seizures. During follow up, four patients were evaluated for thrombophilia. One among them had protein C deficiency developed deep venous thrombosis and pulmonary thromboembolism during follow-up requiring reinitiation of long-term oral anticoagulation. Her maternal aunt too had history of postpartum CVST. Another patient had elevated antithrombin III levels. Two patients subsequently had successful pregnancy. Recurrent CVST occurred during postpartum period in one patient.

DISCUSSION

Antepartum CVST is a high-risk pregnancy due to the disease burden and poses therapeutic challenge. Pregnancy related CVST in the published literature is frequent during later trimester of pregnancy and postpartum period. Incidence of pregnancy related CVST is 9.8-20%.[7,8,9,10,11] There is a decline in pregnancy related CVST globally due to better health care and early diagnosis. CVST registry from our institute has 1012 patients from 2001 to 2025, among whom males were predominant (666 vs 346 patients) with male: female ratio of 1.92:1. Pregnancy related CVST accounted for 13.04% (132 patients) of the entire cohort and antepartum CVST accounted for 1.68% (17 patients). Antepartum CVST in first trimester is rare and may be due to hyperemesis gravidarum, anaemia and inherited thrombophilia, etc.[3,6] During later trimester and postpartum period physiological changes which include altered haematocrit, protein S deficiency and acquired protein C resistance, predispose

these women for CVST.[3,4] Majority of the studies include CVST during antepartum and postpartum period.[6,12,13,14] As it is a therapeutic challenge, our study focused solely on antepartum related CVST.

Raised intracranial tension due to cerebral edema and malignant haemorrhagic venous infarction may be life threatening.[15] Fourteen patients in our antepartum CVST cohort had symptoms of raised intracranial tension as the commonest presentation requiring antiedema therapy. Antiedema therapy can also be harmful to the foetus and mother causing oligohydramnios, dehydration and nephrotoxicity.[16] Two of our patients required decompressive craniectomy due to malignant cerebral edema and both had good outcomes. Decompressive craniectomy is a life-saving measure with proven benefit.[17,18] Acute symptomatic seizures are common due to parenchymal injury because of CVST. Eleven patients in our cohort had symptomatic seizures, among whom one developed status epilepticus. Seizures during pregnancy can lead to poor foetal outcomes resulting in hypoxia, lactic acidosis, foetal distress, bradycardia, preterm birth and low birth weight.[19] Antiseizure medications during first trimester of pregnancy can cause major congenital malformations and poor cognitive outcomes.[20] Seizures can also cause increased maternal mortality due to injuries and SUDEP.[19] Diligent management of symptomatic seizures during pregnancy is thus crucial. These patients also require frequent drug monitoring due to altered drug levels during pregnancy.[21] Focal deficits in CVST are due to cerebral infarction. Superior sagittal sinus is the commonest sinus involved in CVST and deep venous system involvement is less frequently involved.[9,22] In our study, superficial venous system was involved in all fifteen patients and deep venous system was involved in only two patients. Iron deficiency anaemia is one of the common causes for CVST in developing countries requiring correction to prevent progression of the disease process.[23] Six women with anaemia in the present study were managed with supplements. Good antepartum care and nutritional supplements can have a beneficial effect. Hyperhomocysteinemia is another common cause of CVST.[24] Nine patients in our study group were evaluated and had normal homocysteine levels. Inherited thrombophilia occurs in about 15% during pregnancy.[25] Four patients were evaluated for inherited thrombophilia during follow up and two among them had thrombophilia with protein C deficiency in one patient and elevated antithrombin III in another patient. Parenteral anticoagulation is the mainstay of treatment in antepartum CVST as oral anticoagulants are contraindicated due to their deleterious effect on the foetus.[2] Eight patients in our study group were concerned about the need and adverse effects of prolonged anticoagulation, disease burden, poor foeto-maternal outcome and hence opted for medical termination of pregnancy. Five patients who continued pregnancy, were treated with parenteral anticoagulants and were transitioned to oral anticoagulants after delivery. All five patients who continued pregnancy had good foeto-maternal outcomes. Foeto-maternal outcomes maybe better justified in studies with larger sample sizes. Recent medical advances have reduced pregnancy related CVST mortality to under 15%, with in-hospital deaths at 6% and 30-day rates falling to 4% or less.[1] In the present study only two patients (13.33%) succumbed to the illness. Follow up period ranged from 25 to 216 months (mean 103 months). Short-term functional outcomes at discharge were mixed, with 40% experiencing poor outcomes (mRS > 2), 20% good outcomes (mRS = 2), and 40% excellent outcomes (mRS 0-1). Suboptimal discharge scores were closely tied to large initial infarct volumes, multiple sinus involvement, low presentation GCS, and severe anaemia. Eleven women continued to improve with good mRS scores at long term follow up. This finding aligns with available data demonstrating improved survival in pregnancy-related CVST due to early neuroimaging, timely anticoagulation, and aggressive critical care or surgical intervention.[5,6,17,25,26] This study demonstrates higher occurrence of CVST during first trimester, making it a high-risk pregnancy. This study highlights the nuances of management of antepartum CVST. Despite the high short-term morbidity and the profound therapeutic dilemmas, it underscores early diagnosis, targeted seizure control, prompt anticoagulation, and timely neurosurgical intervention to achieve good foetal outcome and long-term maternal functional outcomes. Long term follow up of our cohort is the strength of the study, however a smaller sample size and single centre study is the limitation. There is a need to allay the fear these women have regarding continuation of pregnancy, break the myths about anticoagulation and foeto-maternal outcomes.

