Original article:

Association of Hypertension and Cerebral Venous Thrombosis among the Women in the Puerperal Period – A Prospective Study

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Abstract

Background: Pregnancy and puerperium are important risk factors for CVT. CVT can be caused by a number of prothrombotic states and disorders of clotting system such as inherited cause is Protein C resistance secondary to Factor V Leiden polymorphism, Protein C and S resistance, and antithrombin III deficiency. Pre-existing hypertension, pregnancy induced hypertension, pre-eclampsia and eclampsia were considered as independent risk factors in the development of CVT among the antenatal and puerperal mothers.

Aim: To assess the association between hypertension and CVT among the antenatal and puerperal mothers and also to analyse the clinical profile and the outcome of all those patients with CVT.

Methodology: A prospective study was carried out over a period of three years in the Neurology department of Coimbatore medical college. Pregnancy and puerperium associated CVT patients whom were confirmed by magnetic resonance imaging (MRI), MR venogram , plain/contrast CT were included in the study. A total of 102 patients were enrolled for the study in the period of 3 years. The patients demographic details including the diabetic and hypertensive status along with their family history was obtained by using a detailed questionnaire.

Results: Majority of them were between the age group of 18 - 25 years. CVT was more common among the multipara with the birth order of 2 or more when compared to the primi mothers. Headache was found to be the most common symptom followed by nausea/vomiting and seizures. 70% of the patients with CVT had either a history of pre-existing hypertension, pregnancy induced hypertension or being detected as a new case of hypertension.

Conclusion: Regular screening of blood pressure and early identification of high blood pressure and effective intervention both in the form of pharmacological management and life style modification will bring down the incidence of CVT due to hypertension.

Keywords: cerebral venous thrombosis, puerperium, antenatal, hypertension, anticoagulant

Introduction:

Pregnancy and puerperium are important risk factors for CVT and researchers have reported that it accounts for about 20% of all CVT cases.[1,2] It is still more common in developing world.[3,4] As every woman of reproductive age has potential to become pregnant and hence is at risk of cerebral venous thrombosis (CVT). The association was first described by Abercrombie in 1828 and latter by Collier.[5,6] CVT usually presents either late in pregnancy or puerperium but reports had proven that it can occur as early as 8 weeks. Majority of studies have reported a higher prevalence of CVT during puerperium rather than the antenatal priod.[7-9] The ratio of CVT during puerperium and pregnancy is reported to be 2.1:1 to 3.25:1 from European countries and 13:1 to 14:1 from developing countries like Mexico and India. Higher risk during puerperium has been attributed to bad obstetrical practices i.e. home deliveries by untrained dais and restriction of water early after delivery, which is much more commonly practiced in developing countries like India even today.[10]

CVT can be caused by a number of prothrombotic states and disorders of clotting system such as inherited cause is Protein C resistance secondary to Factor V Leiden polymorphism, Protein C and S resistance, and antithrombin III deficiency. Cantu et al noted significantly higher proportion of anaemia and ESR in puerperal cases compared to non puerperal cases.[5] A significant association has constantly been found with young age from developing as well as developed countries.[8,9]

Caesarean section and infections have been found to be independent risk factors for CVT and they increase the risk by three times during the puerperal period. Caesarean section may increase the risk by postsurgical decline of protein C levels, presumably because surgically induced tissue damage induces the activation of blood clotting with increased thrombin generation, which in turn both activates protein C and accelerates its clearance from plasma.[11]

Pregnancy induced hypertension and excessive vomiting have also been reported to contribute independently in development of obstetric CVT.[12]

