

# Relationship between cerebral venous sinus thrombosis and intracranial arteritis during pregnancy and post partum

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## ABSTRACT

Our study was conducted to explore the relationship between cerebral venous sinus thrombosis (CVST) and intracranial arteritis during the time of pregnancy as well as puerperium. The current retrospective case study involved a total of 153 patients with pregnancy-related CVST. CVST was diagnosed mainly based on clinical manifestations and imaging results. Detailed information on demographics, risk factors (excluding intracranial arteritis), and pregnancy outcomes was systematically recorded. The average age of patients diagnosed with CVST was  $28.67 \pm 3.54$  years old. Among these patients, there were 62 cases of puerperal CVST and 91 cases of pregnancy-related CVST. The clinical manifestations of patients with CVST included headache in 55 cases (35.95%), symptomatic seizures in 26 cases (16.99%), symptomatic limb weakness in 22 cases (14.38%), symptomatic nausea/vomiting in 18 cases (11.76%), symptomatic disturbance of consciousness in 15 cases (9.80%), symptomatic blurred vision in 10 cases (6.54%), and symptomatic fever in 7 cases (4.58%). A proportion of patients reported higher abnormal cerebrospinal fluid pressure (98.28%), white cell count (79.31%), total cholesterol (71.55%) and low-density lipoprotein (62.93%) ( $p < 0.01$ ). The proportion of intracranial arteritis lesions and CVST lesions was high, including 51 cases (43.97%) on the left side and 31 cases (26.72%) on the right side. Bilateral CVST lesions occurred in 13 cases (11.20%) of unilateral intracranial arteritis lesions, and bilateral intracranial arteritis lesions occurred in 16 cases (13.79%) of unilateral CVST lesions. In summary, CVST indicates a potential positive link to intracranial arteritis at the time of pregnancy and puerperium.

## INTRODUCTION

Cerebral venous sinus thrombosis (CVST) is known as a rare occurring neurological emergency among women, with a trend toward a higher incidence during pregnancy and puerperium compared with the general population.<sup>1</sup> The overall incidence of CVST throughout the world is about five per million people, accounting for 0.5%–1% of all patients who had a stroke.<sup>2</sup> It has been indicated by earlier studies that the high rate of CVST among women is associated

## Significance of this study

### What is already known about this subject?

- Pregnant women are more likely to suffer from cerebral venous sinus thrombosis (CVST) than non-pregnant women, and the treatment for pregnant women is relatively complicated.
- Patients with CVST are mostly young and middle-aged and pregnant and lying-in women.

### What are the new findings?

- The etiology of CVST is complicated, leading to a higher rate of misdiagnosis during pregnancy.
- CT or MRI can provide strong evidence for the diagnosis of CVST during pregnancy.

### How might these results change the focus of research or clinical practice?

- This study offers insight and valuable information on improving the prognosis of patients harboring pregnancy-related CVST.

with the different physiological characteristics of pregnancy and puerperium, which is approximately 11.6 cases per 100,000 deliveries every year in developed countries, varying from 6% to 64% of patients harboring pregnancy-related strokes.<sup>3</sup> Other countries in Asia, by comparison, have reported limited studies concerning the incidence of pregnancy-related CVST.<sup>4</sup> The incidence of pregnancy-related CVST in India is 450 cases per 100,000 births and has been shown to result in an even higher trend than in developed countries.<sup>5</sup> While the clinical characteristics are already playing an important clinical role in pregnancy-related CVST, the risk factors responsible for the prognosis of patients with pregnancy-related CVST have remained largely unknown. Several recent prospective meta-analyses showed that long-term predictors of poor prognosis in patients harboring CVST may include the following: central nervous system infection, all types of cancer, intracranial hemorrhage, deep venous thrombosis and mental disorders.<sup>6–8</sup> Possible theoretical risk factors for pregnancy-related CVST may include clinical conditions such as dehydration,



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cesarean section, anemia, elevated homocysteine level, traumatic delivery, as well as low cerebrospinal fluid pressure caused mainly by dural puncture with neuroanesthetics.<sup>9 10</sup> However, it remains unclear in a general or specific way whether these risk factors affect the overall prognosis of patients with CVST at the time of pregnancy and puerperium. Hence, the current study was conducted to explore the mechanism and development of CVST during pregnancy and puerperium and its association with intracranial arteritis.

