

Fetal thrombophilia, perinatal stroke, and novel ideas about CP

Recent research findings point to thrombophilia and to stroke before or right after birth as one more basis for cerebral palsy. But can the knowledge make a difference in outcome?

Thrombosis is hypothesized to be the more common mechanism underlying cerebral palsy in many cases of maternal or fetal thrombophilia; for that reason, understanding the impact of maternal and fetal thrombophilia on pregnancy outcome is of paramount importance when counseling patients.

Is a maternal and fetal thrombophilia work-up needed in women who give birth to a term infant with cerebral palsy? Prospective studies are needed to evaluate whether that is the case. In this article, we review the literature on fetal thrombophilia and its role in explaining some cases of perinatal stroke that lead, ultimately, to cerebral palsy.

The several causes of cerebral palsy

Cerebral palsy is the most common chronic motor disability of childhood. Approximately 2 to 2.5 of every 1,000 children are given a diagnosis of this disorder every year.^{1,2} The condition appears early in life; it is not the result of recognized progressive disease.¹ Risk factors for cerebral palsy are multiple and heterogeneous^{1,3,4-6}:

- **Prematurity.** The risk of developing cerebral palsy correlates inversely with gestational age.^{7,8} A premature infant who weighs less than 1,500 g at birth has a risk of cerebral palsy that is 20 to 30 times greater than that of a full-term, normal-weight newborn.^{3,4}

- **Hypoxia and ischemia.** These are the conditions most often implicated as the cause of cerebral palsy. Fetal heart-rate monitoring was introduced in the 1960s in the hope that interventions to prevent hypoxia and ischemia would reduce the incidence of cerebral palsy. But monitoring

Caroline L. Stella, MD

Dr. Stella is a Fellow in the Division of Maternal-Fetal Medicine at the University of Cincinnati College of Medicine, Cincinnati, Ohio.

Helen Y. How, MD

Dr. How is a Professor in the Division of Maternal-Fetal Medicine at the University of Cincinnati College of Medicine, Cincinnati, Ohio.

Baha M. Sibai, MD

Dr. Sibai is a Professor in the Division of Maternal-Fetal Medicine at the University of Cincinnati College of Medicine, Cincinnati, Ohio.

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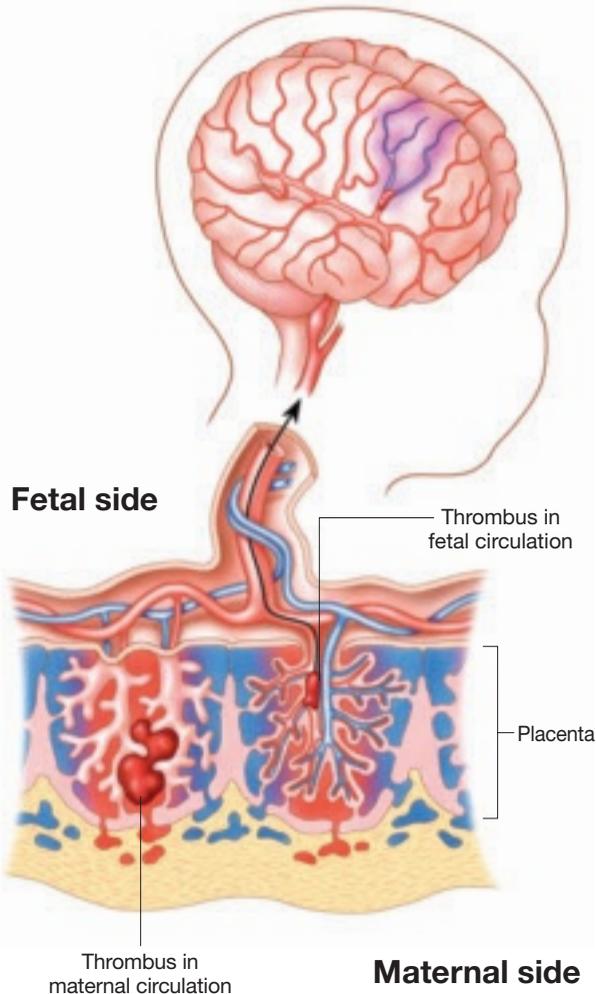
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Thrombophilia can lead to thrombosis at the maternal or the fetal interface



Thrombosis on the maternal side may lead to severe preeclampsia, intrauterine growth restriction, abruptio placenta, or fetal loss. Thrombosis on the fetal side can be a source of emboli that bypass hepatic and pulmonary circulation and travel to the fetal brain and cause a catastrophic event, such as perinatal arterial stroke via arterial thrombosis, cerebral sinus venous thrombosis, or renal vein thrombosis.