Pre-eclampsia is a pregnancy-specific multi-system disorder affecting 2–10% of pregnancies,[13] and is defined as new onset of raised blood pressure with proteinuria after 20 weeks' gestation. Eclampsia is characterised by the new onset of seizures in a woman with pre-eclampsia. The association between eclampsia and cerebral haemorrhage has been recognised since 1881,[14] and this is reported to be the most common cause of death in patients with eclampsia.[15] Sharshar et al[16] found eclampsia to be associated with both cerebral haemorrhage and non-haemorrhagic stroke, and, since then, several studies have reported an increased risk of stroke associated with both pre-eclampsia and eclampsia.[17]The proportion of patients with pregnancy-related stroke who have pre-eclampsia or eclampsia is 25–45%.[16]The risk of ischaemic stroke associated with pre-eclampsia appears to persist even beyond pregnancy and the puerperium, and data from the Stroke Prevention in Young Women Study suggest that women with a history of preeclampsia are 60% more likely to have a non-pregnancy-related ischaemic stroke.[15]

A recent case series presented by James et al showed that 80% of patients with stroke related to pre-eclampsia did not exhibit sustained diastolic pressures of more than 105 mm Hg before stroke. The exact pathophysiology of pre-eclampsia remains

unclear, although endothelial dysfunction appears to play a significant role.[18]

As of today only very few studies had been done to assess the association between hypertension and CVT among the puerperal women's. So this study was undertaken to assess the association between hypertension and CVT among the puerperal women's and also to analyse the clinical profile and the outcome of all those patients with CVT.

Materials and methods:

A prospective study was carried out over a period of three years in the Neurology department of Coimbatore medical college. The study was approved by the institutional ethical committee. Pregnancy and puerperium associated CVT patients whom were confirmed by magnetic resonance imaging (MRI), MR venogram , plain/contrast CT were included in the study. A total of 102 patients were enrolled for the study in the period of 3 years. All the patients were treated in the intensive care unit under standard guidelines and protocols. Patients with diagnosis of CVST were treated in intensive care unit. Patients with diagnosis of CVST were treated with intravenous fluids to correct dehydration, decongestive agents, anticonvulsant drugs, antibiotics, low-molecular weight heparin (LMWH) (if not contraindicated), decompressive craniotomy, methylcobalamin and folic acid supplementations, and so on. The patients demographic details including the diabetic and hypertensive status along with their family history was obtained by using a detailed questionnaire. All patients underwent basic investigations, such as hemogram, electrolytes, blood sugar levels, renal function tests, and chest radiographs. Liver function tests, coagulation studies, inflammatory markers, and homocysteine levels were done in selected patients because of financial constraints. All data were entered in SPSS version 17 and analysed. The mean, standard deviation, and Chi-square test was used to analyze the data and $P < 0.05$ was considered as statistically significant.

Results:

The age wise distribution of the study population was shown in table1. It is seen from the table that the mean age among the study population was 23.5±3.5 years. Majority of them were between the age group of 18 - 25 years. It can be inferred from the table that the CVT was more common among the younger age group antenatal or puerperal mothers than the older age group and this difference was found to be statistically significant (P<.001). The parity wise distribution of the study population had shown that CVT was more common among the multipara with the birth order of 2 or more when compared to the primi mothers and the difference was found to be statistically significant (P<.001) (table2).

Among the various symptoms presented to the patients with CVT headache (84.3%) was found to be the most common symptom followed by nausea/vomiting (70.5%) and seizures (59.8%). Neurological deficit like hemiparesis was found in 27 patients and papilloedema was seen among 24 patients (table3). Majority of the patients had experienced the CVT attack during their puerperal period(68.6%) and only 31.3% of the patients were in the antenatal period and the difference was found to be statistically significant (P<.001) (table4). It can be inferred that during the pregnancy period CVT was more common in the puerperal period rather than the antenatal period.

Table 5 shows the association of hypertension among the patients with CVT. Almost 70% of the patients with CVT had either a history of pre-existing

hypertension, pregnancy induced hypertension or being detected as a new case of hypertension. It is inferred from the table that there is a statistically significant association (p=.006) between hypertension and development of CVT among the pregnant mothers. Hypertension can be considered as an independent risk factor for cerebral vascular thrombosis.

