Placental pathologic lesions associated with stroke in term neonates

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Objective: To determine the birth prevalence of perinatal stroke in term born infants at our high-volume delivery center and assess the frequency of both gross and histologic placental pathologies associated with perinatal stroke using the Amsterdam Placental Workshop Group Consensus Statement guidelines and definitions.

Study Design: A single-center retrospective cohort study spanning 2010-2020.

Results: There were 129,759 live births at Parkland Hospital during the study period and a total of 18 term born infants leading to a birth prevalence of 1 in 6,829 infants. Perinatal risk factors were found in all but one patient, and 74% presented with seizures. Pathologic placental examination was available in 56% of the cohort and only one patient had normal placental examination. Acute histologic chorioamnionitis was described in five placentas (50%) and an additional two had isolated umbilical and/or chorionic plate vasculitis with or without funisitis compared to a rate of 28% with acute inflammation in a Control group. Chronic inflammation in the form of villitis of unknown etiology was described in three of the acutely inflamed placentas and was high-grade in each of those while none of the placentas from our Control group showed evidence of any chronic lesion.

Conclusion: Both acute and chronic placental inflammation are common in perinatal stroke; placental examination should be considered an essential component to the diagnostic workup.

Keywords
perinatal stroke, placenta, chorioamnionitis, villitis, perinatal asphyxia, vascular malperfusion, neonatal brain, neonatal seizure
Introduction

Perinatal stroke is defined as cerebrovascular injury occurring between 20 weeks gestational age until the 28th postnatal day. Perinatal stroke affects an estimated 1 in 2,300 to 1 in 5,000 term born infants (1–3). In broad terms, perinatal stroke comprises several entities including arterial ischemic stroke (AIS), cerebral sinus venous thrombosis (CSVT), and intracranial hemorrhage (ICH). Perinatal AIS is the most common form of stroke in term neonates and is a leading cause of hemiplegia in pediatric patients (4, 5). Perinatal AIS is characterized by imaging findings of parenchymal infarct in a specific arterial territory, and outcomes vary widely depending on timing of injury, lesion size, and location (6–8). Perinatal CSVT is less common entity most frequently affecting the sagittal and/or lateral sinus (9–11).

Numerous risk factors have been associated with perinatal stroke (12–20), which can be divided into maternal, fetal, and neonatal complications. Suspected maternal risk factors include preeclampsia and prothrombotic disorders, while fetal risk factors include intrauterine growth restriction, prolonged rupture of membranes, and congenital heart disease. Neonatal factors associated with perinatal stroke involve birth asphyxia, infection, and hematologic disorders. Despite numerous studies attempting to define risk factors for perinatal stroke, the etiology of the injury remains unclear in most cases. Some experts hypothesize that for AIS, a thromboembolus may originate from the placenta, enter fetal circulation, and cross the patent foramen ovale to result in cerebral artery obstruction (21), but no studies to date have confirmed this mechanism (22, 23). As much as 30% of neonatal AIS is multifocal, even in the absence of congenital cardiac disease (4), and recurrence postnatally is exceedingly rare, supporting this hypothesis of a placental origin of thromboembolism. The connection of the placenta to CSVT and ICH is less clear, but may be associated with chronic placental inflammation, a type of pathology linked to other neurologic morbidities (24, 25). Overall, there is a paucity of existing evidence directly linking placental disease to neonatal stroke.

The objective of this study was to determine the birth prevalence of perinatal stroke in term born infants at our high-volume delivery center, describe the clinical factors associated with perinatal stroke in our cohort, and assess the frequency of both gross and histologic placental pathologies associated with perinatal stroke using the Amsterdam Placental Workshop Group Consensus Statement guidelines and definitions. We hypothesized that perinatal stroke would be associated with acute inflammation of the placenta, maternal pregnancy complications, fetal congenital heart disease, and birth asphyxia.

