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The Role of the Placenta in Perinatal Stroke: A Systematic Review

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Abstract

Context: Placental pathology may be an important missing link in the causal pathway of perinatal stroke. The study aim was to systematically review the literature regarding the role of the placenta in perinatal stroke. MEDLINE, Embase, Scopus, and Web of Science electronic databases were searched from 2000 to 2019. Studies were selected based on predefined criteria. To enable comparisons, placental abnormalities were coded using Redline's classification. **Results:** Ten studies met the inclusion criteria. Less than a quarter of stroke cases had placental pathology reported. Placental abnormalities were more common among children with perinatal stroke than in the control group. The most frequent placental abnormality was Redline's category 2 (thrombo-inflammatory process). **Conclusions:** Placental abnormalities appear to be associated with perinatal stroke, supporting additional indirect evidence and biological plausibility of a causative role. However, the results should be interpreted cautiously considering the low frequency of placental examination and lack of uniformity in placental pathology reporting. **Clinical Trial Registration:** PROSPERO Registration no: CRD42017081256.

Keywords

placental pathology, placental disease, stroke in children

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Perinatal stroke is the most common type of vascular stroke in children.[1] It is defined as a cerebrovascular event occurring from 20 weeks' gestation up to 28 postnatal days due to ischemia (secondary to embolism or anatomical narrowing of the blood vessels) or hemorrhage in a blood vessel of the brain. Perinatal stroke is classified by the timing and presentation of stroke: acute symptomatic perinatal stroke presenting in the neonatal period and presumed perinatal stroke presenting in infancy or childhood. Acute symptomatic perinatal stroke includes (1) neonatal arterial ischemic stroke, (2) neonatal cerebral sinovenous thrombosis, and (3) neonatal hemorrhagic stroke. Presumed perinatal stroke includes (1) arterial presumed perinatal ischemic stroke, (2) periventricular venous infarction, and (3) presumed perinatal hemorrhagic stroke.[2]

The true incidence of perinatal stroke is likely to be higher with better detection from advanced diffusion-weighted magnetic resonance imaging (MRI), especially in the case of hyperacute and acute stroke.[3] The estimates suggest an incidence of perinatal stroke between 1 in 1600 and 1 in 3000 live births.[4-6]

The pathogenesis of perinatal stroke is complex and multifactorial and includes an array of possible associations and putative risk factors. Neonatal infection such as meningitis may cause acute inflammatory processes in the cerebral arteries of the neonatal brain and may be an independent risk factor for arterial ischemic stroke.[7] Other likely independent risk factors include maternal smoking during pregnancy, intrapartum maternal fever (>38°C), low Apgar score at 5 minutes (<7), and neonatal hypoglycemia (blood glucose level <2 mmol/L).[8,9] Maternal use of cocaine during pregnancy is another risk factor for arterial stroke due to vasoconstriction and vasospasm in the fetus.[10]

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Hematologic conditions such as the physiological prothrombotic state during pregnancy prevents fetal, maternal, and neonatal bleeding at the time of delivery by increasing clotting factors V, VII, VIII, IX, X, and XII, von Willebrand factor, and plasma fibrinogen levels that could predispose to thromboembolism, thus elevating the risk of neonatal arterial ischemic stroke.[1] However, a case-control study (n = 182 cases and controls each) showed no difference in thrombophilia markers at 12 months of age, but the possible role of coagulopathy could not be excluded at the time of the perinatal stroke.[11] In addition, inherited prothrombotic conditions from genetic mutations like methylenetetrahydrofolate reductase and factor V Leiden gene mutations, and deficiency in protein C or S, are possible risk factors for neonatal arterial ischemic stroke but the evidence is weak and inconsistent.[12-14]

A direct link between congenital heart disease and perinatal stroke is not clear, although a cardioembolic event secondary to cardiac catheterization or cardiac surgery is a plausible cause of ischemic stroke.[15] A small population-based case-control study (n = 40) could not confirm a link between congenital heart disease in infants with perinatal arterial stroke, but the small sample size means the results should be interpreted cautiously.[16] Consensus exists that it is important to evaluate neonates with congenital heart disease for risk of perinatal stroke.[17]