The MRI findings of the patients were tabulated in table6. Majority of the patients had an hemorrhagic infarct than the non hemorrhagic infarct and most of the lesion was presented unilaterally rather than bilateral and 10.7% of the patients had intracerebral hemorrhage.

All patients were treated with intravenous heparin and it was discontinued after achieving the INR of 2 and from the second day oral anticoagulants were started on them. At the end of six months patients were advised to stop anticoagulation after CT and M R venogram follow up. Of the total 102 patients only one patient admitted with status epilepticus and further work up proved secondaries brain where the primary was from ovarian origin.

Discussion:

A wide variety of conditions can cause or predispose to CVT, and it varies accordingly from different country to country, based on their ethnicity and geographical conditions.[19,20] In India as such the prevalence of CVT ranges between 4.5-7/1000 obstetric women.[21] In the present study all 102 cases of CVT were associated with pregnancy and puerperium over a period of 2 years. According to obstetric CVT,[22] symptoms of CVT usually starts in the first 3 weeks after delivery in the majority of cases and among the Indian women CVT was more common among mothers who had home deliveries and poor antenatal care. CVT should be suspected in any woman who develops neurological symptoms in the immediate postpartum period, since nearly 25% of our cases occurred in the first 2 days after a normal childbirth. CVT occurred 13 times more often during puerperium than during pregnancy.[23] Although in the Indian population, multiparas are more often affected than primiparas,[21] which was almost in par with our study. In our study females in the age group of 18 – 25 years were commonly affected than the females of the older age group.

Only very few had reported previously about the mortality associated with pregnancy related strokes. The three investigations by Lanska and Kryscio found no fatalities attributed to CVT, but stroke fatality rates of 2.2, 2, 3.3, 3 and 14.7 per 100,000 deliveries [9]in chronological order of analysis in the Nationwide Inpatient Sample database, similarly in our study there was no mortality reported among the 102 patients studied. The death rate from CVT was comparatively lower in pregnant than in non-pregnant women of the same comparable age.[5] The most recent Nationwide Inpatient Sample analysis done in US had reported that 4.1% case fatality rate was associated with pregnancy-related stroke, and a mortality rate of only 1.4 per 100,000 deliveries.[24] This was much lower when compared with the average case fatality rate for stroke at any age (24%), and even compared with the range of case fatality rates for stroke in young adults (4.5–24%).[24]

The most common symptom presented by the patients in our study was headache, followed by seizures and neurological deficit. Similar type of clinical features were described by many authors in their studies. Nagaraja et al. [25](2007) stated that the pregnancy and puerperium increase the risk of thrombotic events, and these risks are likely to be increased in women who are carriers of

thrombophilic gene polymorphisms. He also stated that hyperhomocysteinemia is a known risk factor for venous thrombosis. Hyperhomocysteinemia is associated with an increased risk of puerperal CVST occurring in Indian women and low folate levels contribute significantly to hyperhomocysteinemia. Nutritional folate and vitamin B_{12} deficiency can cause hyperhomocysteinemia and pregnancy may contribute to this deficiency.

Variability in the clinical signs was due to extensive collateral circulation within the cerebral venous system, which allows for compensation in the early stages of venous occlusion. The small cerebral veins drain into the large veins such as vein of galen.[26]

As indicated in a study by Kuklina et al,[27] hypertension plays a major role in the development of CVT in pregnancy. Many studies have also shown the similar results.[8,9,16,28] Hypertension had been identified by many neurologist as the number one preventable risk factor in pregnant female. Hypertension in pregnancy can be pre-existing, gestational or secondary to pre-eclampsia or eclampsia. Compared with women without hypertension, women with hypertension complicating pregnancy are six- to nine-fold more likely to have DVT.[8,9] Our study had also proven that women with gestational hypertension or pre-existing hypertension had more risk of developing CVT. Other risk factors associated with pregnancy-related stroke include hypertension, diabetes, valvular heart disease, hypercoagulable disorders, sickle cell disease, lupus, abuse of tobacco and other substances, and migraines.[24] Complications of pregnancy, labor and delivery have also been associated with increased risk of developing CVT.

