Perinatal thrombosis: implications for mothers and neonates

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Stroke is more likely to occur in the perinatal period than any other time in childhood, and these events can lead to a lifetime of intellectual and motor disabilities, epilepsy, and behavioral challenges. This review describes the epidemiology and natural history of perinatal arterial ischemic stroke (PAIS) and cerebral sinovenous thrombosis (CSVT), risk factors for these complications, recent evidence regarding treatment strategies, and current gaps in knowledge. Existing evidence demonstrates the multifactorial etiology of symptomatic ischemic stroke in neonates, which includes a combination of maternal, delivery, and neonatal factors. The importance of inherited thrombophilia in the pathophysiology and long-term outcomes of perinatal stroke requires additional study. At this time, there is no evidence to support routine extensive thrombophilia screening outside of a research setting. Despite the frequency of perinatal stroke and its association with substantial morbidity, treatment strategies are currently limited, and prevention strategies are nonexistent. Anticoagulation is rarely indicated in PAIS, and more work needs to focus on neuroprotective prevention and alternate treatment strategies. Anticoagulation does appear to be safe in CSVT and may prevent thrombus progression but clinical equipoise remains, and clinical trials are needed to obtain evidence regarding short- and long-term efficacy outcomes.

Learning Objectives

- The reader should be able to summarize the major risk factors for perinatal stroke and their classifications (maternal, delivery, and neonatal) and recognize that risk factors overlap between arterial and venous perinatal stroke
- The reader should be able to contrast the evidence supporting anticoagulation therapy in arterial and venous perinatal stroke and summarize current guidelines regarding indications for anticoagulation in these settings

Stroke is more likely to occur in the perinatal period than any other time in childhood. In fact, the most focused lifetime risk for stroke is actually during the week surrounding birth, with a risk triple the weekly stroke risk of a smoking adult with diabetes and hypertension.[1] Perinatal stroke refers to a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolism, occurring between 20 weeks of gestation and postnatal day 28 and confirmed by neuroimaging or neuropathological studies.[2] Although there are several subtypes of perinatal stroke, this review will focus on perinatal arterial ischemic stroke (PAIS) and cerebral sinovenous thrombosis (CSVT). Perinatal stroke is the most common cause of hemiparetic cerebral palsy, and these thrombotic events can lead to a lifetime of epilepsy, intellectual disabilities, motor delays, and behavioral challenges. Despite its frequency and association with substantial morbidity, treatment strategies are currently limited, and prevention strategies are nonexistent. This review will focus on the epidemiology and natural history of perinatal stroke, risk factors (with a focus on the effect of thrombophilia), recent evidence regarding treatment strategies, and current gaps in knowledge.

Epidemiology and clinical presentation

Although childhood stroke occurs in ~1 in 100 000 children, rates of perinatal stroke are much higher, occurring in at least 1 in 3500 live births.[3] PAIS is more common than CSVT, with reported incidences of between 1-1600 and 1-5000 newborns.[4,5] Although the exact mechanism of PAIS is unknown, it is assumed that the patent foramen ovale in neonates allows for the passage of thrombi from the placental or venous circulation, resulting in the occlusion of an artery.[6] Although CSVT has a much lower reported incidence of 0.6-12 per 100 000 live births, it is more likely to be underdiagnosed as a result of a more nonspecific clinical and radiologic presentation.[6]

Both PAIS and CSVT consistently occur more often in males, a finding confirmed in a large cohort from the International Pediatric Stroke Study (IPSS; n = 1187, 60% males).[7] Gender-specific differences have also been identified in cell death pathways in animal stroke models, but the reasons for male predominance are not clearly elucidated.[8] PAIS and CSVT both affect term and preterm infants. It has been suggested that CSVT is more common in premature infants, but this finding is likely attributable to the fact that these infants routinely undergo cranial ultrasound.

