Prenatal, perinatal and neonatal risk factors for perinatal arterial ischaemic stroke: a systematic review and meta-analysis

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The aim of the present study was to perform a meta-analysis of published data to determine the significance of clinical factors and exposures to the risk of perinatal arterial ischaemic stroke (PAIS) and provide guidance for clinical diagnosis and treatment. A comprehensive literature search of the PubMed, Embase, MEDLINE and Cochrane Library databases for relevant observational studies (cohort/case–control) from March 1984 to March 2016 was undertaken. Two review authors independently examined the full text records to determine which studies met the inclusion criteria and evaluated risk factors for PAIS. Risk ratios, odds ratios and 95% confidence intervals were estimated. A total of 11 studies were included in the analyses. Intrapartum fever >38°C, pre-eclampsia, oligohydramnios, primiparity, forceps delivery, vacuum delivery, fetal heart rate abnormalities, abnormal cardiotocography tracing, cord abnormalities, birth asphyxia, emergency caesarean section, tight nuchal cord, meconium-stained amniotic fluid, umbilical arterial pH <7.10, Apgar score at 5 min <7, resuscitation at birth, hypoglycaemia, male gender and small for gestational age were identified as risk factors for PAIS. This systematic review and meta-analysis provides a preliminary evidence-based assessment of the risk factors for PAIS. Patients with any of the risk factors identified in this analysis should be given careful consideration to ensure the prevention of PAIS. Future studies focusing on the combined effects of multiple prenatal, perinatal and neonatal risk factors for PAIS are warranted.

Introduction

Perinatal ischaemic stroke is a cerebrovascular disease that results in ischaemic and haemorrhagic injury around focal or multifocal cerebral vessels [1]. In 2006, perinatal ischaemic stroke was defined as ‘a group of heterogeneous conditions in which there is focal disruption of cerebral blood flow secondary to arterial or cerebral venous thrombosis or embolization, between 20 weeks of fetal life through to the 28th postnatal day, confirmed by neuroimaging or neuropathological studies’ [2].

Perinatal ischaemic stroke can be divided into perinatal arterial ischaemic stroke (PAIS) and cerebral sinovenous thrombosis (CSVT). The incidence of PAIS ranges from 1 in 2300 to 1 in 5000 births [3–9], while the incidence of CSVT is much lower, ranging from 0.6 to 12 per 100 000 live births [10]. PAIS is associated with substantial morbidity, including long-term neurological disabilities, such as cerebral palsy and epilepsy, and cognitive abnormalities [3,11–16]. Several studies have identified potential risk factors for PAIS, including oligohydramnios, chorioamnionitis, premature rupture of membranes, pre-eclampsia and low Apgar score at 1 or 5 min [17–20]. Other reports suggest the risk of PAIS may
increase in the presence of multiple risk factors [19,21].

Numerous studies have focused on specific antepartum, intrapartum and neonatal exposures as possible risk factors for PAIS. Many support the hypothesis that prenatal [e.g. primiparity, pre-eclampsia, intrauterine growth restriction (IUGR), reduced fetal movement], perinatal (e.g. chorioamnionitis, prolonged rupture of membranes, fetal heart rate abnormality, emergency caesarean delivery) and neonatal (e.g. Apgar score ≤7 at 5 min, resuscitation at birth, umbilical arterial pH ≤7.10, hypoglycaemia) exposures increase the risk of PAIS [22–25].

The aetiology and pathogenesis of PAIS is considered complex and multifactorial and is currently not well understood. There is an unmet need for a systematic review and meta-analysis investigating prenatal, perinatal and neonatal risk factors for PAIS to provide guidance for clinical diagnosis and treatment. The aim of the present study was to perform a meta-analysis of published data to determine the significance of clinical factors and exposures on the risk of PAIS.