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has not had that effect—most likely, because some cases of cerebral palsy are caused by perinatal stroke.⁹ In fact, a large, population-based study has demonstrated that potentially asphyxiating obstetrical conditions account for only about 6% of cases of cerebral palsy.⁶

• **Thrombophilia.** Several recent studies report an association between fetal thrombophilia and both neonatal stroke and cerebral palsy.¹⁰⁻¹⁴ That association provides a possible explanation for adverse pregnancy outcomes

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TABLE 1 Case reports reveal an association between fetal thrombophilias and cerebral palsy

Study (type)	Cases of CP	Thrombophilias present	
		Number	Type
Harum et al ³⁶ (case report)	1	1	Factor V Leiden
Thorarensen et al ³⁷ (case report)	3	3	Factor V Leiden
Lynch et al ² (case series)	8	8	Factor V Leiden
Halliday et al ³⁸ (case series)	55	5	Factor V Leiden; prothrombin mutation
Smith et al ³⁹ (case series)	38	7	Factor VIIIc
Nelson et al ⁴⁰ (case series)	31	20	Factor V Leiden; protein C deficiency

TABLE 2 How often is a fetal thrombophilia the likely underlying cause of cerebral palsy?

Thrombophilia*	Prevalence of CP†	Odds ratio
Factor V Leiden	6.3%	0.62 (0.37–1.05)
Prothrombin gene	5.2%	1.11 (0.59–2.06)
MTHFR 677	54.1%	1.27 (0.97–1.66)
MTHFR 1298	39.4%	1.08 (0.69–1.19)
MTHFR 677/1298	15.1%	1.18 (0.82–1.69)

* Heterozygous or homozygous

† Among 354 subjects with thrombophilia studied⁴¹

Key: MTHFR, methyltetrahydrofolate reductase

that have otherwise been ascribed to events during delivery.^{15–23} Although thrombophilia is a recognized risk factor for cerebral palsy, the strength of the association has still not been fully investigated. **TABLE 1** and **TABLE 2** summarize studies that have examined this association. Given the rarity of both inherited thrombophilias and cerebral palsy, however, an enormous number of cases would be required to fully establish a causal relationship.

Understanding thrombophilia

“Thrombophilia” describes a spectrum of congenital or acquired coagulation disorders associated with venous and arterial thrombosis.²⁴ These disorders can occur in the mother or in the fetus, or in both concomitantly.

Fetal thrombophilia has a reported incidence of 2.4 to 5.1 cases for every 100,000 births.²⁵ Whereas maternal thrombophilia has a substantially higher incidence, both maternal and fetal thrombophilia can lead to adverse maternal and fetal events.

The incidence of specific inherited fetal thrombophilias is summarized in **TABLE 3**. Maternal thrombophilia is generally associated with various adverse pregnancy outcomes, particularly cerebral palsy and perinatal stroke.^{9,26}

Thrombophilia leads to thrombosis at the maternal or fetal interface (**FIGURE**, page 27):

- When thrombosis occurs on the **maternal side**, the consequence may be severe pre-eclampsia, intrauterine growth restriction, abruptio placenta, or fetal loss.^{27–29}
- Thrombosis on the **fetal side** can be a source of emboli that bypass hepatic and pulmonary circulation and travel to the fetal brain.³⁰ As a result, the newborn can sustain a catastrophic event such as perinatal arterial stroke via arterial thrombosis, cerebral sinus venous thrombosis, or renal vein thrombosis.²⁵

Perinatal and neonatal stroke

Perinatal stroke is defined as a cerebrovascular event that occurs between 28 weeks of gestation and 28 days of postnatal age.³⁰ Incidence is approximately 17 to 93 cases for every 100,000 live births.⁹

Neonatal stroke occurs in approximately 1 of every 4,000 live births.³⁰ In addition, 1 in every 2,300 to 4,000 newborns is given a diagnosis of ischemic stroke in the nursery.⁹

Stroke and cerebral palsy

Arterial ischemic stroke in the newborn accounts for 50% to 70% of cases of congenital hemiplegic cerebral palsy.¹¹ Factor V Leiden

TABLE 3 Inherited thrombophilias among the general population

Study	Number	Protein gene		
		Factor V Leiden	mutation	MTHFR
Gibson et al ⁴¹ (2003)	708	9.8%	4.7%	15.1%*
Dizon-Townson et al ⁴² (2005)	4,033	3.0%	Not reported	Not reported
Infante-Rivard et al ⁴³ (2002)	472	3.3%	1.3%	43% to 49%
Stanley-Christian et al ⁴⁴ (2005)	14	0	0	0
Currie et al ⁴⁵ (2002)	46	13.0%	Not reported	Not reported
Livingston et al ⁴⁶ (2001)	92	0	2%	4%
Schlembach et al ⁴⁷ (2003)	28	4.0%	2%	Not reported
Dizon-Townson et al ⁴⁸ (1997)	130	8.6%	Not reported	Not reported

