Obstetric Cerebral Venous Thrombosis
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Abstract
Pregnancy and puerperium are most prevalent prothrombotic states leading to cerebral venous thrombosis. Likelihood of stroke to be of venous origin is greater in stroke associated with pregnancy compared to stroke unrelated to pregnancy. Pregnancy induces several changes in coagulation system, which persists at least during early puerperium, rendering it a prothrombotic state. Hypercoaguability worsens further after delivery as a result of volume depletion and trauma. During puerperium additional risk factors include infection and instrumental delivery or Caesarean section. The management follows general rules as for the venous thrombosis unrelated to pregnancy, however the prognosis is different.

Introduction
Pregnancy and puerperium are well established causes of venous thromboembolism (VTE), including intracranial venous thrombosis.1,2 Several physiological changes in coagulation system render pregnancy and puerperium prothrombotic states.3-8 Since 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.9,10 It is important to discuss the association since no factor is as prevalent as pregnancy. However, not every pregnant woman develops CVT and it (along with puerperium) accounts for only 20% of cases.11,12 Further more the entity may be more common in developing world.13,14 We will discuss physiology of coagulation system during pregnancy, epidemiology of obstetric CVT (CVT during pregnancy and puerperium), its pathophysiology, clinical features, management and prognosis.

Coagulation during pregnancy and puerperium
Changes in coagulation system i.e. enhancement of procoagulants and inhibition of anticoagulants, during pregnancy are considered to be physiological adaptations of the body in order to face the haemostatic challenge of delivery. Significant changes include reduction in protein S levels, rise in activated protein C (APC) resistance, increments in fibrinogen, plasminogen activator inhibitors (PAI), prothrombin fragments 1 and 2 (F 1+2), and coagulant activity of factors V and VIII.

Protein S (total and free) begins to fall around 10 weeks of gestation and continue to fall through out pregnancy.3,4,7 The protein S activity falls by approximately 50% compared to normal controls.3,4 Resistance to APC increases through out pregnancy and at term seen in more than half of normal pregnant women compared to normal non pregnant controls. 3,5 Interestingly no reduction occurs in absolute levels of protein C, rather it increases during early postpartum period.3,7 Similarly no change occurs in antithrombin (AT) levels.3 Resistance to APC has been attributed to rise in factors V and VIII.3 The Factor V activity increases after 16 weeks of gestation and the activity increases by 29% at term.3 Fibrinogen levels start to rise as early as 6-7 weeks and continue to rise thereafter.4 From 20th week onwards prothrombin time shortens, probably as a result of increased levels of factor VII.4 Changes in protein S, resistance to APC, factors V and VIII, and fibrinogen persist during puerperium, at least a few days.3-6 The levels of F1+2 rise through out pregnancy and fall during puerperium.3 Fibrinolytic system is inhibited by elevation of PAI-1 during 3rd trimester.4

Platelets play a very important role in coagulation. Their concentration remains same during pregnancy.
Epidemiology of obstetric CVT

Pregnancy and puerperium are important risk factors for CVT and European researchers have reported that it accounts for about 20% of all CVT cases. However, literature from developing countries revealed a higher proportion of obstetric CVT. In his series of 113 patients, Cantu C et al from Mexico reported that obstetric CVT accounted for 59% of the cases. The estimated annual incidence of CVT (overall) is 3-4 cases per million population and 75% adult patients are women. Using National hospital discharge survey data from US (1979-1991), Lanska DJ et al estimated risk of peripartum CVT about 8.9/100,000 deliveries. The risk is even higher i.e. 11.4/100,000 deliveries for entire period of pregnancy. Recently data from healthcare cost and utilization project (1993-1994) revealed a risk of 11.6/100,000 deliveries for peripartum intracranial venous thrombosis. The entity is more common in developing countries. Bansal et al, from India, reported prevalence of 4.5/1000 obstetric cases during early 80s. In their autopsy series, Banerjee K et al during late 80s, found that CVT accounts for approximately 10% of all strokes. Recently Panagariya et al from India reported that CVT accounts for half of all young strokes and 40% of strokes in women.

Despite the fact that pregnancy and puerperium increase risk of both venous and arterial stroke the proportion of venous stroke is much higher in pregnancy related stroke as compared to stroke unrelated to pregnancy. Jiaji-Shing et al from Taiwan reported that in women of 15-40 years of age, with first ever stroke- proportion of CVT is 39% in pregnancy related stroke as compared to only 5% in pregnancy unrelated stroke.