## METHODS

The present retrospective case study involved a total of 153 patients with pregnancy-related CVST who delivered in our hospital from January 2016 to June 2019. The diagnosis of CVST in our study was mainly based on overall clinical manifestations and screening imaging of patients. The treatment approaches and progress of the disease were performed and monitored by obstetricians and neurologists. Detailed information on demographics, risk factors (excluding intracranial arteritis), and pregnancy outcomes was systematically recorded. The diagnosis of CVST was confirmed by MRI and magnetic resonance venography, CT venography, or conventional angiography.

### Inclusion criteria

Patients enrolled were pregnant or less than 6 weeks post partum, with pregnancy-related CVST confirmed by neuroimaging examinations, not using contraceptives (such as levonorgestrel-intrauterine device) or had received hormone replacement therapy, and over 20 years of age.

### Exclusion criteria

Patients with CVST but not pregnant or in puerperium, older than 40 years old, smoking, with cardiovascular history, and without informed consent were excluded.

### Medical ethics issues

Before the commencement of the study, agreement and written informed consent were obtained from all subjects. Guidelines and related regulations were strictly followed by all methods and research activities of the current report.

### Measures

Our investigator collected and further evaluated the medical records of all subjects according to the following clinical parameters: (1) baseline demographic and clinical features, such as age, number of births, average length of stay (days), average time from onset to admission (days), mode of delivery, time of pregnancy onset, outcomes and risk factors; (2) initial signs and symptoms, as well as abnormal test results; (3) neuroimaging and other test results at the time of evaluation; and (4) treatment approaches and prognosis. Hypercoagulable status of CVST was further assessed with dyslipidemia tests (decreased high-density lipoprotein cholesterol, elevated low-density lipoprotein cholesterol, or other abnormalities in lipid) and other laboratory tests (C reactive protein and platelets).

### Follow-up

Patients who were willing to participate in the present study were arranged for counseling or given a telephone

interview. The standardized case report form for the evaluation of each pregnancy after CVST was applied as a guide for further clinical interviews. The following information will be extracted by investigators if a patient reports pregnancy after CVST: maternal outcome (CVST/intracranial arteritis/non-thrombotic complications), antithrombotic prophylaxis (3 months of pregnancy and post partum), and fetal outcome (induced abortion/spontaneous abortion/fetal death/congenital abnormalities/preterm birth). Puerperium was defined as the period from completion of delivery to the sixth week after delivery. An imaging examination was required to diagnose recurrent CVST or intracranial arteritis. The diagnosis of intracranial arteritis was made mainly using MRI, cerebral angiography, and the patient's clinical symptoms.

### Statistical analysis

All continuous variables used in our study were expressed as mean±SD. The investigators involved also analyzed the classification variables. Besides, the ORs and their 95% CIs were further calculated for each demographic factor, complications, side effects, and intervention to analyze the main outcome of mortality. The 95% CI was calculated by the Wilson method. Multiple logical regression analysis was carried out to distinguish independent associations.  $P < 0.05$  was considered statistically significant across the study. All statistical analyses were carried out using SPSS V.19.0.

## RESULTS

### Demographics of pregnancy-related CVST

The study involved a total of 153 hospitalized patients diagnosed with pregnancy-related CVST between January 2016 and June 2019. The average age of patients with CVST was  $28.67 \pm 3.54$  years old (the respective minimum and maximum ages were 20 and 40 years old). Among the patients, there were 62 cases of puerperal CVST and 91 cases of pregnancy-related CVST. After a cesarean section, the shortest time from onset of obvious clinical symptoms to admission was 0.5 days, while the longest time after delivery was 40 days (table 1).