The clinical presentations of PAIS and CSVT overlap to a fair degree.[8-11] In both diseases, infants typically present in the first week of life, with the majority developing symptoms within the first 48-72 hours. Seizures are the most common symptom, occurring in

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70%-90% of neonates with PAIS and approximately two-thirds of those with CSVT. However, seizures may be subtle and go unnoticed, leading to delays in diagnosis. In a case-control study using Kaiser health system data, investigators searched for children with motor impairment and then reviewed medical records to identify diagnoses of PAIS. Of 38 cases, 28 (68%) had a delayed diagnosis, presenting after 3 months of age with either hemiparesis or seizures.[12] In addition to seizures, signs of either PAIS or CSVT include apnea, lethargy, feeding difficulties, and respiratory distress. In PAIS, neonates may also present with asymmetry of tone during the first days to weeks of life, with hypotonia rather than hypertonia on the affected side.[6]

Although it is important to recognize the acute symptoms of perinatal stroke to make a rapid diagnosis, the long-term outcomes of these events are of equal if not even greater clinical significance. In PAIS, motor deficits, particularly unilateral spastic cerebral palsy, are the most frequently observed sequela, seen in up to 50% of cases.[6] Recurrence of seizures is also seen in almost half of patients. Other possible outcomes include cognitive delay, behavioral problems, and visual function abnormalities.

Fewer studies have been published on outcomes in perinatal CSVT, but the available evidence suggests that 60%-80% of children develop some type of deficit, whether it is cerebral palsy, cognitive delay, or epilepsy. In a prospective cohort of 90 neonates with CSVT, complete thrombus recanalization occurred in 90% of infants by 3 months of age.[13] However, epilepsy (17% of patients) and neurologic deficits (56%) were commonly seen, including moderate-to-severe language, sensorimotor, and cognitive–behavioral deficits. Patients with thalamic injury appear to have a particularly high risk of developing epilepsy.[6]

Radiologic findings

PAIS more frequently affects the left hemisphere and often involves the middle cerebral artery territory, perhaps because the origin of the left carotid artery from the aorta allows a more direct route for cardiac emboli.[8] In the largest PAIS cohort study (n = 248, 57% males, 10% premature), published by the IPSS investigators, infarcts preferentially involved the anterior circulation and left hemisphere and were multifocal in 30% of infants.[10] Imaging findings do appear to differ according to gestational age. In one study of preterm neonates, involvement of one or more lenticulostriate branches was most common among infants 28-32 weeks of gestation with PAIS, whereas main cerebral artery branch involvement was seen only in those infants >32 weeks of gestation.[14]

In contrast to PAIS, it is important to consider that CSVT often presents with hemorrhage on imaging (even small clots can cause severe venous infarction and hemorrhage in both gray and white matter), which is one of the reasons it is likely an under-diagnosed entity. Therefore, CSVT should always be considered in a full-term infant with intraventricular hemorrhage, particularly when observed in combination with a thalamic hemorrhage or bilateral white matter injury.[15,16] A recent review moves this concept one step forward, stating that a term baby with intraventricular hemorrhage has CSVT until proven otherwise, again especially when thalamic infarction or bleeding is noted.[3] As with PAIS, imaging findings often differ between premature and term infants with CSVT. Premature infants with CSVT typically demonstrate more extensive white matter damage compared with the thalamic hemorrhage and punctate white matter lesions more commonly found in full-term infants.[15]

In a study of 242 premature infants (gestational age <29 weeks) undergoing cranial ultrasonography, CSVT was identified in 4.4% of infants, all of whom were asymptomatic.[17] Because of the high incidence of CSVT identified in this study, the authors recommend that screening cranial ultrasonography in premature infants include color Doppler imaging with scans obtained through the mastoid fontanelle. Including the mastoid fontanelle allows for visualization of the transverse sinus, which was the most frequently affected area in this study of premature infants with CSVT.

Risk factors

Historically, the most active area of research in perinatal stroke has surrounded the identification of risk factors for PAIS and CSVT. There is a great deal of overlap in known risk factors for these diseases, and maternal, perinatal, and neonatal characteristics have all been identified.