Subjects and methods

Study subjects

This single-center retrospective cohort study was approved by the Institutional Review Board at University of Texas Southwestern Medical Center. All infants born at Parkland Hospital between 2010-2020 with a diagnosis of stroke were evaluated for inclusion in the study. Control placentas were collected as part of a separate prospective study, previously reported (26) with inclusion criteria of gestational age of at least 37 weeks, singleton pregnancy without diagnosis of fetal anomalies or fetal growth restriction, and no history of fetal asphyxia.

Demographic information was collected on both mother and infant including maternal age, gestational age at birth, infant sex, race, and ethnicity. Maternal pregnancy complications, fetal diagnoses, and birth characteristics were collected and percentiles for anthropometric data (27). Specific factors affecting risk for placental pathology were collected including maternal gravidity status, maternal diabetes mellitus (DM; both gestational and pre-gestational), any form of maternal hypertension, and presence of placenta accreta spectrum disease.

Placental pathology

In general, the approach to selection of placentas for pathologic examination include any maternal or fetal pregnancy complication, or any abnormality during labor or delivery including the need for advanced neonatal resuscitation. The standardized approach of our institution to placental pathology has been previously described (24). In summary, gross examination includes assessment of the umbilical cord, membranes, and placental disc. The trimmed placental weight is measured after removal of umbilical cord, fetal membranes, and non-adherent blood clots. Gross pathologies include placental size abnormalities [small for gestational age (SGA), <10th percentile; and large for gestational age (LGA), >90th percentile], umbilical cord anomalies, and aberrant placental disc shapes. To determine histopathology, placental discs are sectioned at 1-2 cm intervals and representative sections of parenchyma, as well as umbilical cord and fetal membranes, are examined. Lesions identified during sectioning are also examined. Based on the Amsterdam criteria (28), histopathologic abnormalities were divided into the following subcategories:

1. Acute histologic chorioamnionitis (AHC), further categorized as maternal inflammatory response (MIR) and fetal inflammatory response (FIR), also classified by stages and grades.
2. Villitis of unknown origin (VUE) including low grade, high grade, and villitis with avascular villi.
3. Maternal vascular malperfusion (MVM), which encompasses maternal vascular lesions (e.g. decidual arteriopathy, murtal hypertrophy, incomplete transformation of spiral arteries, and decidual necrosis), infarcts, hemorrhage or hematoma, thrombi (involving >5% of parenchyma), villous changes (e.g. chorangiosis, syncytial knots, distal villous hypoplasia, and accelerated villous maturation), and placcental hypoplasia.
4. Fetal vascular malperfusion (FVM) further divided into two patterns, a) segmental FVM, indicating thrombotic occlusion of chiorionic or stem villous vessels, or stem vessel obliteration, and b) global FVM, characterized by partially obstructed umbilical blood flow accompanied by venous ectasia, intramural fibrin deposition in large vessels, and/or small foci of avascular or karyorrhectic villi.
5. Other inflammatory lesions such as chronic deciduitis with plasma cells, massive chronic intervillitis, perivillous fibrin, and histiocytic intervillitis; and, delayed villous maturation, and villous edema.
6. Abnormalities in placental size – either small for gestational age (<10th percentile, SGA) or large for gestational age (>90th percentile, LGA).

**Characteristics of stroke and risk factors**

In our patient cohort, 13 had AIS, four had hemorrhagic stroke, and two were diagnosed with CSVT (Table 2). Of the patients with AIS, six were left-sided, four were right-sided, and three were bilateral. AIS was multifocal in eight patients and most commonly occurred in the distribution of the MCA. Hemorrhagic stroke presented on the left side in three patients and on the right in one patient. In addition to parenchymal hemorrhage, there was associated IVH in two patients. CSVT affected the dorsal aspect of intracebral veins and vein of Galen in one patient and the deep medullary veins in the other patient. Neither of these patients had concomitant IVH. One or more perinatal risk factor was present in nearly every patient with maternal infectious concerns the leading maternal risk factor (occurring in 6 maternal patients) (Table 3). Maternal preeclampsia was diagnosed in three patients and diabetes mellitus in two. Meconium-stained amniotic fluid was common in our cohort occurring in 12 patients. In addition, non-reassuring fetal heart tones (defined as Category II or III fetal heart rate tracings) occurred in seven patients and delivery room resuscitation was required in nine patients that had stroke. A total of five stroke patients were diagnosed with hypoxic-ischemic encephalopathy and six patients had congenital heart disease, which was primarily ASD with or without VSD. Clinical chorioamnionitis was diagnosed in four patients, but histologic evidence of acute inflammation was more common, as described with placental findings.