The placenta is a vascular gestational organ carrying blood to and from the fetus and could have a significant role in the etiology of perinatal stroke via (1) placental blood flow abnormalities inducing clots, (2) sudden catastrophic events such as placental abruption creating acute hemodynamic instability or hypoperfusion in the fetus resulting in stroke, or (3) chorioamnionitis. The precise mechanism of placental abnormality and perinatal stroke is not well understood, partly because the placenta is commonly discarded before the clinical presentation of perinatal stroke.[18] Other placental abnormalities such as small or hypoplastic placenta, large placental infarcts, thrombosis, knot in the umbilical cord, narrow umbilical cord diameter, or abnormal insertion of the cord may trigger perinatal stroke because of placental vascular malperfusion.[19]

Aim

The aim of this study was to conduct a systematic review of published literature to explore the frequency of placental examination in perinatal stroke and to evaluate the role of the placenta in perinatal stroke within the studies.

Method

Study Design

A systematic review was conducted using the Cochrane recommendations for conducting a review, and the findings were reported using the Meta-analyses Of Observational Studies in Epidemiology (MOOSE) checklist.[20]

Data Source

MEDLINE, Embase, Scopus, and Web of Science (Science and Social Science Citation Index) electronic databases were systematically searched. A further hand search was conducted of publications using a sensitive methodological filter for placental pathology studies. Search terms were (placental pathology*) OR (aetiol* OR etiol*) AND perinatal stroke, as well as MeSH (Risk Factor OR Aetiology) AND perinatal stroke with limits of English language and human studies. A full list of search terms can be found in the Supplementary File and PROSPERO registration.

Study Selection

Studies from January 2000 to August 2019 were included for analysis if they met all the following criteria:

1. Perinatal stroke was the primary outcome (diagnosis of stroke was based on the reporting paper and not viewing of the original neuroimaging).
2. Risk factors were identified in the fetus and/or all live births.
3. Placental pathology data were available for any perinatal stroke case within the study.
4. All outcomes (including deaths) were reported.
5. All types of study designs
6. The articles were published in English.

The exclusion criteria were as follows:

1. Review papers
2. Abstracts and conference abstracts

Figure 1 summarizes the study flow using a PRISMA diagram.[21]

Data Extraction

Publications were reviewed to identify perinatal stroke cases that met the study selection criteria for stroke in a fetus, or an infant born preterm or term, or in a baby post term age. The principal reviewer (BR) and an independent second reviewer (IN) devised the search strategy. The reference lists of these selected studies were hand searched for further relevant articles, but no additional publications were identified.

An a priori designed data extraction tool was used based on recommendations from the Cochrane group. Extraction included study design, country of the study, gestational age, perinatal stroke types, risk factors of stroke, numbers of cases with placental examination, specific placental abnormality, clinical presentation and outcome of stroke and unadjusted and adjusted odds ratios if reported. Extraction of data from each of the 10 studies was carried out independently by both extractors (BR and IN). The quality of included studies was assessed using the Oxford Centre for Evidence-Based Medicine 2011 Levels of Evidence.[22]

Stroke Types

The article specifically sought to identify cases with a vascular cause of infarction to elucidate cases at higher risk of placental abnormality. Inconsistent terminology has been used in the literature to classify types of perinatal stroke. To enable aggregation of data, we recoded the strokes uniformly using Dunbar and Kirton's contemporary classifications.[2] The following variables were