**Methods**

**Search strategy and selection criteria**


**Inclusion and exclusion criteria**

Perinatal arterial ischaemic stroke was defined as stroke that occurred *in utero* or up to 28 days after birth [19]. Inclusion criteria were (i) case–control studies (defined as incidence, prevalence or nested case–control studies) or cohort studies; (ii) on PAIS, neonatal stroke or neonatal cerebral infarction; (iii) describing risk factors in the perinatal or neonatal period; and (iv) reporting odds ratios (ORs) in case–control studies or relative risks (RRs) in cohort studies with 95% confidence intervals (CIs); or, if 95% CIs were not available, the reported data were sufficient to calculate them.

Exclusion criteria were (i) studies that were not published as full reports, (ii) studies without control subjects or (iii) reviews, case reports or studies on other factors or outcomes.

**Study selection**

Titles and abstracts were independently examined by two review authors (CL, JM) to select eligible studies. The full text of potentially relevant studies was retrieved. The full text records were independently examined by two review authors (CL, JM) to determine which studies met the inclusion criteria. Disagreements about study selection were resolved by discussion with a third review author (YH) until consensus.

**Data extraction**

Data from eligible studies, including first author’s last name, publication year, country where the study was performed, study period, participants’ sex and age, sample size (cases and controls or cohort size), measure and range of exposure, variables adjusted for in the analysis and outcome measures, were independently extracted by two review authors (CL, JM).

Outcome measures were OR or RR estimates with corresponding 95% CIs. The primary analysis was focused on ORs and RRs that were adjusted for potential confounders. Study authors were contacted to retrieve missing information, when necessary.

Disagreements about data extraction were resolved by discussion with a third review author (YH) until consensus.

**Quality assessment**

Methodological quality was independently assessed by two review authors (CL, JM) using the Newcastle–Ottawa Scale for case–control or cohort studies as appropriate [26]. The scale assesses potential selection bias, comparability of cases and controls or cohorts, and ascertainment of outcome (case–control studies) or exposure (cohort studies). Points (or ‘stars’) are awarded for high-quality elements. Stars are summed and used to compare study quality in a quantitative manner, as recommended by the Cochrane Non-Randomized Studies Methods Working Group. For the purpose of this analysis, studies with ≥5 stars were considered high quality and were included; those with <4 stars were considered low quality and excluded. Disagreements about quality assessment were resolved by discussion with a third review author (YH) until consensus.
Data analysis

Statistical analysis was performed using RevMan 5.2. Study outcomes were pooled using the Mantel–Haenszel formula (fixed-effects model) or the Dersimonian–Laird formula (random-effects model). Heterogeneity amongst studies was evaluated using the chi-squared test and inconsistency index ($I^2$) [27]. A random-effects model was used to pool studies with significant heterogeneity ($I^2 > 50\%$, $P < 0.1$). A fixed-effects model was used to pool studies with no evidence of heterogeneity ($I^2 < 50\%$, $P > 0.1$).

Beggar’s regression test was used to investigate publication bias. Sensitivity analysis involved comparing fixed-effects and random-effects models.

Results

Study identification

This meta-analysis was conducted in accordance with PRISMA guidelines (Appendix S1). The searches identified 375 potentially relevant articles; two conference-related publications were identified from other sources. Titles and abstracts were screened, and 33 studies were considered potentially eligible for inclusion. Full text articles were retrieved, and 22 studies were excluded. Of these, 13 studies did not include a comparison group, four studies did not provide complete data (missing information included risk factors, adjusted hazard ratios or ORs, or contingency tables), three studies focused on CSVT, one study included presumed perinatal stroke, and one study focused on periventricular–intraventricular haemorrhage. Eleven studies were found to be eligible for inclusion according to our criteria for considering studies in this review (Fig. 1).

Characteristics of included studies

The characteristics of the 11 included studies are shown in Table 1. Of these, three were from the USA, two were from the UK, two were from France, one each were from Denmark, Netherlands, Iran, and one was published by the International Pediatric Stroke Study.

The studies included 32 potential risk factors for PAIS (Table 2). Breech presentation, vaginal blood loss, congenital heart diseases and umbilical venous catheterization were not considered because the studies were small or too few (<5 patients or <2 studies).