CVT usually presents either late in pregnancy or puerperium but cases have been reported as early as 8 weeks. Majority of studies have reported a higher proportion of CVT during puerperium compared to pregnancy. However, US literature reported more or less similar proportion. 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.

Pathogenesis and Risk Factors of obstetric CVT

Hypercoagulability plays an important role in development of CVT during pregnancy and puerperium. As mentioned earlier several changes occur in coagulation system, which are more marked during the third trimester, and render it a hypercoaguable state. In addition dehydration as a result blood loss during delivery and bad obstetric practices and local trauma during delivery worsen the thrombotic state. The hypercoaguable and venous stasis as a result of prolonged bed rest, instrumental delivery or Caesarean section will lead to thrombosis. Occlusion of cerebral veins lead to cytotoxic and vasogenic edema, and infarction while occlusion of major sinuses leads to intracranial hypertension.

In addition to these pathophysiologic processes and factors, several other risk factors have also been noted by various investigators.

Cantu et al noted significantly higher proportion of anemia and ESR in puerperal cases compared to non puerperal cases. A significant association has constantly been found with young age from developing as well as developed countries. Lanska et al reported that younger group 14-25 years is more vulnerable. In a series of 138 cases from India, 112 were under 30 years of age. Caesarean section and infections have been found to be independent risk factors of obstetric CVT and they increase the risk by three times. 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. Pregnancy induced hypertension and excessive vomiting have also been reported to contribute independently in development of obstetric CVT. Multiparity has been over represented in obstetric CVT, from developing countries. Bansal et al reported a statistically significant rise in serum triglycerides, phospholipids, free fatty acids, blood platelet count, platelet adhesive index, and fall in blood fibrinolytic activity as compared to normal controls.

Several isolated cases of pregnancy associated CVT have been reported in whom other risk factors were documented so it is wise to remember other risk factors e.g. homocysteinemia, hypercoaguable states (protein C deficiency, factor V Leiden, mutations in prothrombin gene 2001), vasculitic and other inflammatory processes, trauma and drugs.

Clinical features

Major clinical features of obstetric CVT are similar to CVT unrelated to pregnancy. These include headache, focal deficits, seizures and mental status changes. However, certain important differences have been noted by Cantu et al. They found more acute course and early stabilization.
They also noted lesser frequency of motor findings and
generalized seizures, and higher frequency of focal seizures at
presentation. However, during the course of disease the dif-
fferences in frequency of seizure type and motor deficits
vanish.\textsuperscript{9} Mental status changes especially somnolence/
drowsiness were more common in obstetric CVT.\textsuperscript{9} On the
contrary isolated intracranial hypertension was more fre-
quen in CVT unrelated to pregnancy.\textsuperscript{9}

\textbf{Differential Diagnosis}

It is important to differentiate this condition from
other pregnancy associated central nervous system (CNS)
disorders i.e eclampsia and postpartum cerebral angiopathy.
It is also important to exclude arterial strokes, parenchymal
haemorrhages unrelated to CVT, subarachnoid haemorrhage
(SAH) and CNS infections.

\textbf{Diagnosis}

Most important diagnostic test is MRI and MRV of
brain. LP may be needed to exclude CNS infection. Work
up for hypercoaguablelity, especially genetic disorders-, inflammatory and vasculitic disorders is required in select-
ed cases.