**Gross and histologic placental pathology**

Ten of our patients with stroke had placental pathologic examination performed (53%), and results are summarized in Table 4. Only one of these placentas had no gross or histologic abnormalities compared to 29 (72.5%) of Control placentas with no abnormalities. Three placentas in our Stroke cohort were found to be SGA and one was LGA while no size abnormalities were present in the Control group. One placenta from a neonate with stroke had borderline hypercoiled umbilical cord and none of the placentas had abnormalities of disc shape. Similarly, no cord insertion abnormalities were reported in either group. All but one placenta in the Stroke group had gross and/or histologic evidence of meconium staining while only four placentas in the Control group had evidence of meconium. Acute inflammatory lesions were highly prevalent in the Stroke cohort with five placentas diagnosed with acute histologic chorioamnionitis, all with Maternal Inflammatory Response (MIR) Stage 2, and nearly all Grade 1. Fetal Inflammatory Response (FIR) was present in six placentas: isolated FIR Stage 2, Grade 1 without MIR in one placenta; Stage 2, Grade 1 in four placentas; Stage 1, Grade 1 in one placenta; and Stage 3, Grade 2 in one placenta.
Only one placenta from the Stroke group with MIR did not demonstrate associated FIR. Acute inflammation was the only lesions in the Control placentas, and MIR was present in 11 (28%) with six of those showing associated FIR. In the Stroke group, chronic inflammation in the form of VUE was described in three of the acutely inflamed placentas and was high-grade in each of those. No placentas had VUE with avascular villitis. MVM was described in four placentas from neonates with stroke, with three showing placental hypoplasia and one with extensive thrombosis, infarcts comprising >5% of the parenchyma, and diffuse fibrin. FVM was found in none of the study placentas. Chronic deciduitis with plasma cells occurred in two placentas from the Stroke group. Delayed villous maturation and villous edema were not present in any placentas.

**Discussion**

In this single-center cohort study we demonstrated that 1) pathologic placental lesions often accompany perinatal stroke, particularly acute and chronic inflammatory conditions, and 2) placental examination is frequently missed in the clinical investigation to determine stroke etiology, even in centers with robust guidelines for placental pathology practices. Nevertheless, placental examination in 53% of our perinatal stroke cohort is significantly higher than prior studies where rates of placental examination for neonates diagnosed with stroke ranged from 6-13% (31). The most likely explanation for the low rate of placental pathology in these cases is the delayed onset of symptoms and diagnosis of perinatal stroke, by which time the placenta may have already been discarded.

Perinatal stroke is an infrequent but important cause of both immediate and long-term morbidity in neonates. Our single-center data show an overall birth prevalence of perinatal stroke of 1 in 6,829 over a 10-year period at our high-volume delivery center, which differs from other reports and indicates that some patients may have gone undiagnosed during postnatal hospital stay. Furthermore, our report includes only one case of presumed perinatal stroke, which likely contributes to the difference we report in birth prevalence of perinatal stroke compared to other studies (1, 18, 32, 33). Since our NICU readmits patients from home for a limited range of indications only within the first week after birth, these results exclude many patients who are later diagnosed due to seizures, early handedness, hemiparesis, or delayed achievement of developmental milestones. This brings attention to the fact that perinatal stroke diagnosis requires a high level of clinical suspicion and for many patients, may go undetected until later. Presumed perinatal stroke accounts for a significant number of perinatal stroke cases and typically presents before one-year of age (3, 34).