CONCLUSION

Antepartum CVST poses therapeutic challenges and requires good multi-speciality care and counselling in order to achieve good foeto-maternal outcome. The apprehensions towards continuing pregnancy with parenteral anticoagulation among these women need to be addressed as majority of our patients chose medical termination. Decompressive craniectomy proved beneficial and lifesaving.

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Mrs Score	discharge n (%)	1 month n (%)	3 monthn (%)	Last follow up n (%)
0	4 (26.66%)	7 (46.66%)	8 (53.33%)	11 (73.33%)
1	2 (13.33%)	2 (13.33%)	2 (13.33%)	0

2	3 (20%)	1 (6.66%)	0	0
3	3 (20%)	1 (6.66%)	1 (6.66%)	0
4	1 (6.66%)	0	0	0
5	1 (6.66%)	0	0	0
6	1 (6.66%)	2 (13.33%)	2 (13.33%)	2 (13.33%)
Unknown	0	2 (13.33%)	2 (13.33%)	2 (13.33%)

Table 1. Functional outcome using mRS at discharge, 1 month, 3 months and last follow up in the antepartum CVST patients. Two patients were lost follow-up after discharge.

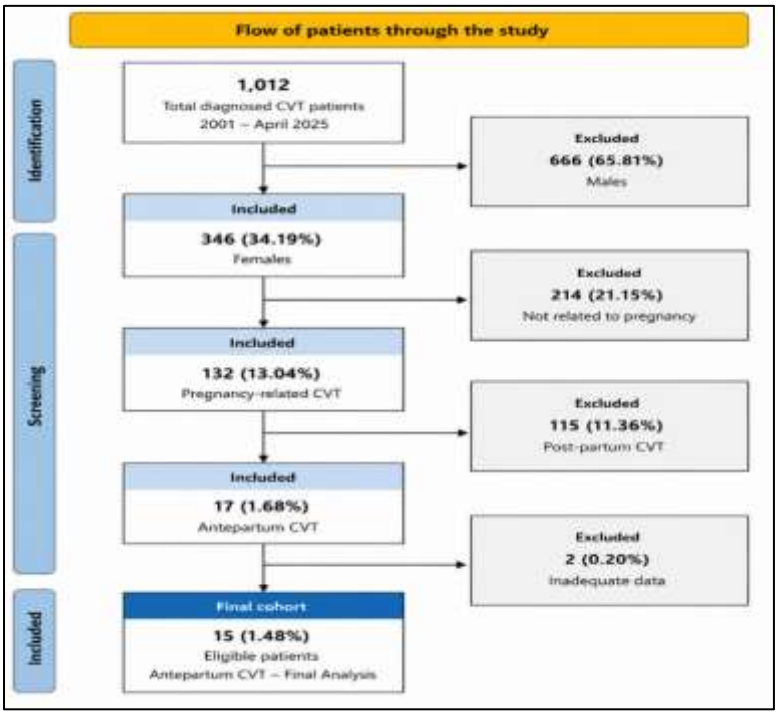

Figure 1 showing antepartum CVST patient selection from the CVST cohort.