Risk factors in PAIS

Among infants with PAIS, unequivocal major thrombotic risk factors, such as congenital heart disease or meningitis, are identified in approximately one-third of cases, although the majority of cases appear to be multifactorial.[3] Several case-control studies have been published investigating the maternal, infant, and delivery characteristics associated with PAIS.[5,12,14,18] A recent meta-analysis demonstrated a large overlap between the clinical presentation and risk factors of PAIS and global hypoxic ischemic encephalopathy, suggesting that hypoxia plays a major role in the pathogenesis of PAIS.[19]

Preeclampsia is an often-identified maternal risk factor, because this condition is known to reduce placental blood flow, resulting in fetal cerebral hypoperfusion and the potential for ischemic injury.[8] Other maternal risk factors include a history of infertility, primiparity, fever, prolonged rupture of membranes, and chorioamnionitis. Consumption of cocaine during pregnancy places a fetus at risk for arterial stroke attributable to vasoconstriction and vasospasm. A retrospective case-control study from France specifically looked at the question of whether maternal risk factors for thrombosis (such as increased age, obesity, and hypertension) are potential risk factors for PAIS.[20] These authors were the first to identify the potential role of maternal smoking as a promoter of symptomatic PAIS, likely as a result of inflammation/thrombosis of the placenta. However, in a large cohort of neonates with PAIS from the IPSS (n = 248), maternal health and pregnancies were usually normal.[10]

Identified risk factors at the time of delivery include meconium-stained amniotic fluid, instrument deliveries, and emergency cesarean section. However, it is unknown whether these or other identified risk events during delivery (such as fetal bradycardia, fetal decelerations, or prolonged labor) represent a true causal relationship or rather are reflective of ongoing stroke.[8] Fetal risk factors for PAIS include intrauterine growth restriction, 5-minute Apgar scores <7, hypoglycemia, congenital heart disease, early-onset sepsis/meningitis, dehydration, extracorporeal membrane oxygenation, and arterial dissection. In the international stroke cohort described above, 30% of the 248 neonates with PAIS required resuscitation during delivery, 23% had systemic illnesses, and <20% had identified cardiac or prothrombotic abnormalities.[10]

Risk factors in CSVT

Similar to perinatal arterial stroke, CSVT is a multifactorial disease, and maternal, perinatal, and neonatal risk factors have all been

identified.[6] In a large cohort of 104 neonates with CSVT, a single major risk factor was identified in 48% of cases and multiple risk factors in 39% of cases.[13] Specific risk factors overlap to a great degree with PAIS and include preeclampsia, chorioamnionitis, gestational diabetes, complicated delivery, meconium aspiration, and intubation at birth. Identified infant risk factors include meningitis, sepsis, dehydration, congenital heart defects, and extracorporeal membrane oxygenation. In one cohort of 52 neonates with CSVT, more than half (62%) of patients had a complicated delivery, such as vacuum-assisted vaginal delivery, forceps delivery, or emergency cesarean section.[21] The authors hypothesized that the etiology for this association could be severe changes in cerebral sinus venous flow during peripartum skull molding, leading to disruption of venous endothelium, activation of the coagulation cascade, and thrombus formation.

Although it has long been thought that placental pathology is a contributing factor to perinatal stroke, this has been the poorest studied risk factor. Elbers et al[22] reported on 12 patients from the Canadian Pediatric Ischemic Stroke Registry (5 with PAIS, 7 with CSVT) in which the placenta was available for pathologic examination. Placental lesions were present in 10 of 12 cases and were classified as thromboinflammatory process ($n = 6$), sudden catastrophic event ($n = 5$), decreased placental reserve ($n = 3$), and stressful intrauterine environment ($n = 2$). In another study of 15 infants with cerebral palsy and placentas available for examination, thrombi were identified in 11 of the placentas.[23]

Thrombophilia and perinatal stroke

The role of genetic thrombophilias in the pathogenesis of perinatal stroke is controversial and poorly understood. A major challenge in this research arena has been the difficulty in obtaining comprehensive thrombophilia evaluations in medically complicated neonates. Even in a cohort study of neonates from the Canadian Pediatric Ischemic Stroke Registry, in which standardized testing was part of the protocol, only 58% of neonates (48 of 83) had complete testing.[24]

Thrombophilia in PAIS

In a large case-control study of PAIS, thrombophilias were more often observed in cases (68%) than in age and sex-matched controls (24%).[25] A meta-analysis on the effect of thrombophilia on risk of first childhood stroke included a subanalysis of six studies investigating thrombophilia in PAIS, which demonstrated an odds ratio of 3.56 for Factor V Leiden (95% confidence interval, 2.29-5.53) and 2.02 for prothrombin gene variant (95% confidence interval, 1.02-3.99).[26] The presence of thrombophilia is also associated with poor neurological outcome in PAIS, specifically an increased risk of unilateral spastic cerebral palsy. In a small but striking study, 8 of 11 patients with PAIS and hemiplegia or global developmental delay had Factor V Leiden or elevated Factor VIII levels, whereas only one of the 13 PAIS patients with normal neurodevelopmental outcomes had an abnormal thrombophilia screen.[27] The strength of this study was that all 24 patients had the same comprehensive thrombophilia evaluation performed, which, as stated previously, has not been the case in larger outcomes studies.