While numerous studies have outlined risk factors associated with perinatal stroke (12, 15, 21, 34, 35), the exact etiology remains unknown and is likely multifactorial, including maternal, peripartum, and neonatal factors. Nearly all our patients had one or more perinatal risk factor(s) and seizures were the most frequent presenting symptom in our cohort, as has been previously reported (5). In a meta-analysis of eight studies including 550 cases of neonatal AIS, maternal preeclampsia imparted a significantly increased risk of neonatal AIS (36). In our small cohort, preeclampsia was less prevalent than maternal infectious concerns which ranged from asymptomatic bacteriuria to hidradenitis suppurativa. In addition, clinical chorioamnionitis was diagnosed in 60% of the maternal patients in our cohort. In prior reports, inflammatory conditions including chorioamnionitis have been prominent risk factors for perinatal stroke (31).

Our understanding of the role of the placenta in perinatal AIS has evolved in recent years with new evidence emerging that there are high rates of multiple placental histopathologies in perinatal stroke, particularly AIS (37, 38). Our cohort confirms those findings with 90% of stroke patients having at least one placental abnormality. This is similarly high to the rate of placental lesions in a cohort of patients we recently studied with congenital heart disease (78%) (39). Placental inflammatory conditions seem to play a prominent role in perinatal stroke pathophysiology (38), and our cohort has similar findings with 80% showing acute and/or chronic inflammation of the placenta. These inflammatory processes may contribute to formation of emboli of placental origin that reach the fetal cerebrovasculature through the PFO (38, 40). Further evidence supporting a placental origin of emboli are that an estimated 30% of neonatal stroke is multifocal, even in the absence of CHD and the recurrence of AIS postnatally is exceedingly rare (4). Infarcts were multifocal in 42%
of our cohort and to our knowledge, none of the cohort experienced stroke recurrence, although our study is limited by the information available in the medical records. Our study was also limited by the small number in our cohort, the potential for ascertainment bias in the placentas sent for pathologic examination, and the limited outcome data available. Similarly, nearly half of the cohort did not have placental pathologic examination performed, which underscores the selection bias involved in placentas sent for pathology, although our center has a culture of commonly sending placentas to pathology for any indication related to maternal or fetal pregnancy or peripartum risk factors such as pregnancy complications (e.g. maternal