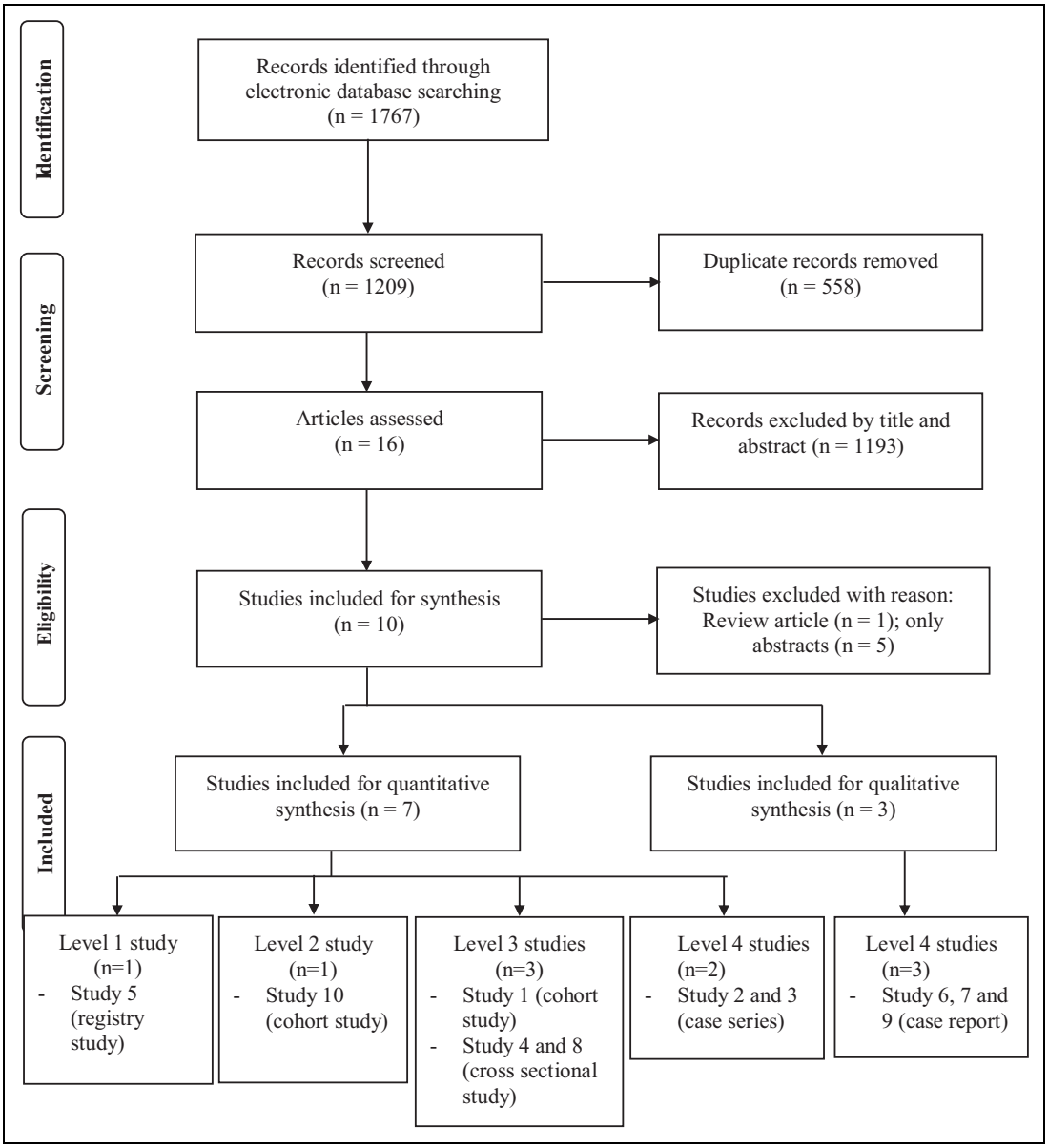

Figure 1. Study selection: Placental pathology in perinatal stroke.

extracted to name the different types of perinatal stroke: (1) age when stroke happened (fetal or in utero, neonatal from 0 to 7 days of age, and perinatal from 0 to 28 days of age), (2) type of vessel affected (arterial or venous), and (3) etiology (ischemic or hemorrhagic). Arterial ischemic stroke and cerebral stroke nomenclatures were also used interchangeably. It is important to note that some authors used the term *cerebral infarction* to describe a type of stroke. We acknowledge that cerebral infarction is not a reliable indicator of ischemic stroke as it is also used to describe cerebral infarction due to hypoxic-ischemic encephalopathy. After careful analysis of the cases from the reporting papers where authors used the term *cerebral infarction*, it could be confirmed that all cases had indeed experienced ischemic stroke. Discrepancies regarding classification of stroke and any potential chance of systematic bias were discussed and a final decision was made without requiring further adjudication (Table 1).

Risk Factors

Some of the included studies analyzed clusters of risk factors, which cannot be considered synonymous with true causation. The plausible causative factor among the variety of risk factors identified by the placental pathologist author (SA) are underlined for each of the perinatal stroke cases (Table 2). It is important to note that the term *fetal thrombotic vasculopathy*, which was used in some of the studies has now been superseded in the literature by the more accurate term *fetal vascular malperfusion*.[34,35] These terminologies were coded as interchangeable events.