* Heterozygous and homozygous carriers of MTHFR C677T and A1298C
Key: MTHFR, methyltetrahydrofolate reductase

mutation, prothrombin gene mutation, and a deficiency of protein C, protein S, and antithrombin III have, taken together in two studies, been identified in more than 50% of cerebral ischemic strokes.^{31,32} In addition to these thrombophilias, important risk factors for perinatal and neonatal stroke include:

- thrombosis in placental villi or vessels
- infection
- use of an intravascular catheter.³³

What causes perinatal stroke?

The mechanism that underlies perinatal stroke is a thromboembolic event that originates from either an intracranial or extracranial vessel, the heart, or the placenta.¹⁰ A recent meta-analysis by Haywood and colleagues found a statistically significant correlation between protein C deficiency, MTHFR C677T (methyltetrahydrofolate reductase), and the first occurrence of arterial ischemic stroke

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in a pediatric population.³⁴ Associations between specific thrombophilias and perinatal stroke, as well as pediatric stroke, have been demonstrated (TABLE 4, page 32), but we want to emphasize that the absolute risks in these populations are very small.^{34,35} In addition, the infrequency of these thrombophilias in the general population (TABLE 3, page 29) means that their positive predictive value is extremely low.

Brain injury

The brain is the largest and most vulnerable fetal organ susceptible to thrombi that are formed either in the placenta or elsewhere.¹⁶ A review of cases of cerebral palsy has revealed a pathologic finding, fetal thrombotic vasculopathy (FTV), that has been associated with brain injury.¹⁶ Arias and colleagues¹⁷ and Kraus¹⁸ have observed a correlation among cerebral palsy, a thrombophilic state, and FTV.

Furthermore, Redline found that the presence of severe fetal vascular lesions correlated highly with neurologic impairment and cerebral palsy.¹⁹

What is the take-home message?

Regrettably for patients and their offspring, evidence about the relationship between thrombophilia and an adverse neurologic outcome is insufficiently strong to offer much in the way of definitive recommendations for the obstetrician.

We can, however, make some *tentative* recommendations on management:

Consider screening. When cerebral palsy occurs in association with perinatal stroke, fetal and maternal screening for thrombophilia can be performed.³⁴ The recommended thrombophilia panel comprises tests for:

- factor V Leiden
- prothrombin G20210
- anticardiolipin antibody
- MTHFR mutation.¹⁰

Family screening has also been suggested in cases of **1)** multiple prothrombotic risk factors in an affected newborn **and 2)** a positive family history.⁹

The cost-effectiveness of screening for thrombophilia has not been evaluated in prospective studies, because the positive predictive value of such screening is extremely low.

Consider offering prophylaxis, with cautions. A mother whose baby has been given a diagnosis of thrombophilia and fetal or neonatal stroke can be offered thromboprophylaxis (heparin and aspirin) during any

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TABLE 4 Fetal thrombophilia is detected in as many as two thirds of study cases of perinatal and neonatal stroke

Study	Infants	Thrombophilia	Type of thrombophilia					
			FVL	APCR	ACA	AT	PC	PS
Golomb et al ³¹	22	14 (63%) *	1 *	3 *	12 *	0	0	0
Bonduel et al ³²	30	9 (30%) †	n/a	n/a	n/a	2	1	2
deVeber et al ⁴⁹	92	35 (38%) ‡	0	6	23 [‡]	10 [‡]	6 [‡]	3 [‡]
Mercuri et al ⁵⁰	24	10 (42%)	5	n/a	n/a	0	0	0
Günther et al ³⁵	91	62 (68%)	17	n/a	3	0	6	0
Govaert et al ⁵¹	40	3 (8%)	3	n/a	n/a	n/a	n/a	n/a

* FVL, APCR, and ACA diagnoses overlapped.

† Three patients had anticardiolipin antibody and plasminogen deficiency.

‡ Of 35 children, 21 had multiple abnormalities (combined coagulation deficiencies).

Key: ACA, anticardiolipin antibody; APCR, activated protein C resistance; AT, antithrombin deficiency;

FVL, factor V Leiden; PC, protein C deficiency; PS, protein S deficiency; n/a, not available or not studied



A mother whose baby has been given a diagnosis of thrombophilia and fetal or neonatal stroke can be offered thromboprophylaxis during any subsequent pregnancy

subsequent pregnancy. The usefulness of this intervention has not been well studied and is based solely on expert opinion, however,

so it is imperative to counsel patients on the risks and benefits of prophylactic therapy beforehand. ☺

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