Prenatal risk factors

The meta-analysis demonstrated that pre-eclampsia (defined as a physician diagnosis of either pre-eclampsia or pregnancy-induced hypertension) [5,19,23,28,29] (PAIS, $n = 229$; control, $n = 1231$; OR 1.92, 95% CI 1.17–3.13; Z = 2.60; $P = 0.009$; heterogeneity $P = 0.20$, $I^2 = 34\%$; Fig. 2) and primiparity [19,22–24,28,29] (PAIS, $n = 302$; control, $n = 1348$; OR 2.03, 95% CI 1.55–2.65; Z = 5.18; $P < 0.001$; heterogeneity $P = 0.09$, $I^2 = 48\%$; Fig. 2) were significant risk factors for PAIS. IUGR [manifested as neonates with low birthweight or small for gestational age (SGA)] [5,19,24,29] (PAIS, $n = 505$; OR 1.53, 95% CI 0.85–2.75; Z = 1.43; $P = 0.15$; heterogeneity $P = 0.160$, $I^2 = 42\%$; gestational diabetes [5,19,24,30] (PAIS, $n = 121$; OR 1.55, 95% CI 0.79–3.04; Z = 1.27; $P = 0.20$; heterogeneity $P = 0.16$, $I^2 = 42\%$; oxytocin induction [19,23,24,29] (PAIS, $n = 151$; OR 1.31, 95% CI 0.85–2.03; Z = 1.22; $P = 0.22$; heterogeneity $P = 0.27$, $I^2 = 24\%$) and previous miscarriage [19,22,23,29] (PAIS, $n = 167$; OR 1.07, 95% CI 0.69–1.66; Z = 0.29; $P = 0.77$; heterogeneity $P = 0.50$, $I^2 = 0\%$) were not associated with PAIS.

Based on a limited number of studies ($n < 4$), the meta-analysis indicated that oligohydramnios [19,24] and intrapartum fever >38°C [22,23] were significant risk factors for PAIS. Decreased fetal movement (based on a maternal report of decreased fetal movement before labour or a non-stress test) [19,22,29] was not associated with PAIS.

Perinatal complications

The meta-analysis demonstrated vacuum delivery [5,19,22,23] (PAIS, $n = 206$; control, $n = 720$; OR 1.69, 95% CI 1.11–2.57; Z = 2.44; $P = 0.01$; heterogeneity $P = 0.61$, $I^2 = 0\%$; Fig. 2), fetal heart rate abnormalities [19,23,24,29] (PAIS, $n = 152$; control, $n = 455$; OR 5.21, 95% CI 3.43–7.90; Z = 7.77; $P < 0.001$; heterogeneity $P = 0.73$, $I^2 = 0\%$; Fig. 2), prolonged second stage of labour (defined as a second stage of labour longer than 2 h) [19,22–24] (PAIS, $n = 171$; control, $n = 588$; OR 4.13, 95% CI 2.40–7.10; Z = 5.12; $P < 0.001$; heterogeneity $P = 0.40$, $I^2 = 0\%$; Fig. 2), emergency caesarean section [because of abnormal cardiotocography (CTG) tracing or obstructed labour] [5,19,22–24,28,29] (PAIS, $n = 361$; control, $n = 1466$; OR 4.14, 95% CI 2.49–6.90; Z = 5.46; $P < 0.001$; heterogeneity $P = 0.01$, $I^2 = 62.8\%$; Fig. 2) and meconium-stained amniotic fluid [5,17,19,22–24] (PAIS, $n = 250$; control, $n = 833$; OR 2.82, 95% CI 1.64–4.85; Z = 3.74; $P < 0.001$; heterogeneity $P = 0.04$, $I^2 = 56.1\%$; Fig. 2) were significant risk factors for PAIS. Prolonged rupture of membranes [5,19,22–24,29,31] (PAIS, $n = 359$; control,
$n = 978$; OR 2.04, 95% CI 0.88–4.73; $Z = 1.66$; $P = 0.10$; heterogeneity $P = 0.001$; $I^2 = 73.0$%; (Fig. 2) was not associated with PAIS.