| Patient | Sex | Race/Ethnicity | Gestational Age | Delivery | Apgar Scores | Clinical Presentation | MRI Findings | Placental Exam |
|---------|-----|----------------|-----------------|----------|--------------|----------------------|--------------|---------------|
| 1       | M   | Hispanic       | term            | C/S      | 4, 7, 8      | encephalopathy after delivery | Hemorrhagic transformation of ischemic infarct – left temporal lobe, occipital lobe, parietal lobe; bilateral grade 1 IVH | Yes           |
| 2       | F   | Hispanic       | term            | C/S      | 3, 8         | seizure @ 1 HOL          | Multifocal bilateral ischemic infarcts – left parietal, occipital, frontal lobes, left posterolateral thalamus, right parietal lobe; MR angiogram with asymmetrically small right internal carotid artery with hypoplastic right A1 segment of the ACA | Yes           |
| 3       | M   | Hispanic       | post dates      | C/S      | 8, 9         | seizure @ 2 DOL           | Multifocal unilateral ischemic infarcts – left parietal lobe, left occipital lobe | No            |
| 4       | F   | Hispanic       | term            | C/S      | 9, 9         | seizure @ 15 DOL          | Multifocal unilateral ischemic infarcts – right precentral gyrus, lower central semiovale-corona radiata extending to caudate nucleus, posterior limb of internal capsule | No            |
| 5       | F   | Asian          | term            | SVD      | 6, 9         | seizure @ 2 DOL           | Multifocal unilateral ischemic infarcts – right frontal lobe, parieto-occipital region, posterior temporal lobe; hemorrhagic transformation | No            |
| 6       | M   | Hispanic       | term            | C/S      | 8, 9         | seizure @ 5 DOL           | CSVT (dorsal aspects of intracerebral veins and vein of Galen) with associated multifocal infarcts | Yes           |
| 7       | M   | Hispanic       | term            | C/S      | 9, 9         | seizure @ 4 DOL           | Multifocal unilateral ischemic infarcts – right frontal lobe, deep white matter in centrum semiovale and corona radiata | Yes           |
| 8       | M   | Hispanic       | term            | C/S      | 8, 9         | hemiparesis @ <1 year DOL | Remote ischemic infarct – left frontal and parietal lobes; MR angiogram with extremely diminished caliber of left internal carotid artery and left MCA | No            |
| 9       | F   | Black          | term            | C/S      | 1, 2, 3      | seizure @ 1 DOL           | Focal unilateral ischemic infarct – right frontal and parietal lobes | Yes           |
| 10      | F   | Hispanic       | term            | C/S      | 8, 9         | seizure @ 2 DOL           | Multifocal unilateral ischemic infarcts – left parieto-occipital lobe and posterior limb of the internal capsule | No            |
| 11      | F   | Hispanic       | term            | SVD      | 9, 9         | seizure @ 1 DOL           | Hemorrhagic transformation of ischemic infarct – right temporal and occipital lobes with midline shift and left lateral ventricular dilatation; MR venogram with severe compression of patent right transverse and proximal sigmoid sinuses secondary to hemorrhage | No            |
| 12      | F   | Hispanic       | term            | C/S      | 6, 8         | apnea @ 4 HOL             | Focal unilateral ischemic infarct – left internal capsule; MR angiogram with diminished flow of the left carotid terminus, A1 segment of ACA, and MCA secondary to thrombus | Yes           |
| 13      | M   | Hispanic       | term            | SVD      | 8, 9         | seizure @ 2 DOL           | Multifocal bilateral ischemic infarcts – parieto-occipital lobes, right greater than left associated | No            |
| 14      | M   | Hispanic       | term            | C/S      | 9, 9         | seizure @ 3 DOL           | Focal unilateral ischemic infarct – left frontoparietal lobe; MR arteriogram with occlusion at small branch of distal left MCA at level of the superior insula | No            |
| 15      | F   | Hispanic       | term            | C/S      | 2, 8         | seizure @ 2 DOL           | Focal unilateral ischemic infarct – left posterior insular cortex | Yes           |
| 16      | M   | Hispanic       | term            | C/S      | 8, 9         | encephalopathy @ 2 HOL    | CSVT of deep medullary veins with no associated hematoma or IVH | Yes           |
| 17      | F   | Hispanic       | term            | C/S      | 1, 6, 6      | encephalopathy after delivery | Hemorrhagic transformation of ischemic infarct – left temporal lobe, perialarial white matter, putamen, and scattered areas of cerebellar parenchyma; grade II IVH | Yes           |
| 18      | M   | Hispanic       | term            | C/S      | 2, 7         | seizure @ 9 DOL           | Hemorrhagic transformation of ischemic infarct – left temporal and frontal lobes | Yes           |
| Patient | Maternal Perinatal Stroke Risk Factors | Neonatal Other Clinical Findings |
|---------|--------------------------------------|----------------------------------|
| 1       | severe preeclampsia meconium, required DR resuscitation with respiratory assistance | moderate HIE with therapeutic hypothermia, VSD | none |
| 2       | none prolonged rupture of membranes, non-reassuring fetal heart tones, meconium, required DR resuscitation with endotracheal intubation | none | none |
| 3       | hidradenitis suppurativa, oligohydramnios meconium, chorioamnionitis | ASD | hypoglycemia, thrombocytopenia |
| 4       | none | none | none |
| 5       | none chorioamnionitis, meconium, required DR resuscitation with respiratory assistance including intubation | none | none |
| 6       | advanced maternal age non-reassuring fetal heart tones, chorioamnionitis, meconium, forceps | none | hyperbilirubinemia |
| 7       | Non-reassuring fetal heart tones, prolonged rupture of membranes | none | |
| 8       | morbid obesity, recurrent dacrocystitis oligohydramnios, meconium | moderate HIE with therapeutic hypothermia | anemia, hyperbilirubinemia, sickle cell disease |
| 9       | severe preeclampsia non-reassuring fetal heart tones, face presentation with difficult C/S extraction, required advanced DR resuscitation with chest compressions, epinephrine, and endotracheal intubation | none | none |
| 10      | none | none | PFO, small muscular VSD |
| 11      | gestational hypertension, teen pregnancy large for gestational age | PFO versus small secundum ASD, small muscular VSD | none |
| 12      | type 2 diabetes meconium | PFO versus small secundum ASD, anemia | metopic synostosis with mild trigonocephaly and hypotelorism, congenital fusion of radius and ulna, global hypotonia, concern for Saethre-Chotzen syndrome |
| 13      | advanced maternal age, severe preeclampsia, varicella infection during pregnancy | none | hypoglycemia with negative metabolic workup |
| 14      | gestational diabetes, positive red blood cell antibody screening | none | early brief hypoglycemia mild laryngomalacia |
| 15      | history of multiple ectopic pregnancies chorioamnionitis, non-reassuring fetal heart tones, meconium, required DR resuscitation with respiratory assistance | small secundum ASD | none |
| 16      | trichomoniasis infection during pregnancy non-reassuring fetal heart tones, meconium, required DR resuscitation with respiratory assistance | herpes simplex infection of mucous membranes, moderate HIE and underwent therapeutic hypothermia | none |
| 17      | advanced maternal age, gestational diabetes, positive Zika screen (IgG positive, IgM negative), asymptomatic bacteriuria meconium, non-reassuring fetal heart tones, nuchal cord x4, required DR resuscitation with respiratory assistance including intubation | moderate HIE and underwent therapeutic hypothermia, feto-maternal hemorrhage, thrombocytopenia at birth, initial hypoglycemia | non-occlusive IVC thrombus, postnatal transaminitis |
| 18      | grand multiparity (gravida 7), asymptomatic bacteriuria, oligohydramnios, gestational thrombocytopenia meconium, required DR resuscitation with respiratory assistance | mild HIE, moderate secundum ASD | cholestasis, hypospadias, dysmorphic features with normal chromosomal microarray |
TABLE 4 Placental gross and histopathologic findings.

