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ORIGINAL ARTICLE

Risk factors for perinatal stroke in term infants: A case–control study in Australia

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Aim: The aetiology of perinatal stroke is poorly understood. This study aimed to prospectively confirm the risk factors and identify any previously unknown variables.

Methods: A prospective case–control study was conducted in Australia. Univariate odds ratios (ORs), associated 95% confidence intervals (CIs) and multivariable logistic regression models fitted with backwards stepwise variable selection were used.

Results: Sixty perinatal stroke cases reported between 2017 and 2019 included 95% (57/60) with multiple risk factors. Univariate analysis identified emergency caesarean section rather than NVD ($P < 0.01$), low Apgar score (<7) at 1, 5 and 10 min of age ($P < 0.01$), resuscitation at birth ($P < 0.01$), abnormal cord blood gas ($P < 0.01$), neonatal infection/sepsis ($P < 0.01$), congenital heart disease ($P < 0.01$) and hypoglycaemia ($P < 0.01$) as significant risk factors. Multivariate analysis found smoking during pregnancy (OR: 1.48; 95% CI: 1.09–1.99), 1-min Apgar score < 7 (OR: 1.54; 95% CI: 1.15–2.08), 10-min Apgar score < 7 (OR: 1.26; 95% CI: 1.02–1.54) and hypoglycaemia (OR: 1.49; 95% CI: 1.07–2.06).

Conclusions: Perinatal stroke is associated with multiple risk factors. Exposure to smoking, 10-min Apgar score < 7, neonatal infection and hypoglycaemia were independent risk factors. Emergency caesarean section, resuscitation at birth and abnormal cord blood gas were additional risk factors.

Key words: aetiology; neonatology; neurology; perinatal stroke; risk factors.

What is already known on this topic

1 Perinatal stroke is an important cause of neurological disability in infants.
2 The diagnosis is often missed because of multifactorial risk factors and non-neurological presentation.

What this paper adds

1 Exposure to smoking during pregnancy, 10-min Apgar score < 7, neonatal infection and hypoglycaemia were identified as independent risk factors.

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Conflict of interest: None declared.

Author contributions: Dr Bithi Roy, Prof Iona Novak and Prof Nadia Badawi conceptualised and designed the study and designed the data collection instrument. Dr Bithi Roy collected data, carried out the initial analyses, drafted the initial manuscript and revised the manuscript. Prof Iona Novak critically analysed, reviewed and revised the manuscript for important intellectual content. Prof Nadia Badawi assisted in data collection, critically reviewed and revised the manuscript for important intellectual content. Clinical Prof Karen Walker and Dr Catherine Morgan assisted in data collection, and critically reviewed and revised the manuscript for important intellectual content. Annabel Webb carried out the initial analyses, and critically analysed and revised the manuscript. All authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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Perinatal stroke is a known cause of neurodevelopmental disability in infants. The reported annual incidence of perinatal stroke is about 1 in 2500–4000 live births.[1] Although previous studies have identified several risk factors, aetiology is still poorly understood, making it difficult to identify the population at highest risk. Pregnancy elevates the risk for maternal stroke, particularly in the presence of hypertensive disease of pregnancy.[2–4] This increased vulnerability in the mother activates clotting and poses an increased risk of arterial ischemic stroke in the neonate. Studies have included nulliparity, male sex, maternal fever, premature rupture of membranes, meconium-stained liquor, neonatal sepsis and meningitis as significant risk factors for perinatal arterial ischemic stroke.[5–7] A meta-analysis of mostly retrospective studies, not based on individual patients, suggested chorioamnionitis and fetal-placental insufficiency are also closely associated with perinatal arterial ischemic stroke.[8]

Some stroke risk factors are also present in healthy infants, compounding the difficulty of identifying infants at risk. This

study aimed to prospectively confirm stroke risk factors in a case–control study and identify any previously unknown variables.

Methods

Study design

This was an Australian case–control study of term infants (>37 weeks' gestational age) with perinatal stroke. The comparison group included three healthy controls for every infant with stroke, matched for gestational age and date of birth (≤7 days).