Thrombophilia in CSVT

As in PAIS, prothrombotic factors are found frequently in neonates with CSVT, but their role remains unclear. One study revealed higher incidences of Factor V Leiden and methylene tetrahydrofolate reductase (MTHFR) polymorphisms[9] and another study reported a high incidence of MTHFR polymorphisms,[21] but all infants had documented normal homocysteine levels. Furthermore, there is growing evidence that MTHFR polymorphism testing has minimal clinical utility and should not be included in a routine evaluation for thrombophilia.[28]

The body of published work does support the idea that inherited thrombophilias increase the risk of thrombosis in a neonate, perhaps allowing a thrombotic event to be triggered by an otherwise minor adverse perinatal event.[27] However, the low rate of thrombus recurrence in both PAIS and CSVT support the idea that thrombophilias are only one of many factors that contribute to the development of a perinatal stroke. Also, unlike studies of thrombophilia screening in older children with venous thrombosis or spontaneous ischemic stroke, combination thrombophilias are rarely identified in perinatal stroke.[25] At this time, the value of performing a comprehensive thrombophilia evaluation outside of a research setting remains unclear. Although a positive thrombophilia screen could predict worse neurodevelopmental prognosis, one could argue that the neurodevelopment of any infant who has experienced a cerebral infarct should be monitored closely, with aggressive early intervention services in place.

The value of thrombophilia testing is also diminished because we do not know the effect of a positive thrombophilia screen in this setting on the risk of future thrombotic events. The only data available regarding the effect of thrombophilias on risk of recurrence comes from a study of 215 neonates with PAIS followed for a median of 3.5 years (range, 1-8 years).[29] Only 7 patients had recurrent thrombosis (acute arterial ischemic stroke, $n = 4$; CSVT, $n = 2$; deep vein thrombosis, $n = 1$). Five of the 7 patients had underlying clinical risk factors at the time of recurrence (mastoiditis during a CSVT recurrence, congenital heart disease, two diarrheal illnesses, and one patient with congenital heart disease, a central venous line, and immobilization). The thrombophilias identified in this small cohort included protein C deficiency ($n = 1$) and elevated lipoprotein(a) ($n = 2$). One patient had MTHFR C677T genotype and moderately elevated homocysteine, and two patients [including one of the elevated lipoprotein(a) patients] had MTHFR T677T genotype. However, since the time of publication of this review, there has been growing evidence that MTHFR polymorphism testing has minimal clinical utility and should not be ordered as part of a routine evaluation for thrombophilia.[28]

Such limited evidence (one study with a short timeframe of follow-up) cannot answer many of the questions that hematologists face in clinical practice. Can an adolescent female with a history of perinatal stroke be prescribed oral contraceptives? Should a 14-year-old male with a history of perinatal stroke receive thromboprophylaxis after orthopedic surgery? Thrombophilia testing is likely most informative in neonates without other identified etiologies for their thrombotic events or those with positive family history of thrombosis and, as always, should be considered on a case-by-case basis.

Use of anticoagulants and other management strategies

For neonates with PAIS, there is a lack of evidence supporting the routine use of anticoagulation, and evidence-based guidelines from the American College of Chest Physicians recommend anticoagulation only for infants with an ongoing cardioembolic source.[30] In a cohort of 248 infants with PAIS from the IPSS, antithrombotic therapy was initiated in only 21% of patients, and its use varied internationally.[10] In the 52 infants receiving anticoagulation, agents

included low–molecular–weight heparin (54%), unfractionated heparin (23%), aspirin (27%), warfarin (4%), and multiple medications (19%). Anticoagulation was more commonly used in Europe and in infants with congenital heart disease or inherited thrombophilias. Although there has been some interest in using thrombolysis in older children with arterial stroke, thrombolysis will likely not be explored in neonates as a result of increased safety concerns and the fact that symptoms of PAIS typically occur after 24 hours of life rather than at the time of acute injury.