### Clinical manifestations of patients with CVST

According to the clinical manifestations of patients with CVST during pregnancy and puerperium, there were 55 cases (35.95%) of symptomatic headache, 26 cases (16.99%) of symptomatic seizures, 22 cases (14.38%) of symptomatic limb weakness, 18 cases (11.76%) of symptomatic nausea/vomiting, 15 cases (9.80%) of symptomatic disturbance of consciousness, 10 cases (6.54%) of symptomatic blurred vision and 7 cases (4.58%) of symptomatic fever. Three-dimensional reconstruction of CT cephalic venography

**Table 1** Basic characteristics of patients with cerebral venous sinus thrombosis

Item	Index
Age	28.67±3.54
Body mass index (kg/m <sup>2</sup> )	25.32±2.64
Days in hospital	19.72±1.33
Time from symptom onset to admission (days)	9.54±1.39
Time of pregnancy onset (phase 1, phase 2, phase 3)	96, 34, 23

**Table 2** Clinical manifestations

Symptoms	Case (%) (N=153)
Headache	55 (35.95)
Seizures	26 (16.99)
Limb weakness	22 (14.38)
Nausea/vomiting	18 (11.76)
Disturbance of consciousness	15 (9.80)
Blurred vision	10 (6.54)
Fever	7 (4.58)

showed there was CVST in the jugular vein, sigmoid sinus, as well as the left transverse sinus. Another non-occlusive thrombus could also be observed in the right cervical bulb (online supplemental figure 1, [table 2](#)).

### Abnormal laboratory results

In the study sample, patients showed several laboratory abnormalities of pregnancy-related CVST. The most common abnormal test results found included increased levels of cerebrospinal fluid pressure, platelet count, white cell count, C reactive protein, triglyceride, total cholesterol, high-density lipoprotein, and low-density lipoprotein. The proportion of patients with abnormal cerebrospinal fluid pressure (98.28%), white cell count (79.31%), total cholesterol level (71.55%), and low-density lipoprotein level (62.93%) was higher ( $p < 0.01$ ) ([table 3](#)).

### Relationship between intracranial arteritis and CVST

The statistical results for intracranial arteritis and CVST showed that there was a high proportion of intracranial arteritis lesion side and CVST lesion side, including 51 cases (43.97%) on the left side, 31 cases (26.72%) on the right side, 13 cases (11.20%) of bilateral CVST lesions in unilateral intracranial arteritis lesions, 16 cases (13.79%) of bilateral intracranial arteritis lesions in unilateral CVST lesions, and 5 cases (4.31%) of bilateral intracranial arteritis in bilateral CVST lesions ([table 4](#)).

### Pregnancy outcomes of patients with CVST

According to the pregnancy results of patients with CVST, there were 64 cases (55.17%) of full-term delivery, 18 cases (15.52%) of preterm delivery, 4 cases (3.45%) of stillbirth, 21 cases (18.10%) of spontaneous abortion, and 9 cases (7.76%) of other abortions ([table 5](#)).

### Univariate regression analysis of CVST-related factors

Univariate regression analysis was performed to identify the predictors of pregnancy-associated CVST outcomes. Also, the regression variables included demographic variables, infection, intracranial arteritis, and seizures. The results showed that CVST during pregnancy and puerperium had no association with age and time from onset of symptoms to admission ( $p > 0.05$ ), but positively correlated with time of onset of pregnancy, infection, intracranial arteritis, and seizures ([table 6](#)).