Statistics

Descriptive statistics, n (%), were used for the etiologic and clinical variables extracted from papers. We intended to conduct a meta-

Table 1. Characteristics of Studies Included in the Systematic Review.

Study no:	Author (publication year)	Study origin	Study design	Study population	Study period	Sample size	Placental availability (percentage)	Placental abnormality (percentage)	Level of evidence as per OCEBM[22]
Study 1	Bernson-Leung (2018)[23]	USA	Retrospective Cohort study Case-control study	Preterm = 7	2005-2015	Cases → 46 Controls → 99	Cases → 46/46 Controls → 99/99	Cases → 41/46 (89%) Controls → 61/99 (62%) Reported *P* value (cases vs controls) *0.0007*	Level 3
Study 2	Fluss (2016)[24]	Switzerland (2 cases); France (3 cases)	Case series	Term; male = 3, female = 2	NR	5	2/5	2/2	Level 4
Study 3	Magnetti et al (2014)[25]	Italy	Retrospective Case series	Term = 3, Preterm = 2; male = 4, female = 1	2009-2013	5	5/5	3/5	Level 4
Study 4	Takenouchi et al (2012)[26]	USA	Retrospective Cross sectional study	Term	2004-2009	4	4/4	3/4	Level 3
Study 5	Elber et al (2011)[27]	Canada	Retrospective Registry study	34 wk to 28 postnatal days	1992-2006	186	12/186 (6%)	10/12 (83%)	Level 1
Study 6	Dueck (2009)[28]	Canada	Case report	Term	NR	1	1/1	1/1	Level 4
Study 7	Das (2008)[29]	USA	Case report	36 wk	NR	1	1/1	1/1	Level 4
Study 8	Curry (2007)[30]	USA	Prospective Cross-sectional study	NR	1997-2005	60	8/60 (13%)	7/8 (88%)	Level 3
Study 9	Ghidini (2006)[31]	USA	Case report	Fetus	NR	1	1/1	1/1	Level 4
Study 10	Lee (2005)[32]	USA	Retrospective Cohort study Case-control study	NR	1997-2002	Cases → 40 Controls → 120	Cases → 3/40 (8%) Controls → 11/120 (9%)	Cases → 3/3 (100%) Controls → 5/11 (45%)	Level 2
Total	10 studies		Prospective = 1 Retrospective = 9	Fetus to 28 postnatal days		n = 349	83/349 (24%)	72/83 (87%)	Level I = 1 Level II = 1 Level III = 3 Level IV = 5

*NR – Not Reported.
OCEBM – Level 1 (study 5): 'Local and current random sample survey'; Level 2 (study 10): 'Observational study with dramatic effect'; Level 3 (studies 1, 4 and 8): 'Local non-random sample'; Level 4 (studies 2, 3, 6, 7, 9): 'case-series or historically controlled studies'.

analysis; however, the data could not be extracted at the individual case level, precluding meaningful meta aggregation. Fisher exact associations were conducted for type of stroke and Redline's category classification of placental histopathology. Significance was set at $P < .05$. All analysis was conducted using Stata, version 14 (StataCorp, College Station, TX).

Results

Both reviewers (BR and IN) independently reviewed all 1209 titles/abstracts after excluding the duplicate studies. Sixteen studies were selected for full-text review. Of these, 6 were excluded (1 review paper and 5 abstracts or conference

Table 2. Etiologic Risk Factors and Relationship of Placental Pathology vs Types of Perinatal Stroke.[a]