Based on a limited number of studies ($n < 4$), the meta-analysis also indicated forceps delivery [5,19,22], chorioamnionitis (defined as inflammation of the fetal membranes) [5,19,24], abnormal CTG tracing (including persistent late or variable decelerations, fetal bradycardia and/or reduced fetal heart variability) [17,22], cord abnormalities (including cord entanglements, hypercoiling, true knots, strictures and short cords) [19,24], birth asphyxia (defined as a reduction of serum oxygen levels and nutrient supply to the vital organs of the neonate) [5,19] and tight nuchal cord [5,22] were significant risk factors for PAIS.

**Newborn characteristics**

The meta-analysis demonstrated umbilical arterial pH <7.10 [5,22,23,29] (PAIS, $n = 123$; control, $n = 334$; OR 8.41, 95% CI 1.75–40.39; $Z = 2.66$; $P = 0.008$; heterogeneity $P = 0.012$, $I^2 = 68.8$%; (Fig. 2) and resuscitation at birth (including intubation for ventilation with or without cardiac compressions and epinephrine) [5,19,22,31,32] (PAIS, $n = 514$; control, $n = 46$189; OR 5.31, 95% CI 3.74–7.53; $Z = 9.33$; $P < 0.001$; heterogeneity $P = 0.62$, $I^2 = 0$%; (Fig. 2) were significant risk factors for PAIS. Male gender [5,17,19,22,23,28,29] (PAIS, $n = 320$; control, $n = 1491$; OR 1.27, 95% CI 0.99–1.62; $Z = 1.86$; $P = 0.06$; heterogeneity $P = 0.07$, $I^2 = 49.0$%; (Fig. 2) was not associated with PAIS.

Based on a limited number of studies ($n < 4$), the meta-analysis also indicated hypoglycaemia (defined as blood glucose <45 mg/dl (2.6 mmol/l) within the first 2 days after birth) [23,29] and SGA (defined as a birthweight below the 10th percentile of the birthweight distribution according to gestational age) [22,28] were significant risk factors for PAIS. Gestational age >42 weeks [22,28] was not associated with PAIS.

**Quality assessment and publication bias**

All studies included in our meta-analyses were considered high quality (Table 1). In all analyses, visual assessment of a funnel plot and Beggar’s test showed no evidence of publication bias (Fig. 3).
<table>
<thead>
<tr>
<th>Study (first author)</th>
<th>Study period (years)</th>
<th>Country</th>
<th>Study type</th>
<th>Study design</th>
<th>Case</th>
<th>Control</th>
<th>Neonatal</th>
<th>Quality score</th>
<th>Risk factors reported</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tuckuviene [28]</td>
<td>1994–2006</td>
<td>Denmark</td>
<td>Retrospective</td>
<td>Nested case–control</td>
<td>71</td>
<td>657</td>
<td>Both</td>
<td>8</td>
<td>GA ≥ 42 weeks, SGA (≤10th percentile), Apgar at 5 min &lt;7, emergency caesarean section, primiparity</td>
</tr>
<tr>
<td>Lee [19]</td>
<td>1997–2002</td>
<td>USA</td>
<td>Retrospective</td>
<td>Nested case–control</td>
<td>37</td>
<td>111</td>
<td>Both</td>
<td>6–8</td>
<td>Primiparity, pre-eclampsia, oligohydramnios, decreased fetal movement, chorioamnionitis, prolonged rupture of membranes, prolonged second stage of labour, fetal heart rate abnormality, cord abnormality, vacuum, emergency caesarean delivery, diagnosis of birth asphyxia, Apgar score at 5 min &lt;7, resuscitation at birth, history of infertility</td>
</tr>
<tr>
<td>Benders [29]</td>
<td>1990–2005</td>
<td>USA</td>
<td>Retrospective</td>
<td>Case–control</td>
<td>31</td>
<td>93</td>
<td>Preterm</td>
<td>6–8</td>
<td>TTTS, reduced fetal movement, fetal heart rate abnormalities, hypoglycaemia (&lt;2 mmol/l)</td>
</tr>
<tr>
<td>Chabrier [31]</td>
<td>2003–2006</td>
<td>France</td>
<td>Prospective</td>
<td>Cohort study</td>
<td>100</td>
<td>100</td>
<td>Both</td>
<td>6</td>
<td>Tobacco consumption, caesarean section, low Apgar score, resuscitation at birth, premature rupture of membranes</td>
</tr>
<tr>
<td>Martinez-Biarge [22]</td>
<td>1992–2012</td>
<td>UK</td>
<td>Prospective</td>
<td>Case–control</td>
<td>79</td>
<td>239</td>
<td>Term</td>
<td>6–8</td>
<td>Family history of seizures, family history of neurological diseases, autoimmune disease, gynaecological problems, primiparity, viral infection, abdominal pain, prolonged rupture of membranes, maternal fever &gt;38°C, shoulder dystocia, prolonged second stage, tight nuchal cord, unassisted vaginal, elective prelabour caesarean, emergency caesarean, low Apgar score, arterial cord pH &lt;7.10</td>
</tr>
<tr>
<td>Harteman [23]</td>
<td>2000–2010</td>
<td>Netherlands</td>
<td>Retrospective</td>
<td>Case–control</td>
<td>52</td>
<td>156</td>
<td>Term</td>
<td>7</td>
<td>Primiparity, intrapartum fever &gt;38°C, meconium-stained amniotic fluid, fetal heart decelerations, emergency caesarean section, low Apgar score, arterial umbilical cord pH &lt;7.10, hypoglycaemia (&lt;2 mmol/l), early-onset sepsis/meningitis</td>
</tr>
</tbody>
</table>