Case definition

Babies included those who had acute perinatal stroke before 28 days post-natal age, diagnosed by brain magnetic resonance imaging (MRI) and confirmed by the reporting physician.

Case data collection

An active surveillance system based on pre-specified criteria was used for case identification. Perinatal strokes secondary to non-accidental head injury were excluded. Expert physicians, including neonatologists, paediatricians or neurologists from tertiary hospitals, were asked to report babies with perinatal stroke using a deidentified data sheet to the Australian Paediatric Surveillance Unit (APSU) on a weekly basis from 1 July 2017 to 30 June 2019. The APSU is a national resource that facilitates active surveillance of rare childhood diseases.[9] It is closely affiliated with the University of Sydney's Faculty of Medicine and Health Sciences and the Sydney Children's Hospital Network. Data collected included risk factors found in babies with perinatal stroke and control babies, perinatal stroke types, clinical presentation and outcome. Case reports were independently validated, and the perinatal stroke types (ischemic, haemorrhagic and cerebral sinovenous thrombosis (CSVT)) were confirmed from MRI brain reports by three independent raters (NB, CM and BR). Original MRI images were not sought, to lower respondent burden and reduce the likelihood of missing data.

Control definition

Control babies were born at ≥37 weeks of gestation and were not admitted to the neonatal unit.

Control data collection

Control babies were born at a tertiary neonatal unit in a major public hospital in Sydney, Australia. This single hospital is known to treat patients from diverse socio-economic and geographic backgrounds and is widely considered representative of Australian families. Three presumed healthy controls per baby with stroke, in total 180, were randomly selected and matched for gestational age and actual age of the baby with stroke (≤7 days old). The only exclusion criteria over and above no neonatal unit admission were infants with congenital malformations.

Stroke types

Dunbar and Kirton's classification of acute symptomatic perinatal stroke, including arterial or venous and ischemic or haemorrhagic subtypes, were used in this study.[10] Arterial stroke included neonatal arterial ischemic stroke (NAIS) and venous stroke included neonatal haemorrhagic stroke (NHS) and CSVT.

Statistical analysis

All statistical analysis was carried out using R.[11] Frequencies and percentages were calculated for prenatal, perinatal and neonatal risk factors for the perinatal stroke cases, and for the controls, as well as for the NAIS, NHS and CSVT stroke subtypes. Rates of missing data for each risk factor of interest were calculated for babies with stroke. Univariate odds ratios (ORs) and associated

Table 1 Patient population

	Perinatal stroke cases	Controls
Total (*n*)	60	180
Gestational age (weeks), range (mean)	37–42 (39)	37–41 (39)
Birthweight (g), range (mean)	2114–4470 (3294)	1743–4760 (3324)
Male:Female	35:25	98:82

n, frequency counts.

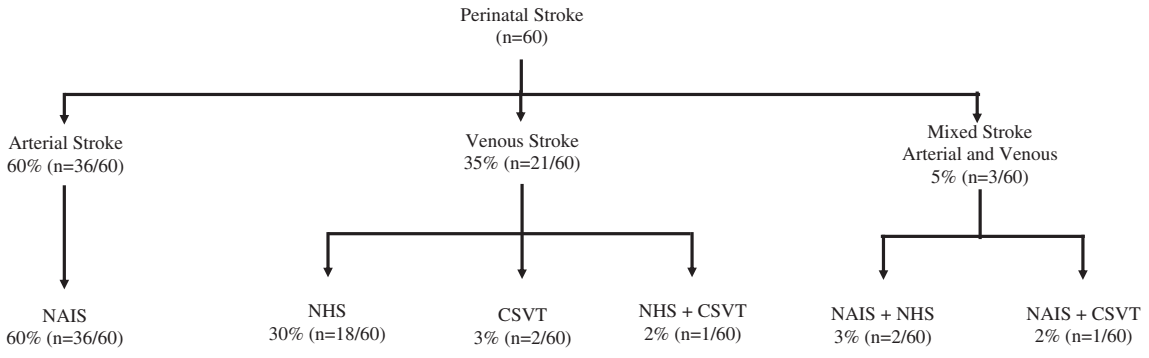

Fig. 1 Types of perinatal stroke ($n = 60$). CSVT, cerebral sinovenous thrombosis; NAIS, neonatal arterial ischemic stroke; NHS, neonatal hemorrhagic stroke.