| Patient | Stroke Type | Summary Placental Findings | Acute Inflammation | Chronic Inflammation | Maternal/Fetal Malperfusion | Other Lesions |
|---------|-------------|----------------------------|--------------------|----------------------|-----------------------------|---------------|
| 2       | Ischemic stroke | 1. One vessel umbilical vasculitis | X                  |                      |                             |               |
|         |              | 2. Infarct (<5% of parenchyma) |                    |                      |                             |               |
|         |              | 3. Meconium exposure         |                    |                      |                             |               |
| 7       | Ischemic stroke | 1. Acute chorioamnionitis    | X                  |                      |                             |               |
|         |              | 2. Intervillous thrombus     |                    |                      |                             |               |
|         |              | 3. Meconium exposure        |                    |                      |                             |               |
| 9       | Ischemic stroke | 1. Infarct (<2% of parenchyma) | X                  |                      |                             |               |
|         |              | 2. Meconium exposure        |                    |                      |                             |               |
| 12      | Ischemic stroke | No gross or histologic pathology | X                  |                      |                             |               |
| 15      | Ischemic stroke | 1. Severe acute chorioamnionitis |                      |                      |                             | X             |
|         |              | 2. Three vessel umbilical vasculitis |                    |                      |                             |               |
|         |              | 3. Funisitis                 |                    |                      |                             |               |
|         |              | 4. Chorionic plate vasculitis |                    |                      |                             |               |
|         |              | 5. Meconium exposure         |                    |                      |                             |               |
|         |              | 6. Borderline hypercoiled umbilical cord |     |                      |                             |               |
| 1       | Hemorrhagic stroke | 1. Acute chorioamnionitis   | X                  | X                    | X                           | X             |
|         |              | 2. Single vessel umbilical vasculitis |                    |                      |                             |               |
|         |              | 3. Patchy chronic villitis  |                    |                      |                             |               |
|         |              | 4. Focal basal villitis     |                    |                      |                             |               |
|         |              | 5. Small for gestational age |                    |                      |                             |               |
|         |              | 6. Meconium exposure        |                    |                      |                             |               |
| 17      | Hemorrhagic stroke | 1. One vessel umbilical vasculitis | X                  |                      |                             |               |
|         |              | 2. Funisitis                 |                    |                      |                             |               |
|         |              | 3. Chorionic plate vasculitis |                    |                      |                             |               |
|         |              | 4. Meconium exposure        |                    |                      |                             |               |
| 18      | Hemorrhagic stroke | 1. Acute chorioamnionitis (stage 1) | X                  | X                    | X                           | X             |
|         |              | 2. Patchy (high grade) chronic villitis |                    |                      |                             |               |
|         |              | 3. Diffuse basal villitis   |                    |                      |                             |               |
|         |              | 4. Small for gestational age |                    |                      |                             |               |
|         |              | 5. Meconium exposure        |                    |                      |                             |               |
|         |              | 6. Chronic deciduitis with plasma cells |                    |                      |                             |               |
| 6       | CSVT          | 1. Multifocal basal chronic villitis | X                  |                      | X                           | X             |
|         |              | 2. Small for gestational age |                    |                      |                             |               |
|         |              | 3. Meconium exposure        |                    |                      |                             |               |
|         |              | 4. Chronic deciduitis with plasma cells |                    |                      |                             |               |
| 16      | CSVT          | 1. Slight acute chorioamnionitis | X                  |                      | X                           | X             |
|         |              | 2. Single vessel umbilical vasculitis |                    |                      |                             |               |
|         |              | 3. Extensive intervillous thrombi |                    |                      |                             |               |
|         |              | 4. Infarcts (>5% of parenchyma) |                    |                      |                             |               |
|         |              | 5. Increased perivillous fibrin |                    |                      |                             |               |
|         |              | 6. Large for gestational age |                    |                      |                             |               |
|         |              | 7. Meconium exposure        |                    |                      |                             |               |