GA, gestational age; TTTS, twin-to-twin transfusion syndrome; IPSS, International Pediatric Stroke Study.
Discussion

To the authors’ knowledge, this is the first systematic review and meta-analysis investigating prenatal, perinatal and neonatal factors as risk factors for PAIS. Published data on risk factors for stroke in the neonatal period are sporadic and non-uniform, making it difficult for the scientific and clinical community to interpret. This meta-analysis consolidated the evidence on PAIS to provide guidance for clinical diagnosis and treatment.

Prenatal risk factors for PAIS were intrapartum fever >38°C, pre-eclampsia, oligohydramnios and primiparity. PAIS may occur due to changes in the maternal environment. Intrapartum fever is suggestive of intrauterine inflammation [19,33,34] and the presence of inflammatory cytokines, which may damage the central nervous system in the fetus, resulting in PAIS [35]. Pre-eclampsia is a vascular defect in the placental bed that can reduce uteroplacental blood flow and may cause fetal hypoxia and PAIS [36–39]. Several studies prove that pre-eclampsia is related to maternal prothrombotic disorders, a maternal history of thromboembolism, as well as thrombotic lesions in the placenta [5,19,23]. Evidence suggests that pre-eclampsia is associated with a variety of adverse pregnancy outcomes including IUGR, neonatal encephalopathy, neonatal sinovenous thrombosis and fetal death [36,40–43]. The current meta-analysis suggests that pre-eclampsia may also be associated with PAIS. Primiparity was strongly related to PAIS [19,22]. In our study, the association of primiparity and PAIS was significant. However, as primiparity may predispose some women to experience more intrapartum complications, such as prolonged second stage of labour, primiparity may be identified as a predictor rather than a risk factor for PAIS [19].