Study no:	Cases	Nonplacental risk factors/associations	Placental abnormalities	Redline's categories[b]				Other[c]	Type of stroke	Outcome
				1	2	3	4			
Study 2	Case 1	Severe perinatal asphyxia, emergency CS, MSL, high serum lactate, maternal and infant protein C deficiency	Placental gross hypotrophy with chronic ischemic lesions, retroplacental hematoma			✓		Placental hypotrophy, Retroplacental hematoma	NAIS	Left spastic CP, epilepsy, mildintellectual disability
	Case 2	Neonatal protein C deficiency	Severely abnormal with multiple thrombosis, ischemic areas, fetal vasculopathy		✓	✓			NAIS	CP
Study 3	Case 3	Maternal hypodysfibrinogenemia	FTV, inflammatory lesions		✓				CSVT + NAIS	NR
	Case 4	Maternal infection, PROM, preeclampsia	Placental infarction, focal edema villi			✓		Focal edema of villi	CSVT + NAIS	NR
	Case 5	Neonatal sepsis, patent foramen ovale	Necrotizing chorioamnionitis		✓				NAIS	NR
Study 4	Case 6	NR	FTV		✓				NAIS	NR
	Case 7	NR	FTV		✓				NAIS	NR
	Case 8	NR	FTV		✓				NAIS	NR
Study 5	Case 9	IUGR, nuchal cord, oligohydramnios, polycythemia, CHD	Chronic villitis, distal villous immaturity, placental infarct, placental weight <3rd percentile			✓			NAIS	Mild motor dysfunction
	Case 10	IUGR, emergency CS, anaemia, CHD	Chronic villitis, chronic intervillositis, villous edema, positive immunostaining for $CD68^+$ cells		✓				NAIS	Lost to follow-up
	Case 11	GBS positive, abnormal FHR, emergency CS, feto-maternal hemorrhage, anaemia	Chorionic thrombosis, avascular fibrotic villi, increased nucleated red blood cells		✓				NAIS	Mild motor dysfunction
	Case 12	Abnormal FHR, emergency CS, anaemia, systemic thrombosis, CHD	Cord overcoiling, distal villous immaturity	✓					NAIS	Mild motor dysfunction
	Case 13	Infertility, placental abruption, emergency CS, DIC	Velamentous cord insertion, cord venous congestion, chronic villitis, chronic intervillositis, placental infarction, distal villous immaturity, placental weight <10th percentile	✓	✓	✓			NAIS	Mild motordysfunction, language delay

(continued)

Table 2. (continued)

Study no:	Cases	Nonplacental risk factors/associations	Placental abnormalities	Redline's categories[b]				Other[c]	Type of stroke	Outcome
				1	2	3	4			
	Case 14	GBS positive, PROM, sepsis, DIC	Severe and diffuse funisitis, acute cord thrombosis, cord venous congestion, severe chorioamnionitis, chorionic thrombosis, stem villous thrombosis, distal villous immaturity, villous chorangiosis		✓			Villous chorangiosis	CSVT	Language delay
	Case 15	APH, abnormal FHR, emergency CS, chorioamnionitis, sepsis, anaemia	Retroplacental hematoma, cord hemangioma, moderate chorioamnionitis, avascular fibrotic villi, distal villous immaturity		✓			Retroplacental hematoma	CSVT	Normal
	Case 16	Abnormal FHR, emergency CS	Marginal cord insertion, acute stem vessel thrombosis, acute chorionic thrombosis	✓	✓				CSVT	Mild motor dysfunction, language delay
	Case 17	CHD, postcardiac surgery	True cord knot and stricture, acute chorionic thrombosis, acute cord thrombosis, retro membranous hematoma	✓					CSVT	Language delay
	Case 18	Abnormal FHR, emergency CS	Cord stricture, stem villous thrombosis, chorionic thrombosis, placental infarct, distal villous immaturity, placental weight <10th percentile		✓	✓			CSVT	Mild motor dysfunction, language delay
Study 6	Case 19	Vacuum delivery	Chorioamnionitis, funisitis, vasculitis, layered deposition of fibrin, inflammatory material (lines of Zahn) within the umbilical vein confirmed thrombosis within the vein	✓	✓				NAIS	NR
Study 7	Case 20	MSL, anemia, thrombocytopenia	Large chorangioma with thrombosis, hemorrhage and infarction					Chorangioma	NAIS	NR

(continued)

Table 2. (continued)