### DISCUSSION

Based on previous studies, infection in pregnancy and puerperium is known as one of the major pathophysiological findings typically linked to pregnancy-related CVST.<sup>11</sup> Specific pathophysiological findings include changes in platelet function, iron deficiency anemia, and changes in prethrombotic and antithrombotic protein function and levels, as well as other symptoms caused by bleeding or acute trauma during delivery.<sup>12</sup> As a consequence of the abovementioned pathophysiological changes, the primary clinical manifestations of pregnancy-related CVST include the following: focal neurological impairment, sudden headaches, blurred vision, changes in consciousness levels, and seizures.<sup>13</sup> It is worth noting that the abovementioned symptoms are unspecific and could easily be confused with normal pregnancy, making it a tricky issue to seek an early diagnosis as well as treatment of the disease, posing a great threat to the lives of patients harboring pregnancy-associated CVST and their fetuses.<sup>14</sup> On the contrary, patients who seek early intervention are prone to a better prognosis than non-pregnant patients with CVST. Therefore, there is an urgent need to characterize the clinical characteristics of the condition to promote early diagnosis of pregnancy-related CVST.<sup>15</sup> Our study is the first to analyze and identify a large population of women with pregnancy-related CVST reported so far throughout China. According to the cases of CVST in our hospital, there was a higher incidence of CVST in comparison with developed countries, but lower incidence when compared with developing countries. In our hospital, the mortality rate of patients with pregnancy-related CVST was 11.63%, which is consistent as well with earlier reports.<sup>16</sup> Based on our analysis, several variables were linked to an increased risk of poor prognosis, including demographic variables, intracranial arteritis, infection, and seizures. Among the mentioned clinical factors, infection, intracranial arteritis, and seizures are particularly attributable to the

**Table 3** Laboratory indexes

Item	Normal laboratory results		Abnormal laboratory results		T value	P value
	n (%)	Value	n (%)	Value		
CSF (mmH <sub>2</sub> O)	2 (1.72)	126.33±13.52	114 (98.28)	365.14±21.17	3.824	0.003
WCC (×10 <sup>6</sup> /L)	24 (20.69)	5.14±0.52	92 (79.31)	37.48±2.42	6.137	0.025
Platelet (×10 <sup>9</sup> /L)	74 (63.79)	175.87±16.32	42 (36.21)	382.74±26.93	1.156	0.037
CRP (mg/L)	104 (89.66)	1.31±0.14	12 (10.34)	32.57±3.46	2.225	0.009
TG (mmol/L)	101 (87.07)	1.24±0.18	15 (12.93)	4.76±0.67	4.172	0.016
TC (mmol/L)	33 (28.45)	3.89±0.73	83 (71.55)	7.11±1.06	3.452	0.012
HDL (mmol/L)	112 (96.55)	1.22±0.28	4 (3.45)	2.95±0.34	5.137	0.007
LDL (mmol/L)	43 (37.07)	2.03±0.61	73 (62.93)	4.84±0.58	6.834	0.026

CRP, C reactive protein; CSF, cerebrospinal fluid; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TC, total cholesterol; TG, triglyceride; WCC, white cell count.

**Table 4** Comparison of the incidence of intracranial arteritis and CVST

Intracranial arteritis, n (%)	CVST, n (%)			
	Left side	Right side	Both sides	Total
Left side	51 (43.97)	0 (0.00)	7 (6.03)	58 (50.00)
Right side	0 (0.00)	31 (26.72)	6 (5.17)	37 (31.90)
Both sides	10 (8.62)	6 (5.17)	5 (4.31)	21 (18.10)
Total	61 (52.59)	37 (31.9)	18 (15.52)	116 (100.00)

CVST, cerebral venous sinus thrombosis.

death of patients with pregnancy-related CVST. The risk factors identified were linked to poor prognosis, and might be beneficial in selecting candidates for more active treatment as early as possible after CVST diagnosis.

The estimated incidence of perinatal CVST in this study was higher than previously reported in developed countries (11.6 per 100,000), but lower in comparison with that reported in developing countries (450 per 100,000), and is consistent with previous studies showing a higher incidence of pregnancy-related CVST in developing countries in comparison with developed countries. Besides, our hospital is a treatment referral center for pregnant patients who are diagnosed with cerebrovascular diseases, which may be a factor responsible for the increased incidence of pregnancy-associated CVST in our patient sample.