### Table 2 Prenatal, perinatal and neonatal risk factors for PAIS

<table>
<thead>
<tr>
<th>Complications</th>
<th>Number of studies</th>
<th>Cases of PAIS</th>
<th>OR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Prenatal complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous miscarriage</td>
<td>4</td>
<td>32</td>
<td>1.07 (0.69, 1.66)</td>
</tr>
<tr>
<td>Intrapartum fever &gt;38°C</td>
<td>2</td>
<td>16</td>
<td>6.00 (2.58, 13.97)</td>
</tr>
<tr>
<td>Decreased fetal movement</td>
<td>3</td>
<td>25</td>
<td>3.61 (0.98, 13.29)</td>
</tr>
<tr>
<td>Gestational diabetes</td>
<td>3</td>
<td>10</td>
<td>1.55 (0.79, 3.04)</td>
</tr>
<tr>
<td>Oligohydramnios</td>
<td>2</td>
<td>7</td>
<td>3.77 (1.23, 11.62)</td>
</tr>
<tr>
<td>Oxytocin induction</td>
<td>4</td>
<td>46</td>
<td>1.31 (0.85, 2.03)</td>
</tr>
<tr>
<td>Pre-eclampsia</td>
<td>5</td>
<td>28</td>
<td>1.92 (1.17, 3.13)</td>
</tr>
<tr>
<td>IUGR</td>
<td>4</td>
<td>19</td>
<td>1.53 (0.85, 2.75)</td>
</tr>
<tr>
<td>Primiparity</td>
<td>6</td>
<td>199</td>
<td>2.03 (1.55, 2.65)</td>
</tr>
<tr>
<td><strong>Perinatal complications</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Forceps delivery</td>
<td>3</td>
<td>15</td>
<td>2.51 (1.25, 5.02)</td>
</tr>
<tr>
<td>Abnormal CTG tracing</td>
<td>2</td>
<td>45</td>
<td>6.87 (3.81, 12.38)</td>
</tr>
<tr>
<td>Breech presentation</td>
<td>3</td>
<td>3</td>
<td>NA</td>
</tr>
<tr>
<td>Chorioamnionitis</td>
<td>3</td>
<td>16</td>
<td>3.41 (1.68, 6.92)</td>
</tr>
<tr>
<td>Fetal heart rate abnormalities</td>
<td>4</td>
<td>72</td>
<td>5.21 (3.43, 7.90)</td>
</tr>
<tr>
<td>Vacuum delivery</td>
<td>4</td>
<td>39</td>
<td>1.69 (1.12, 2.57)</td>
</tr>
<tr>
<td>Cord abnormalities</td>
<td>2</td>
<td>17</td>
<td>2.93 (1.43, 6.00)</td>
</tr>
<tr>
<td>Birth asphyxia</td>
<td>2</td>
<td>9</td>
<td>44.04 (5.31, 364.99)</td>
</tr>
<tr>
<td>Prolonged second stage of labour</td>
<td>4</td>
<td>41</td>
<td>4.13 (2.40, 7.10)</td>
</tr>
<tr>
<td>Prolonged rupture of membranes</td>
<td>7</td>
<td>50</td>
<td>2.04 (0.88, 4.73)</td>
</tr>
<tr>
<td>Vaginal blood loss</td>
<td>1</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>Emergency caesarean section</td>
<td>7</td>
<td>122</td>
<td>4.14 (2.49, 6.90)</td>
</tr>
<tr>
<td>Tight nuchal cord</td>
<td>2</td>
<td>14</td>
<td>2.50 (1.22, 5.14)</td>
</tr>
<tr>
<td>Meconium-stained amniotic fluid</td>
<td>6</td>
<td>79</td>
<td>2.82 (1.64, 4.85)</td>
</tr>
<tr>
<td>Umbilical venous catheterization</td>
<td>1</td>
<td>7</td>
<td>NA</td>
</tr>
<tr>
<td><strong>Newborn characteristics</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>7</td>
<td>179</td>
<td>1.27 (0.99, 1.62)</td>
</tr>
<tr>
<td>Umbilical arterial pH &lt;7.10</td>
<td>4</td>
<td>37</td>
<td>8.41 (1.75, 40.39)</td>
</tr>
<tr>
<td>Resuscitation at birth</td>
<td>6</td>
<td>142</td>
<td>5.31 (3.74, 7.53)</td>
</tr>
<tr>
<td>Apgar at 5 min &lt;7</td>
<td>5</td>
<td>41</td>
<td>6.76 (2.30, 19.83)</td>
</tr>
<tr>
<td>Gestational age &gt;42 weeks</td>
<td>2</td>
<td>14</td>
<td>4.48 (0.63, 31.58)</td>
</tr>
<tr>
<td>Hypoglycaemia</td>
<td>2</td>
<td>28</td>
<td>6.85 (1.53, 30.60)</td>
</tr>
<tr>
<td>Congenital heart diseases</td>
<td>1</td>
<td>2</td>
<td>NA</td>
</tr>
<tr>
<td>SGA</td>
<td>2</td>
<td>24</td>
<td>2.29 (1.35, 3.88)</td>
</tr>
</tbody>
</table>
Other perinatal risk factors associated with PAIS were forceps delivery, vacuum delivery, fetal heart rate abnormalities, abnormal CTG tracing, cord abnormalities, birth asphyxia, emergency caesarean section, tight nuchal cord and meconium-stained amniotic fluid. These complications are all indicative of hypoxic-ischaemic events, which may have resulted in a moderate degree of perinatal asphyxia and PAIS [5,17,19,22,24,31,32,44]. In accordance with our data, a previous meta-analysis found an association between hypoxia and PAIS [45]. Chorioamnionitis was also a perinatal risk factor for PAIS. Chorioamnionitis may result in thromboembolism in the placenta and increase the risk for emboli in the fetal brain [23].