Study no:	Cases	Nonplacental risk factors/associations	Placental abnormalities	Redline's categories[b] 1	2	3	4	Other[c]	Type of stroke	Outcome
Study 8	Case 21	NR	Fibrous plaques with increased intervillous fibrin					Fibrous plaques with increased intervillous fibrin	NAIS	NR
	Case 22	NR	Small and 20% infarcted			✓			NAIS	NR
	Case 23	NR	Circumvallate insertion					Circumvallate insertion	NAIS	NR
	Case 24	NR	Small extensive >25% infarcted			✓			NAIS	NR
	Case 24	NR	Small abnormal placenta			✓		Abnormal placenta	NAIS	NR
	Case 26	NR	Extensive dystrophic calcifications >35% with prominent syncytial knots			✓			NAIS	NR
	Case 27	NR	Chorioamnionitis with prominent decidual abscesses		✓				NAIS	NR
Study 9	Case 28	Reduced fetal movement, MSL, elevated nucleated red blood cells	Multiple thrombosed chorangiomas, small hemangiomas					Chorangiomatosis	NAIS	CP
Study 10	Case 29	NR	Staphylococcus positive on fetal side of placenta					Staphylococcus positive on fetal side of placenta	NAIS	NR
	Case 30	Preterm	Funisitis		✓				NAIS	NR
	Case 31		Acute chorioamnionitis, placental infarction		✓	✓			NAIS	NR
Total	31			5/31 = 16%	17/31 = 55%	11/31 = 35%	0/31 = Nil	8/31 = 26%	NAIS=24 CSVT=5 Combination (NAIS+CSVT)=2	

Abbreviations: APH, ante partum hemorrhage; CHD, congenital heart disease; CS, cesarean section; CSVT, cerebral sinovenous thrombosis; CTG, cardiotocography; DIC, disseminated intravascular coagulopathy; FHR, fetal heart rate; FM, fetal movement; FTH, fetal thrombotic vasculopathy; FTV, fetal thrombotic vasculopathy; GBS, group B *Streptococcus*; GDM, gestational diabetes mellitus; IUGR, intrauterine growth restriction; MSL, meconium-stained liquor; NAIS, neonatal arterial ischemic stroke; NR, not reported; PE, pre-eclampsia; PROM, prolonged rupture of membrane; US, ultrasonography.

[a] Study 1 could not be classified as per Redline's classification as the placental findings were not reported on case basis, hence not included in Table 2. The underline denotes a potentially causative risk factor identified by the placental pathologist author (SA).

[b] Redline's placental lesion has 4 categories[27,33]:

Category 1: Sudden catastrophic event: retroplacental hematoma and acute umbilical cord occlusion by thrombosis, true cord knots, cord overcoiling or abnormal cord insertion sites.

Category 2: Thrombo-inflammatory process: chorioamnionitis, villitis, chorionic vessel and stem vessel thrombi, and avascular fibrotic villi.

Category 3: Decreased placental reserve: defined by 2 or more of either multiple placental infarcts, distal villous immaturity, and placental weight <10th percentile for gestational age.

Category 4: Adaptive response to stressful intrauterine environment: increased fetal nucleated red blood cells or villous chorangiosis.

[c] Other: Placental pathology which could not be included in the Redline's categories.

abstracts). Both reviewers unanimously agreed on the 10 studies that met the inclusion criteria for analysis; thus, no arbitration of disputes was required (Figure 1). Ten studies published between 2000 and 2019 met the inclusion criteria (Table 1). All of the studies were conducted in high-income countries, and only 1 study was prospective (study 8). The studies consisted of 349 perinatal stroke cases from the period 1992-2015. Placental pathology reports were available for 24% (83/349) of the perinatal stroke cases. Of these, 87% (72/83) cases had abnormal placental pathology. In 31 cases, the type of stroke and placental pathology was reported on an individual case basis (Table 2).

Stroke

The most common type of perinatal stroke was neonatal arterial ischemic stroke (24/31; 77%). Category 2 of Redline's placental lesion was the most frequently reported placental abnormality (17/31; 55%). Most studies primarily focused on perinatal stroke cases. Perinatal stroke types were inconsistently classified. Studies 3 and 4 reported cases of fetal thrombotic vasculopathy and types of perinatal brain injuries, respectively. These 2 studies included perinatal stroke cases that were extracted and analyzed as per the study design. The characteristics of the selected studies are shown in Table 1. The studies used a standard definition of perinatal stroke applicable to the year they were published, although various nomenclatures were used to describe the type of stroke.[2] The studies included fetus and preterm and term infants up to 28 postnatal days. Some studies only reported data at the group level and not on an individual case basis.

Risk Factors

Of the 31 cases of stroke where the patients could be identified on an individual case-by-case basis (Table 2), 19 cases suggested both non-placental and placental associations related to perinatal stroke. The common nonplacental associations were caesarean section (n = 8/31; 26%), abnormal fetal heart rate (n = 5/31; 16%), anemia (n = 5/31; 16%), and congenital heart disease (n = 4/31; 13%).