diabetes mellitus, fetal growth restriction), or abnormalities during labor or delivery (e.g. perinatal asphyxia, placental abruption).

The suspected pathophysiology of AIS supports the clinical practice of placental pathologic examination in all cases of perinatal stroke (1, 29, 30); however, this retrospective approach is inadequate to change clinical outcomes or prevalence of perinatal stroke. New technologies are required to change perinatal stroke care from a focus on diagnosis and recovery, to one of prevention. This will require creative utilization of what we already know as well as development of new technologies. Recent
studies have focused on identifying inflammatory biomarker signatures in patients at-risk for perinatal stroke (41), which may improve the ability to detect perinatal stroke early and allow initiation of supportive therapies sooner. Some experts have recommended more widespread use of neuroimaging in neonates with risk factors for stroke (42), but clear algorithms are still lacking to define which neonates are at highest risk. Placental pathology may provide input into a stroke risk stratification algorithm, but the timeframe required for placental examination will be a limiting factor until new techniques are developed that can offer real-time, clinically-relevant information. In order to establish preventative strategies, advanced methods of in utero assessment are needed, such as the many emerging methods in advanced placental magnetic resonance imaging (43–46).

Conclusion

Inflammatory conditions including maternal infection and fetal asphyxia are often present in patients with perinatal stroke. Placental pathologic examination has a high yield of abnormal findings and should be considered integral to the diagnostic workup in all neonates with perinatal stroke. Imaging or blood biomarkers may eventually play a role in assessing those at risk for perinatal stroke in order to employ timely and effective interventions.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material. Further inquiries can be directed to the corresponding author.

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Ethics statement

The studies involving human participants were reviewed and approved by University of Texas Southwestern Medical Center Institutional Review Board. Written informed consent from the participants’ legal guardian/next of kin was not required to participate in this study in accordance with the national legislation and the institutional requirements.

Author contributions

Concept: LC, IM, RL. Data Curation: LC, IM. Investigation and Analysis: RL, VK, MA, JT. Drafting. Revising: RL, VK, MA, JT, IM, LC. Final Approval: RL, VK, MA, JT, IM, LC.

Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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