Therefore, the management focus for PAIS will be on therapies that aim to regenerate or remodel the nervous system. Recombinant human erythropoietin (rhEPO), for example, reduces hypoxia-ischemia–induced free radical formation and inflammation and, in animal models of neonatal stroke, has demonstrated a reduction of infarction volumes and improvement of cognitive function.[31] Benders et al[32] recently published their experience with the use of rhEPO in a feasibility and safety study of 21 infants with PAIS. Hemodynamic (heart rate, blood pressure) or hematologic (cytopenias, increase in prothrombin or activated partial prothrombin times) adverse events did not occur with the use of rhEPO. However, in a subanalysis of 10 rhEPO-treated neonates compared with non-treated historical controls, the authors did not identify a difference in residual infarction volumes or neurodevelopmental outcome. Therefore, although rhEPO appears to be a safe therapy, larger studies are needed to evaluate whether there are beneficial effects.

Anticoagulation is more commonly used in CSVT, although clinical equipoise still exists, and practices are known to vary by geographic location. A publication from the IPSS reviewed treatment data for 81 neonates with CSVT.[33] Overall, 53% received an anticoagulant or antiplatelet medication. Fourteen infants received unfractionated heparin, 34 received low–molecular–weight heparin (either alone or after unfractionated heparin), 1 received warfarin, and 2 received aspirin preceded by low–molecular–weight heparin. Neonates from the United States were significantly less likely to receive anticoagulation than neonates from other countries (25% versus 68%). However, neonates in the United States were not more likely to have parenchymal hemorrhage, and no other clinical factors investigated, including the presence of hemorrhage, were found to be predictors of anticoagulation. The authors hypothesized that the lack of association between hemorrhage and treatment was attributable to either the small sample size or clinician familiarity with the adult literature in which anticoagulation to treat CSVT in the presence of cerebral hemorrhage has been shown not to worsen outcomes.

In fact, withholding anticoagulation in CSVT appears to be associated with an increased risk of propagation of ~30% compared with only 5% recurrence in patients receiving anticoagulation.[24] With regards to safety, in one retrospective multicenter study from The Netherlands including 52 neonates with CSVT, no hemorrhagic complications were identified in the 22 patients that received anticoagulation.[21] A small study of 7 neonates with CSVT and thalamic hemorrhage suggests that anticoagulation is even safe in this setting.[34]

The American College of Chest Physicians guidelines recommend that neonates with CSVT receive anticoagulation with low–molecular–weight heparin for 6-12 weeks. If significant hemorrhage is present at the time of diagnosis, clinicians can choose to initiate anticoagulation or choose to observe the patient, with repeat imaging after 5-7 days. If progression is noted on repeat imaging, then anticoagulation is recommended.[30] In contrast, the American Heart Association guidelines published in 2008 recommend anticoagulants in CSVT only in the setting of thrombus progression, multiple emboli, or a severe prothrombotic state.[35] Because clinical equipoise still exists and data are so limited, randomized clinical trials are sorely needed in perinatal CSVT and are under development.[3] For example, it remains unknown whether treatment with anticoagulation results in faster recanalization of occluded vessels or with improved long-term neurodevelopmental outcomes.

Supportive care strategies are also under investigation in perinatal CSVT. Tan et al[36] have demonstrated that the occipital bone compression seen in supine neonates is associated with CSVT, presumably because of increased venous stasis. Later work by this group revealed that a pillow alleviating occipital decompression can increase blood flow in the sigmoid sinus and superior sagittal sinus, thus representing a possible noninvasive neuroprotective intervention for the treatment of CSVT or even a prevention strategy in high-risk neonates.[37]

Summary

The perinatal period is a high-risk time period for stroke. Current evidence demonstrates the multifactorial etiology of perinatal stroke, which includes a combination of maternal, delivery, and neonatal factors. The importance of inherited thrombophilia in the pathophysiology and long-term outcomes of perinatal stroke requires additional study. At this time, there is no evidence to support routine extensive thrombophilia screening outside of a research setting. Anticoagulation is rarely indicated in PAIS, and future work should focus on neuroprotective prevention and alternate treatment strategies. Anticoagulation does appear to be safe in CSVT and may prevent thrombus progression, but clinical equipoise remains, and clinical trials are needed to obtain evidence regarding short- and long-term efficacy outcomes.