\textbf{Management}

Management of obstetric CVT is not different from
that of CVT unrelated to pregnancy. Hence it includes sup-
portive care, seizure control, measures to lower intracranial
pressure, search and treatment of possible infection. To pre-
vent further thrombosis, anticoagulation is the preferred
treatment, currently. This is based on a few small random-
ized trials and extensive anecdotal experience.\textsuperscript{26,27} Local
thrombolysis has also been tried in conjunction with sys-
temic intravenous heparin, with encouraging results.\textsuperscript{28,29}
Except Indians none have reported on anticoagulation
specifically in obstetric CVT. Srinivasan used heparin in
uncontrolled fashion in 80s and noted that mortality was
lower amongst heparin group.\textsuperscript{13} Recently Nagaraja et al
conducted two randomized controlled trials of low dose
(2500 units thrice daily) unfractionated subcutaneous
heparin in contrast to high dose heparin infusion or low
molecular weight heparin, used in earlier trials in patients
with obstetric CVT and found it beneficial.\textsuperscript{30,31} The first
trial published in 1995 and heparin was used only in patients
with CVT with out any haemorrhage.\textsuperscript{29} Second trial pub-
lished in Neurology India in 1999 includes all patients with
puerperal CVT irrespective of the haemorrhage.\textsuperscript{30} This trial
includes 73 patients in heparin group (27 with haemorrhag-
ic stroke) and 77 in control group (27 with haemorrhagic
stroke). Complete recovery was seen in 34 (47%) patients in
treatment arm as compared to 14 (18%) in control group and
mortality was 8 (11%) vs. 18 (23%). This is an important
and encouraging therapeutic trial. However it is limited by
its design as it was not a placebo controlled double blind
trial and by the fact that higher proportion of patients in con-
control arm had status epilepticus which might have con-
tributed to higher mortality in control arm.

\textbf{Prognosis}

Prognosis of CVT is quite variable and the outcome
ranges from total recovery to death. The disease had a fatal
outcome during preimaging era, when neither early diagno-
sis was feasible/possible nor effective therapies and sup-
portive care was available.

Various obstetric CVT series have reported a mortal-
ity rate from 4-33% (Table 1).\textsuperscript{9,11,13,20,31-33}

Cantu et al reported lower mortality i.e. 9.7 vs.

\begin{table}[h]
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\begin{tabular}{|l|l|l|l|l|l|}
\hline
No. & Author & Year & Country & N & Died \\
\hline
1 & Ferro JM et al\textsuperscript{11} & 2004 & Multiple\textsuperscript{1} & 77 & 3 (4) \\
2 & Nagaraja D et al\textsuperscript{31} & 1999 & India & 150 & 26 (17) \\
3 & Panagariya A et al\textsuperscript{20} & 1997 & India & 64 & 12 (19) \\
4 & Hamouda-M’Rad I et al \textsuperscript{34} & 1995 & Tunis & 33 & 12 (36) \\
5 & Cantu C C et al\textsuperscript{9} & 1993 & Mexico & 67 & 6 (9) \\
6 & Sanchetee PC et al \textsuperscript{32} & 1992 & India & 25 & 3 (12) \\
7 & Srinivasan\textsuperscript{13} & 1984 & India & 138 & 28 (20) \\
\hline
\end{tabular}
\caption{Mortality of CVT associated with pregnancy and puerperi-
\textsuperscript{um}**
\textsuperscript{1}Year= year of publication, N= total number of patients in the series
\textsuperscript{2}Percentages in parenthesis
\textsuperscript{3}21 countries from Europe, Canada, Australia and Latin America}
\end{table}

32.6% in Obstetric CVT. However proportion of complete
recovery was similar in both the groups.

Favourable outcome has been reported from 60-76%
cases.\textsuperscript{9,33} Favorable outcome in obstetric CVT has been
attributed to the assumption that the occlusion is limited and
transient with rapid recanalization or by development of
collaterals.\textsuperscript{9}

Neuropsychiatric manifestations and pseudotumor
cerebi like presentations carry favourable prognosis while
acute fulminant course, bilateral haemorrhagic infarctions
and diffuse cerebral oedema are associated with relatively
poor outcome.\textsuperscript{20}

There is no data on long term outcome including
recurrence during subsequent pregnancy in patients with
obstetric CVT. However, Mehrain et al reported that there
is no substantial risk of CVT during subsequent pregnancy in
women who had CVT in past whether obstetric or not.\textsuperscript{34} In
their retrospective review 14/39 women had 22 pregnancies
and none developed CVT over a mean follow up of 10 years.
These 14 women also included 4 women in whom index
CVT was also pregnancy related event.34

Conclusion

Obstetric CVT is not uncommon. It must be considered in young women presenting with any neurologic manifestation related to CNS during pregnancy (especially 3rd trimester) and puerperium. Obstetric CVT has a different course and carries favourable prognosis as compared to CVT unrelated to pregnancy. There is evidence that mortality can be altered favourably by anticoagulation. The treatment of obstetric CVT is similar to CVT unrelated to pregnancy, including conventional anticoagulation. Low dose subcutaneous is viable/feasible and potentially efficacious option, however, this needs to be confirmed in controlled randomized trials.

References