Table 2 Univariable risk factor analysis for perinatal stroke cases versus controls

Risk factors	Perinatal stroke cases $n = 60$ *N* (%)	Controls $n = 180$ *N* (%)	OR (95% CI)	*P* value
Prenatal risk factors				
Indigenous status				
Aboriginal or Torres Strait Islander	1 (2%)	9 (5%)	0.36 (0.01–2.70)	0.46
Non-Indigenous	53 (98%)	171 (95%)		
Maternal age				
<20 years	0 (0%)	0 (0%)	NA	1.00
20–34 years	41 (82%)	112 (62%)	(ref)	–
≥35 years	7 (14%)	68 (38%)	**0.29 (0.10–0.68)**	**<0.01**
History of miscarriage or stillbirth or neonatal deaths	4 (7%)	70 (39%)	**0.12 (0.03–0.35)**	**<0.01**
History of stroke in other children	0 (0%)	0 (0%)	NA	1.00
Multigravida (≥2)	24 (44%)	118 (66%)	**0.42 (0.22–0.82)**	**<0.01**
Parity ≥ 2	19 (35%)	85 (47%)	0.61 (0.30–1.19)	0.16
Multiple births – twins/triplets	1 (2%)	2 (1%)	1.51 (0.03–29.41)	1.00
Pregnancy complications:				
Gestational diabetes	7 (12%)	23 (13%)	0.96 (0.33–2.48)	1.00
Pregnancy hypertension	2 (4%)	5 (3%)	1.27 (0.12–8.03)	0.68
Antepartum haemorrhage	2 (4%)	3 (2%)	2.14 (0.17–19.15)	0.60
Breech	0 (0%)	8 (4%)	NA	0.21
History of smoking	4 (7%)	9 (5%)	1.49 (0.32–5.61)	0.51
History of alcohol	1 (2%)	5 (3%)	0.59 (0.01–6.35)	1.00
History of illicit drugs	1 (2%)	1 (1%)	3.36 (0.04–265.97)	0.41
Perinatal risk factors				
GBS colonisation	8 (14%)	23 (17%)	1.11 (0.40–2.79)	0.83
Prolonged rupture of membranes (>24 h)	1 (2%)	5 (3%)	0.70 (0.02–6.42)	1.00
Mode of delivery				
Normal vaginal delivery	16 (32%)	81 (45%)	(ref)	(ref)
Instrumental (vacuum, forceps)	12 (24%)	32 (18%)	1.89 (0.73–4.81)	0.17
Elective caesarean section	4 (8%)	36 (20%)	0.57 (0.13–1.92)	0.43
Emergency caesarean section	24 (48%)	31 (17%)	**3.88 (1.72–8.98)**	**<0.01**
Breech	0 (0%)	0 (0%)	NA	NA
Type of difficult delivery				
Shoulder dystocia	0 (0%)	2 (1%)	NA	1.00
Multiple vacuum attempts and/or failed vacuum	1 (2%)	0 (0%)	NA	0.22
Neonatal risk factors				
Sex:				
Male	35 (58%)	98 (54%)	1.17 (0.62–2.22)	0.65
Female	25 (42%)	82 (46%)		
Birthweight < 2500 g	6 (11%)	8 (4%)	2.62 (0.71–9.08)	0.10
Small for gestational age (<10th percentile)	13 (25%)	38 (21%)	1.21 (0.54–2.61)	0.58
Large for gestational age (>90th percentile)	5 (9%)	10 (6%)	1.77 (0.45–6.01)	0.54
1-min Apgar score < 7	21 (39%)	12 (7%)	**8.79 (3.72–21.70)**	**<0.01**
5-min Apgar score < 7	9 (17%)	2 (1%)	**17.51 (3.46–171.90)**	**<0.01**
10-min Apgar score < 7	3 (5%)	1 (1%)	**22.66 (1.74–1221.74)**	**<0.01**
Received vitamin K	55 (100%)	180 (100%)	NA	1.00
Resuscitation at birth	25 (46%)	22 (12%)	**5.93 (2.82–12.66)**	**<0.01**
Abnormal cord blood gas	16 (34%)	13 (7%)	**6.55 (2.66–16.47)**	**<0.01**
Infection/sepsis	14 (23.3%)	0 (0%)	NA	**<0.01**
Congenital heart disease	11 (42%)	0 (0%)	NA	**<0.01**
Hypoglycaemia	5 (8.3%)	0 (0%)	NA	**<0.01**

CI, confidence interval; n, frequency counts; OR, odds ratio.