Placenta

Placental findings (Table 2) were described at the individual case level for studies 2 to 10. Findings were also categorized using Redline's classification of placental histology, by BR and an independent expert pathology reviewer (SA). We intended to classify by the more contemporary and uniform comprehensive placental histopathology classification—the Amsterdam Placental Workshop Group Consensus Statement[34]—but could not, because the included studies were conducted and coded in the Redline classification era and data were insufficient for recoding.

For studies 5, 8, and 10, the frequency of placental histopathologic examination was 6% (n = 12/186), 13% (n = 8/60), and 8% (n = 3/40), respectively. Abnormal placental pathology for study 5 was 83% (n = 10/12), study 8 was 88% (n = 7/8), and study 10 was 100% (n = 3/3).

Of the 2 case-control studies (studies 1 and 10), study 1 found 89% (n = 41/46) abnormal placental pathology among the cases, compared with 62% (n = 61/99) in controls with the reported P value of <.001 (cases vs controls). Of note, study 10 found 100% abnormal placental pathology among the cases (n = 3/3) compared with 45% in controls (n = 5/11).

Placental Classifications

Studies 3 and 5 used Redline's placental histology classification[27,33] and study 1 adapted predefined categories of placental abnormality based on a local protocol. There was little uniformity in describing placental pathology across the other studies. To enable comparisons within this review, the placental reports were classified for studies 2 to 10 using Redline's classification (Table 2), and author SA had the final authority in case of any discrepancy.[36] Study 1 cases could not be accommodated within Redline's classification as the placental findings were not reported on an individual case basis.

Some of the placental abnormalities did not meet any of the Redline categories or were lacking sufficient information to permit any coding and thus these events were coded as "other" (Table 2) within our systematic review. The "other" category included (1) placental hypotrophy (case 1); (2) small abnormal placenta (case 25); (3) retroplacental hematoma (cases 1 and 15), which does not necessarily represent abruption and without clinical history or information regarding the chronicity is a common nonspecific finding post placental delivery; (4) chorangioma or chorangiomatosis (cases 20 and 28); (5) fibrous plaques with increased intervillous fibrin (case 21); (6) circumvallate insertion (case 23), which is more commonly associated with a chronic rather than an acute catastrophic event; and (7) Staphylococcal positive on the fetal side of the placenta (case 29) with no inflammatory response, which is likely to be a contaminant.

We also present a detailed description of the association between the type of placental pathology and type of stroke in Table 2. There were no statistically significant associations between the types of stroke and Redline's placental classification codes: category 1 (P = .404), category 2 (P = .102), category 3 (P = .441), or "other" (P = .494). Category 4 could not be analyzed statistically as there were no placental data coded with this placental abnormality.

Discussion

Perinatal stroke occurs because of a constellation of risk factors rather than an isolated event and can also be viewed as a cascading causal pathway.[37,38] The placenta is a very vascular gestational organ that is responsible for blood flow to and from the fetus and is likely to have a pivotal role in the causal pathway of perinatal stroke.[25,39]

Our review investigated the relationship between placental pathology and perinatal stroke among the multitude of possible associations and putative risk factors. We identified 10 studies (n = 349) of varying levels of evidence and potential sources of bias (levels 1, 2, 3, and 4). We found that there was a low frequency of placental examinations within the included studies, even for developed countries, 6%-13% (studies 5, 8, and 10). Nevertheless, when pathology was ordered, the placental pathology was often abnormal. The findings need to be interpreted cautiously as the frequency of placental histopathologic examination was low (studies 2, 5, 8, and 10), in contrast to the studies that directly sought cases of placental pathology (studies 1, 3, 4, 6, 7, and 9).

Plausible reasons for not ordering pathology were nonspecific and may include delayed clinical presentations of perinatal stroke, cost of placental storage and examination, failure of treating physicians to request placental examination, and the common practice of discarding the placenta soon after birth before it is recognized as an important pathology. Furthermore, we found that of the total placental examinations, 87% (Table 1; 72/83) had abnormal placental pathology. The abnormal yield was as follows: 55% (Table 2; 17/31) had a thrombo-inflammatory process at work, 32% (10/31) had decreased placental reserve, 16% (5/31) had a sudden catastrophic event and 19% (6/31) had associated placental risk factors.