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References

1. Kirton A, Deveber G. Life after perinatal stroke. *Stroke*. 2013;44(11):3265-3271.
2. Raju TN, Nelson KB, Ferriero D, Lynch JK, Participants N-NPSW. Ischemic perinatal stroke: summary of a workshop sponsored by the National Institute of Child Health and Human Development and the National Institute of Neurological Disorders and Stroke. *Pediatrics*. 2007;120(3):609-616.
3. Kirton A, deVeber G. Paediatric stroke: pressing issues and promising directions. *Lancet Neurol*. 2015;14(1):92-102.
4. Laugesaar R, Kolk A, Tomberg T, et al. Acutely and retrospectively diagnosed perinatal stroke: a population-based study. *Stroke*. 2007;38(8):2234-2240.
5. Lee J, Croen LA, Backstrand KH, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the infant. *JAMA*. 2005;293(6):723-729.
6. van der Aa NE, Benders MJ, Groenendaal F, de Vries LS. Neonatal stroke: a review of the current evidence on epidemiology, pathogenesis, diagnostics and therapeutic options. *Acta Paediatr*. 2014;103(4):356-364.
7. Golomb MR, Fullerton HJ, Nowak-Gottl U, Deveber G, International Pediatric Stroke Study G. Male predominance in childhood ischemic stroke: findings from the international pediatric stroke study. *Stroke*. 2009;40(1):52-57.