95% confidence intervals (CIs) were computed to investigate the association between risk factors and perinatal stroke, including the stroke subtypes. Multivariable logistic regression models fitted with backwards stepwise variable selection were also used to identify independent factors associated with the odds of stroke. Adjusted ORs and associated 95% CIs were computed from these

models. A significance level of 5% was used for all statistical tests.

Statement on ethics

This study was approved by the Sydney Children's Hospital Network Human Research Ethics Committee (Ethics approval no: 2019/ETH06281).

Results

Sixty babies with perinatal stroke were reported in the selected period, including NAIS, NHS and CSVT (Fig. 1) and 180 controls (Table 1). Results were reported according to the revised STROBE statement.[12]

Perinatal stroke subtypes are shown in Figure 1.

Risk factors for stroke

Prenatal, perinatal and neonatal risk factors for perinatal stroke and its subtypes were compared with the controls (Table 2). Risk factors were identified in 95% (57/60) of the perinatal stroke cases.

Univariate analysis

All stroke types

In the univariate analysis of babies with perinatal stroke versus controls, risk factors that were significantly associated with increased odds of stroke (all subtypes) were: birth via emergency caesarean section rather than NVD ($P < 0.01$); low Apgar score (<7) at 1, 5 and 10 min of age ($P < 0.01$); resuscitation at birth ($P < 0.01$); abnormal cord blood gas ($P < 0.01$); neonatal infection/sepsis ($P < 0.01$); congenital heart disease ($P < 0.01$) and hypoglycaemia ($P < 0.01$) (Table 2). Conversely, factors associated with lowered odds of stroke were maternal age above 35 years ($P = 0.02$), history of miscarriage, stillbirth or neonatal death ($P < 0.01$) and multigravida ($P < 0.01$).

Stroke subtypes

Similarly, when comparing the odds of NAIS versus controls, risk factors significantly associated with increased risk of stroke included birth via emergency caesarean (compared to NVD), low Apgar score (<7) at 1 and 5 min of age, resuscitation at birth and abnormal cord blood gas. History of miscarriage, stillbirth or neonatal death, multigravida and maternal age of 35 or above decreased the odds of NAIS. For NHS versus controls, only low Apgar score (<7) at 1, 5 and 10 min of age, resuscitation at birth and abnormal cord blood gas were identified as significant risk factors, with all these factors associated with higher odds of NHS. Due to small group sizes, ORs and CIs were not computed to compare CSVT and controls.

Multivariate analysis

To identify risk factors independently associated with perinatal stroke, we performed multivariable logistic regression. The multivariable model was constructed using all covariates considered in the univariate analysis, apart from those with a rate of missing data above 20%. The covariates included in the full multivariable model are listed in Table 3. Backwards stepwise variable selection was performed to identify significant independent risk factors of stroke.