We surmise that placental pathologies such as a sudden catastrophic event causing blood flow obstruction to the fetus (Redline's category I), or placental thrombo-inflammatory process (Redline's category II), or decreased placental reserve (Redline's category III) may have caused interruption of cerebral blood flow, thus giving rise to perinatal stroke. In our view, adaptive response to a stressful intrauterine environment (Redline's category IV) may be a fetal stress response to categories I, II, or III and therefore should be considered as a related pathology rather than an independent pathologic entity.

We sought to differentiate between the etiologic and circumstantial risk factors in order to identify the true causal pathway of stroke; for example, perinatal stroke due to thrombus from protein C deficiency (a protein that prevents blood clotting) or due to thrombus and fibrin formation in case of chorioamnionitis. The pathologist author proposed plausible causative factors (see Table 2) but these require confirmation in further research using rigorous methodologies.

It was also noted that, across the studies, perinatal stroke was seldom reported in the same manner. For example, neonatal arterial ischemic stroke was used as a synonym for arterial ischemic stroke, ischemic perinatal stroke, perinatal arterial stroke, and middle cerebral artery stroke. Future research should aim to harmonize terminology to enable aggregation of data.

Limitations and Recommendations:

Reporting quantity and quality. The major limitations of this review were sparse placental examinations, lack of standardization, and nonhomogenous reporting of placental pathology, which precluded aggregation of data. Comparisons between studies could be advanced if standardized methods of reporting key placental lesions such as a catastrophic event, placental infection, or placental adaptive response to stressful intrauterine environment were implemented within clinical care.

Reporting processes. Chorioamnionitis, a known risk factor for cerebral palsy, was the most prevalent risk factor identified in this systematic review, although more clarification of clinical, histologic, associated funisitis, villitis, or more importantly intravascular thrombi abnormalities would have been clinically and etiologically informative.[40] Thus, moving forward, we recommend that placental findings are reported synergistically for expert pathologists and clinicians to further elucidate the etiology and for clinical management of perinatal stroke. We also recommend that all placentas should be stored for 72 hours to create the opportunity for expert histopathologic examination.

Classification and nomenclature. We note that Redline's placental histology classification describes the actual effect rather than the etiology of the placental pathology.[36] For example, category I describes both the event and the cause, whereas category IV codes increased nucleated red blood cells, which may be a secondary downstream event to any of the abnormalities described in categories I, II, or III. In future, widespread adoption of the placental histopathology classification as per the Amsterdam Placental Workshop Group Consensus Statement is likely to yield a clear correlation between placental abnormality and perinatal stroke. Another limitation was the heterogeneity in the nomenclature of stroke type, which made it difficult to make definitive comparisons between the type of stroke and type of placental pathology. We therefore recommend adoption of the contemporary stroke nomenclature.[2]

Etiology and prevention. Proactive prevention of perinatal stroke is a research priority of both parents and clinicians. To make the paradigm shift toward identifying ways to prevent perinatal stroke, we recommend that the field makes a systematic and rigorous effort to elucidate the etiologic role of the placenta in cases of acute symptomatic perinatal stroke, ultimately aiming to identify novel treatment targets. An adequately powered case-control study, with standardized classification of placental pathology, while reporting abnormal placental pathology as well as a standardized nomenclature for stroke type, is needed to confirm a meaningful association between abnormal placental pathology and specific types of perinatal stroke.

Conclusion

In conclusion, placental abnormality appeared more common among children with perinatal stroke than controls. This result must be interpreted cautiously because of the low frequency of placental examination in published cases and the lack of uniformity in placental histopathology reporting. More research is required to verify the precise role of the placenta in the multifactorial etiology of perinatal stroke.

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Author Contributions

BR conceptualized and designed the study, designed the data collection instruments, collected data (first extractor), carried out the initial analyses, and drafted the initial manuscript. IN collected data (second extractor), assisted with the analyses, and critically reviewed the manuscript for important intellectual content. SA (Pathologist) assisted with the designing of data collection instruments, and assisted with interpretation and analyses of placental pathology. CG assisted with statistical analysis and interpretation of data, contributed to drafting and revising it critically for final approval. CM, KW, and NB contributed to the analysis and interpretation of data and critically reviewed the manuscript for important intellectual content.
All authors reviewed and revised the manuscript and approved the final version for publishing.

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