8. Fernandez-Lopez D, Natarajan N, Ashwal S, Vexler ZS. Mechanisms of perinatal arterial ischemic stroke. *J Cereb Blood Flow Metab*. 2014;34(6): 921-932.
9. Fitzgerald KC, Williams LS, Garg BP, Carvalho KS, Golomb MR. Cerebral sinovenous thrombosis in the neonate. *Arch Neurol*. 2006;63(3): 405-409.
10. Kirton A, Armstrong-Wells J, Chang T, et al. Symptomatic neonatal arterial ischemic stroke: the International Pediatric Stroke Study. *Pediatrics*. 2011;128(6):e1402-e1410.
11. Nwosu ME, Williams LS, Edwards-Brown M, Eckert GJ, Golomb MR. Neonatal sinovenous thrombosis: presentation and association with imaging. *Pediatr Neurol*. 2008;39(3):155-161.
12. Wu YW, March WM, Croen LA, Grether JK, Escobar GJ, Newman TB. Perinatal stroke in children with motor impairment: a population-based study. *Pediatrics*. 2004;114(3):612-619.
13. Moharir MD, Shroff M, Pontigon AM, et al. A prospective outcome study of neonatal cerebral sinovenous thrombosis. *J Child Neurol*. 2011;26(9):1137-1144.
14. Benders MJ, Groenendaal F, Uiterwaal CS, et al. Maternal and infant characteristics associated with perinatal arterial stroke in the preterm infant. *Stroke*. 2007;38(6):1759-1765.
15. Kersbergen KJ, Groenendaal F, Benders MJ, et al. The spectrum of associated brain lesions in cerebral sinovenous thrombosis: relation to gestational age and outcome. *Arch Dis Child Fetal Neonatal Ed*. 2011;96(6):F404-F409.
16. Wu YW, Hamrick SE, Miller SP, et al. Intraventricular hemorrhage in term neonates caused by sinovenous thrombosis. *Ann Neurol*. 2003;54(1): 123-126.
17. Raets MM, Sol JJ, Govaert P, et al. Serial cranial US for detection of cerebral sinovenous thrombosis in preterm infants. *Radiology*. 2013; 269(3):879-886.
18. Harteman JC, Groenendaal F, Kwee A, Welsing PM, Benders MJ, de Vries LS. Risk factors for perinatal arterial ischaemic stroke in full-term infants: a case-control study. *Arch Dis Child Fetal Neonatal Ed*. 2012;97(6):F411-F416.
19. Luo L, Chen D, Qu Y, Wu J, Li X, Mu D. Association between hypoxia and perinatal arterial ischemic stroke: a meta-analysis. *PLoS One*. 2014;9(2):e90106.
20. Darmency-Stamboul V, Chantegret C, Ferdynus C, et al. Antenatal factors associated with perinatal arterial ischemic stroke. *Stroke*. 2012;43(9):2307-2312.
21. Berfelo FJ, Kersbergen KJ, van Ommen CH, et al. Neonatal cerebral sinovenous thrombosis from symptom to outcome. *Stroke*. 2010;41(7): 1382-1388.
22. Elbers J, Viero S, MacGregor D, DeVeber G, Moore AM. Placental pathology in neonatal stroke. *Pediatrics*. 2011;127(3):e722-e729.
23. Kraus FT. Cerebral palsy and thrombi in placental vessels of the fetus: insights from litigation. *Hum Pathol*. 1997;28(2):246-248.
24. Moharir MD, Shroff M, Stephens D, et al. Anticoagulants in pediatric cerebral sinovenous thrombosis: a safety and outcome study. *Ann Neurol*. 2010;67(5):590-599.
25. Gunther G, Junker R, Strater R, et al. Symptomatic ischemic stroke in full-term neonates : role of acquired and genetic prothrombotic risk factors. *Stroke*. 2000;31(10):2437-2441.
26. Kenet G, Lutkhoff LK, Albisetti M, et al. Impact of thrombophilia on risk of arterial ischemic stroke or cerebral sinovenous thrombosis in neonates and children: a systematic review and meta-analysis of observational studies. *Circulation*. 2010;121(16):1838-1847.
27. Mercuri E, Cowan F, Gupte G, et al. Prothrombotic disorders and abnormal neurodevelopmental outcome in infants with neonatal cerebral infarction. *Pediatrics*. 2001;107(6):1400-1404.
28. Hickey SE, Curry CJ, Toriello HV. ACMG Practice Guideline: lack of evidence for MTHFR polymorphism testing. *Genet Med*. 2013;15(2):153-156.
29. Kurnik K, Kosch A, Strater R, et al. Recurrent thromboembolism in infants and children suffering from symptomatic neonatal arterial stroke: a prospective follow-up study. *Stroke*. 2003;34(12):2887-2892.
30. Monagle P, Chan AK, Goldenberg NA, et al. Antithrombotic therapy in neonates and children: antithrombotic therapy and prevention of thrombosis, 9th ed: American College of Chest Physicians evidence-based clinical practice guidelines. *Chest*. 2012;141(2 Suppl):e737S-801S.
31. Sola A, Wen TC, Hamrick SE, Ferriero DM. Potential for protection and repair following injury to the developing brain: a role for erythropoietin? *Pediatr Res*. 2005;57(5 Pt 2):110R-117R.
32. Benders MJ, van der Aa NE, Roks M, et al. Feasibility and safety of erythropoietin for neuroprotection after perinatal arterial ischemic stroke. *J Pediatr*. 2014;164(3):481-486.e1-2.
33. Jordan LC, Rafay MF, Smith SE, et al. Antithrombotic treatment in neonatal cerebral sinovenous thrombosis: results of the International Pediatric Stroke Study. *J Pediatr*. 2010;156(5):704-710, 710e1-710.e2.
34. Kersbergen KJ, de Vries LS, van Straaten HL, Benders MJ, Nievelstein RA, Groenendaal F. Anticoagulation therapy and imaging in neonates with a unilateral thalamic hemorrhage due to cerebral sinovenous thrombosis. *Stroke*. 2009;40(8):2754-2760.
35. Roach ES, Golomb MR, Adams R, et al. Management of stroke in infants and children: a scientific statement from a Special Writing Group of the American Heart Association Stroke Council and the Council on Cardiovascular Disease in the Young. *Stroke*. 2008;39(9):2644-2691.
36. Tan M, Deveber G, Shroff M, et al. Sagittal sinus compression is associated with neonatal cerebral sinovenous thrombosis. *Pediatrics*. 2011;128(2):e429-e435.
37. Tan MA, Miller E, Shroff MM, Deveber GA, Kirton A. Alleviation of neonatal sinovenous compression to enhance cerebral venous blood flow. *J Child Neurol*. 2013;28(5):583-588.