Table 3 Multivariable logistic regression models for the odds of stroke

	Full model OR (95% CI)	Reduced model OR (95% CI)
Covariates		
Aboriginal or Torres Strait Islander	0.98 (0.68–1.42)	–
Maternal age > 35 years	0.98 (0.85–1.13)	–
History of miscarriage, stillbirth or neonatal death	0.89 (0.73–1.08)	**0.87 (0.78–0.98)**
Parity ≥ 2	0.93 (0.76–1.14)	–
Multiple birth	0.96 (0.61–1.51)	–
Gestational diabetes	1.09 (0.94–1.26)	–
Pregnancy hypertension	0.99 (0.69–1.41)	–
Antepartum haemorrhage	0.82 (0.59–1.15)	–
History of smoking	**1.48 (1.09–1.99)**	**1.39 (1.06–1.81)**
History of alcohol	1.05 (0.78–1.40)	–
Group B Streptococcus infection	1.10 (0.94–1.28)	–
Prolonged rupture of membranes	0.92 (0.59–1.42)	–
Mode of delivery: Normal vaginal delivery	(ref)	–
Mode of delivery: Instrumental (vacuum, forceps)	1.11 (0.93–1.32)	–
Mode of delivery: Elective Caesarean section	1.06 (0.89–1.27)	–
Mode of delivery: Emergency Caesarean section	0.96 (0.82–1.13)	–
Male	0.96 (0.85–1.08)	–
Birthweight < 2500 g	1.04 (0.81–1.33)	–
1-min Apgar score < 7	**1.54 (1.15–2.08)**	**1.61 (1.38–1.89)**
5-min Apgar score < 7	1.08 (0.81–1.44)	–
10-min Apgar score < 7	**1.26 (1.02–1.54)**	**1.27 (1.05–1.53)**
Resuscitation at birth	1.09 (0.87–1.36)	–
Sepsis/infection	1.35 (0.99–1.82)	**1.39 (1.07–1.80)**
Hypoglycaemia	**2.26 (1.56–3.28)**	**2.07 (1.50–2.86)**

CI, confidence interval; OR, odds ratio.

In the full multivariable logistic regression model (before variable selection), risk factors identified as significantly associated with stroke were: a maternal history of smoking (OR: 1.48; 95% CI: 1.09–1.99); 1-min Apgar score < 7 (OR: 1.54; 95% CI: 1.15–2.08); 10-min Apgar score < 7 (OR: 1.26; 95% CI: 1.02–1.54), and hypoglycaemia (OR: 1.49; 95% CI: 1.07–2.06). After variable selection was performed, all these variables remained significant. Miscarriage, stillbirth and neonatal death were identified as statistically significant but favouring controls. History of miscarriage, stillbirth or neonatal death was associated with a 13% (95% CI: 2–22%) decrease in the odds of stroke in the reduced model.