Our study discovered that intracranial arteritis is not only a risk factor for CVST but also highly associated with the prognosis of patients with pregnancy-related CVST. Moreover, pregnant and postpartum women have increased occurrence of intracranial venous sinus thrombosis, which might likely be attributable to the physiological status at the time of pregnancy and post partum. A normal pregnant patient often shows increased concentrations of VII, VIII, X, and von Willebrand factors, as well as increased fibrinogen.<sup>17</sup> Moreover, free protein S (active, unbound form) generally decreases during pregnancy. Considering the changes from the beginning of conception may not return to baseline levels until over 8 weeks after delivery, a hypercoagulable state could occur during pregnancy. Sweating and bleeding during childbirth, increased blood viscosity and slow blood flow can lead to increased blood clotting and cause thrombosis.<sup>18</sup> In addition, factors such as pregnancy at an older age, reduced exercise, cesarean section, concurrent infections, increased vomiting during pregnancy and puerperal periods, as well as body fluid deficiency may lead to increased risk of CVST 1, 2, 3, 4, and 5. Earlier studies, however, failed to report if intracranial arteritis affects the prognosis of patients with pregnancy-related CVST. Intracranial arteritis increases platelet adhesion and whole blood viscosity, which also enhance the activation of platelet aggregation, resulting in thrombosis. What is more,

it was found in our study that, although the combination of intracranial arteritis and CVST is considered a prognostic risk factor, it does not affect the incidence of death. It was suggested that physicians should pay attention and closely monitor the clinical manifestations of patients with CVST and intracranial arteritis. Symptoms such as vomiting and headache could lead to the potential presence of CVST by obstetricians and neurologists for the prognosis of patients.

The current study also demonstrated the effect on prognosis of other factors in the general population, including the age of patients, infection, time from symptom onset to admission, as well as seizures. Among the factors mentioned, infection and seizures were found to affect the prognosis of patients harboring pregnancy-related CVST. Poor prognosis was identified in studies in Middle East countries with a high rate of infection in the central nervous system. The findings of our study are consistent with an earlier publication of a Pakistan sample where infection and seizures were regarded as independent predictors of adverse outcomes at discharge. According to aggregated results, the effects of infection and seizures on the prognosis of patients with CVST are comparable regardless of pregnancy status. In addition, our results reported that infection-related CVST was linked to a higher risk of poor prognosis regardless of the source of infection. In the present analysis, the high mortality rate of septic thrombosis was found in cavernous and superior sagittal sinus.

Our study is the first to investigate the association between CVST and intracranial arteritis in pregnancy and puerperium, while none of the previously reported cohort studies focused on the topic. The findings will enable doctors to accurately identify pregnancy-related CVST and obtain an early diagnosis and therefore achieve a better prognosis. Nevertheless, some limitations should be acknowledged. Considering the full use of the database from our hospital, the findings and conclusion may be prone to aggregation or bias. The limited number of patients enrolled in the study also contributes to bias. Finally, further research is

**Table 5** Pregnancy outcomes

Item	Index (%) (n=116)
Full-term delivery	64 (55.17)
Preterm delivery	18 (15.52)
Stillbirth	4 (3.45)
Spontaneous abortion	21 (18.10)
Other abortions	9 (7.76)

**Table 6** Predictive factors affecting pregnancy-related prognosis in patients with cerebral venous sinus thrombosis

Item	OR	95% CI	P value
Age	0.03	-0.12 to 0.16	0.564
Time from onset to admission (days)	0.01	-0.37 to 0.86	0.382
Time of pregnancy onset (phase 1, phase 2, phase 3)	0.15	-0.28 to 0.57	0.015
Infection	1.08	0.15 to 1.92	0.018
Intracranial arteritis	1.74	1.03 to 2.87	0.008
Seizures	1.46	0.87 to 2.32	0.003



warranted to evaluate the risk of CVST recurrence associated with pregnancy.

## CONCLUSION

In conclusion, our study presents a detailed summary of clinical features and provides an assessment of prognosis of patients with pregnancy-related CVST. The resulting synthesis of symptoms, including infection, intracranial arteritis, and seizures, shows an association with poor prognosis. Despite several limitations, we believe this study offers insight and valuable information on improving the prognosis of patients harboring pregnancy-related CVST.

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