Cesarean delivery has been associated with peripartum stroke, but a clear cut causal relationship has not been established.[29] Historically, cesarean delivery has been recommended for women with ICH, particularly recent subarachnoid hemorrhage, untreated ruptured arteriovenous malformation (AVM) or unclipped ruptured aneurysm, to circumvent potential risks during labor and delivery.[30] However, studies suggest that outcomes of vaginal and cesarean delivery are probably equivalent after ICH.[31] Similarly in our study also cesarean section dir not showed any association in the development of CVT.

In obstetric cases, the pathophysiological process leading to venous occlusion develops faster but is usually self-limited and resolves itself in a shorter time. Further evidence for this is the shorter period between onset of symptoms and diagnosis in obstetric patients; however, it should be born in mind that puerperium represents an important clue for suspecting CVT.[26]

Majority of the studies had shown that the parenchymal lesion was the lost common lesion among the patients with CVT and it is mostly of hemorrhagic infarct and the findings of our study had almost substantiated the findings. In our patients most of the lesions were unilateral rather than bilateral.[24]

The outcome of CVT during pregnancy ranges from total recovery to death. Since the introduction of MRI, an increasing number of patients with a benign course of CVT have been diagnosed and a prompt management with anticoagulants had made a complete recovery in most of the patients.[8,9] Similarly in our study all the patients were treated with heparin and the results were also quite encouraging where we had not reported any death in the 102 patients who had been treated.

Conclusion:

Our study had proven that hypertension can be an independent risk factor for the development of CVT in antenatal or puerperal mothers. The hypertension may be of a pre-existing type or gestational. Regular screening of blood pressure and early identification of high blood pressure and effective intervention both in the form of pharmacological management and life style modification can very much bring down the incidence of CVT due to hypertension. A proper health education to all the antenatal mothers about the warning signs of CVT is very much warranted for early diagnosis of CVT.

Table 1 : Age wise distribution of the study population

Age group	**Frequency**	**Percentage**	**P value**
18 – 20	2	1.9%	**<.001**
21 – 23	38	37.2%	
24 – 26	46	45%	
27 – 29	15	14.7%	
>29	1	0.9%	
Total	102	100%	
Mean age	**23.5±3.5**		

Table 2 : Parity wise distribution of the study population

Parity	**Frequency**	**Percentage**	**P value**
Prime	30	29.4%	**<.001**
Multi	72	70.5%	
Total	102	100%	

Table 3 : Symptom wise distribution of the study population

Symptom (n=102)	**Frequency**	**Percentage**
Headache	86	84.3%
Seizures	61	59.8%
Neurological deficit	27	26.4%
Nausea/vomiting	72	70.5%
Visual disturbance/papilloedema	24	23.5%

Table 4 : Distribution of the study population based on the time of admission of the patients.

Period of admission	Frequency	Percentage	P value
Antenatal period	32	31.3%	**<.001**
Puerperal period	70	68.6%	
Total	102	100%	

Table 5: Association of hypertension among the patients with CVT

Type of hypertension	Frequency	Percentage	P value
Pregnancy induced hypertension	17	16.6%	
Pre-existing hypertension	24	23.5%	**0.006**
Newly detected hypertensive	30	29.4%	
Normal blood pressure	31	30.3%	
Total	102	100%	

Table 6: MRI findings of the patients with CVT

MRI findings	Frequency	Percentage
Hemorrhagic infarct	62	60.7%
Non hemorrhagic infarct	29	28.4%
Intracerebral hemorrhage	11	10.7%
Unilateral lesion	69	67.6%
Bilateral lesion	33	32.3%

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