Table 4 Risk factors for perinatal stroke types versus controls

Risk factors	NAIS ($n = 36$)	OR† (95% CI)	NHS ($n = 18$)	OR† (95% CI)	Control ($n = 180$)
Prenatal risk factors					
Indigenous status					
Aboriginal or Torres Strait Islander	0 (0%)	NA	1 (7%)	1.35 (0.03–11.1)	9 (5%)
Non-Indigenous	34 (100%)		14 (93%)		171 (95%)
Maternal age					
<20 years	0 (0%)	NA	0 (0%)	NA	0 (0%)
20–34 years	27 (87%)	(ref)	11 (79%)	(ref)	112 (62%)
≥35 years	4 (13%)	**0.25 (0.06–0.75)**	3 (21%)	0.45 (0.08–1.79)	68 (38%)
History of miscarriage or stillbirth or neonatal deaths	3 (9%)	**0.15 (0.03–0.50)**	0 (0%)	NA	70 (39%)
Multigravida (≥2)	14 (44%)	**0.41 (0.18–0.94)**	7 (41%)	0.37 (0.11–1.14)	118 (66%)
Parity ≥ 2	11 (34%)	0.59 (0.24–1.36)	5 (29%)	0.47 (0.12–1.50)	85 (47%)
Multiple births – twins/triplets	1 (3%)	2.52 (0.04–49.8)	0 (0%)	NA	2 (1%)
Pregnancy complications					
Gestational diabetes	5 (14%)	1.10 (0.30–3.28)	1 (6%)	0.40 (0.01–2.83)	23 (8%)
Pregnancy hypertension	2 (6%)	2.05 (0.19–13.2)	1 (6%)	2.05 (0.04–19.9)	5 (3%)
Antepartum haemorrhage	1 (3%)	1.68 (0.03–21.6)	1 (6%)	3.44 (0.06–45.6)	3 (2%)
Breech	0 (0%)	NA	0 (0%)	NA	8 (4%)
History of smoking	2 (6%)	1.19 (0.12–6.13)	1 (6%)	1.12 (0.02–8.97)	9 (5%)
History of alcohol	1 (3%)	1.06 (0.02–9.93)	0 (0%)	NA	5 (3%)
History of illicit drugs	1 (3%)	5.34 (0.07–426)	0 (0%)	NA	1 (1%)
Perinatal risk factors					
Group B Streptococcus colonisation	6 (18%)	1.06 (0.32–3.03)	0 (0%)	0.00 (0.00–1.51)	23 (17%)
Prolonged rupture of membranes (>24 h)	1 (3%)	1.06 (0.02–9.93)	0 (0%)	NA	5 (3%)
Mode of delivery					
Normal vaginal delivery	7 (22%)	(ref)	8 (47%)	(ref)	81 (45%)
Instrumental (vacuum, forceps)	6 (19%)	2.16 (0.55–8.15)	4 (24%)	1.26 (0.26–5.12)	32 (18%)
Elective Caesarean section	5 (16%)	1.60 (0.37–6.32)	0 (0%)	0.00 (0.00–1.41)	36 (20%)
Emergency Caesarean section	16 (50%)	**5.89 (2.05–18.6)**	5 (29%)	1.62 (0.39–6.16)	31 (17%)
Breech	0 (0%)	NA	0 (0%)	NA	–
Type of difficult delivery					
Shoulder dystocia	0 (0%)	NA	0 (0%)	NA	2 (1%)
Multiple vacuum attempts and/or failed vacuum	0 (0%)	NA	1 (6%)	NA	0 (0%)
Neonatal risk factors					
Sex					
Male	22 (61%)	1.31 (0.60–2.97)	10 (56%)	1.05 (0.35–3.20)	98 (54%)
Female	14 (39%)		8 (44%)		82 (46%)
Birthweight < 2500 g	4 (11%)	2.76 (0.57–11.1)	1 (7%)	1.53 (0.03–12.9)	8 (4%)
Small for gestational age (<10th percentile)	9 (27%)	1.40 (0.53–3.45)	3 (20%)	0.94 (0.16–3.71)	38 (21%)
Large for gestational age (>90th percentile)	3 (9%)	1.70 (0.28–7.11)	1 (7%)	1.12 (0.03–9.74)	10 (6%)
1-min Apgar score < 7	15 (44%)	**10.8 (4.10–29.7)**	6 (40%)	**9.13 (2.28–34.9)**	12 (7%)
5-min Apgar score < 7	5 (31%)	**15.0 (2.32–165)**	4 (27%)	**30.8 (3.94–372)**	2 (1%)
10-min Apgar score < 7	1 (4%)	7.98 (0.10–638)	2 (18%)	**37.2 (1.79–2311)**	1 (1%)
Received vitamin K	33 (100%)	NA	17 (100%)	NA	180 (100%)
Resuscitation at birth	17 (50%)	**7.09 (2.94–17.3)**	8 (47%)	**6.29 (1.90–20.6)**	22 (12%)
Abnormal cord blood gas	11 (79%)	**44.8 (10.3–280)**	4 (67%)	**24.6 (3.20–294)**	13 (7%)
Infection/sepsis	7 (19%)	NA	2 (11%)	NA	0 (0%)
Congenital heart disease	9 (45%)	NA	2 (33%)	NA	0 (0%)
Hypoglycaemia	3 (8%)	NA	1 (6%)	NA	0 (0%)

† All ORs are stroke subtype versus control group. CI, confidence interval; n, frequency counts; NAIS, neonatal arterial ischemic stroke; NHS, neonatal hemorrhagic stroke; OR, odds ratio.

Conversely, in the reduced model: maternal history of smoking was associated with a 39% (95% CI: 6–81%) increase in the odds of stroke; a 1-min Apgar score < 7 was associated with a 61% (95% CI: 38–81%) increase in the odds of stroke; a 10-min Apgar score < 7 was associated with a 27% (95% CI: 5–53%) increase in the odds of stroke; neonatal infection/sepsis was associated with a 39% (95% CI: 7–80%) increase in the odds of stroke; and hypoglycaemia was associated with a 107% (95% CI:

50–186%) increase in the odds of stroke. Notably, history of smoking was not found to be a statistically significant predictor of stroke in the univariate analysis but became significant after adjusting for the other maternal and neonatal risk factors included in the logistic regression.

Discussion

The pathophysiology of perinatal stroke remains ambiguous among most babies. A search for specific risk factors justified a prospective case–control study. Most studies to date have been retrospective, preventing an accurate assessment of each of the multiple risk factors. Our study identified exposure to smoking, 10-min Apgar score < 7, neonatal infection and hypoglycaemia as independent risk factors.

Prenatal risk factors

Similar to other studies, perinatal stroke occurred more frequently in nulliparous mothers aged 20–34 years than in mothers aged 35 years or older (82% vs. 14%).[5] In our study, multivariate analysis showed exposure to smoking to be an important risk factor. Except for one study, in which it was reported as an insignificant factor, no other studies investigated smoking exposure.[6] As there was only one baby with an Indigenous background, no conclusions could be drawn regarding ethnicity.[13]

Hypertensive disease of pregnancy,[14,15] gestational diabetes,[7] antepartum haemorrhage, miscarriage, stillbirth, neonatal death, maternal alcohol and illicit drug use were not risk factors in our study. Studies have found inconsistent associations between hypertensive disease of pregnancy, gestational diabetes, and arterial ischemic stroke.[5–7,16,17]

Placental pathology was available in only two of our cases and both were abnormal. In general, studies have shown a low utilisation of placental testing, likely due to placental disposal shortly after birth.[18,19]

Perinatal risk factors

In our study, emergency caesarean section and resuscitation at birth were significant risk factors in the univariate analysis and, on adjusting with other variables, fetal distress and 1-min and 10-min Apgar scores <7 were independent risk factors. An Apgar score of <7 likely reflects adverse events during delivery and suggests an important role for fetal distress, emergency caesarean section and subsequent hypoxia-ischemia in the pathogenic pathway of stroke.

Instrumental delivery may indicate trauma to the head and cause haemorrhagic stroke. In our study (Table 2), instrumental delivery was higher in the perinatal stroke cases (24%) than in the controls (18%, OR: 1.89; 95% CI: 0.73–4.81). Also, when compared within the perinatal stroke types (Table 4), instrumental delivery was higher in the NHS than in the NAIS (24% vs. 19%), supporting the hypothesis, although these were not statistically significant.

As in other studies, prolonged rupture of membranes was not significant in our study.[20]

Neonatal risk factors

In our study, the male:female ratio was higher in perinatal stroke cases than in controls (1.4:1.2), though this was not statistically significant. However, this is in keeping with other neurodevelopmental conditions among male babies.[21,22] There were no uniform results regarding sex and perinatal stroke in previous studies.[17,23,24]

Neonatal infection was an independent risk factor in our study, though GBS colonisation and prolonged rupture of membranes were not significant.[17] Gestational diabetes was similar in both babies with perinatal stroke and controls in our data, but neonatal hypoglycaemia was an independent risk factor. Other studies have also confirmed that hypoglycaemia was an independent risk factor for perinatal arterial ischemic stroke.[5,25] Unlike in some of the published studies, low birthweight, and small and large for gestational age were not risk factors in our study.[8,26] Congenital heart disease is an important risk factor for perinatal arterial ischemic stroke.[27] It was a significant risk factor in our study in the univariate analysis, but it could not be included in the multivariate analysis because of the missing data and a potential risk of bias.

Limitations

Although this study has strengths in its prospective nature, its main limitation was the lack of MRI images of the brain. The diagnosis of stroke was based on MRI reports and reporting physicians. However, in Australia, paediatric MRIs are performed in tertiary care hospitals, so MRI reporting is done by senior radiologists and specialists.

A final limitation of the current study is that small group sizes for some risk factors and some stroke subtypes may have limited the statistical power to detect significant ORs. The CIs for some ORs were extremely wide, which may limit interpretability.

Conclusion

This comparative study confirmed exposure to smoking, 10-min Apgar score < 7, neonatal infection, and hypoglycaemia as independent risk factors for perinatal stroke. Emergency caesarean section, resuscitation at birth and abnormal cord blood gas were additional risk factors. Our study also supports the theory of multifactorial aetiology, with a combination of prenatal, perinatal, and neonatal risk factors being involved in the pathogenesis of perinatal stroke.

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