Newborn characteristics associated with PAIS were umbilical arterial pH <7.10, Apgar score at 5 min <7, resuscitation at birth, hypoglycaemia, male gender and SGA. Umbilical arterial pH is an objective measurement of the physical condition of newborns. An umbilical arterial pH <7.2 may indicate fetal asphyxia [46], and an umbilical arterial pH <7.00 is considered severe fetal acidosis, which increases the risk of subsequent neurological dysfunction [46,47]. Our findings suggest that fetal acidosis is associated with PAIS. Subsequent studies are warranted to determine whether respiratory or metabolic acidosis is the contributing factor. Low Apgar scores often result in a clinical diagnosis of birth asphyxia. Birth asphyxia can lead to congestion, endothelial injury and intravascular coagulation, with subsequent hypoxic-ischaemia and PAIS. Hypoglycaemia is a common metabolic condition in human infants [48]. Previous studies support out findings that hypoglycaemia is a risk factor for PAIS [23,29]. In full-term infants, symptomatic hypoglycaemia is associated with bilateral occipital infarction, [49] and in neonates hypoglycaemia is associated with diffuse cortical and subcortical white matter damage [50]. Male fetuses are more susceptible to placental dysfunction and birth complications [31]. Hormonal status may partly explain this gender disparity in neonatal infants [2]. Several animal studies suggest that oestrogen has neuroprotective effects [51,52]. In a rat stroke model, testosterone increased and oestrogen decreased glutamate toxicity [52].

Intrauterine growth restriction was amongst the factors not associated with PAIS in the current meta-analysis. This is in contrast to other studies, which indicate IGUR is an independent risk factor for PAIS [5]. However, in our study, SGA was a risk factor for PAIS. A large proportion of SGA pregnancies are IUGR and the major proportion of IUGR
pregnancies are SGA [53]. A larger sample size may find a significant association between IUGR and PAIS in future studies. In the current study, decreased fetal movement was not associated with PAIS. This is surprising as a history of decreased fetal movements has been associated with bilateral parasagittal infarction [54].

This study was associated with several limitations. First, the sample sizes in many of the analyses were small. Secondly, most of the included studies were retrospective. Thirdly, the possibility of information and selection biases and unidentified confounders cannot be completely excluded because all the included studies were observational. Lastly, all studies included in our meta-analysis were from high-income countries; therefore, the effects of factors such as environmental air pollution, socioeconomic status, and the level of diagnosis and treatment of PAIS were not considered.

**Conclusion**

In conclusion, this meta-analysis revealed that intrapartum fever >38°C, pre-eclampsia, oligohydramnios, forceps delivery, vacuum delivery, fetal heart rate abnormalities, abnormal CTG tracing, cord abnormalities, birth asphyxia, emergency caesarean section, tight nuchal cord, meconium-stained amniotic fluid, umbilical arterial pH <7.10, Apgar score at 5 min <7, resuscitation at birth, hypoglycaemia and SGA are risk factors for PAIS. As the pathogenesis of PAIS is multifactorial, it is likely that a combination of prenatal, perinatal and neonatal risk factors is involved in
PAIS aetiology. It is suggested that patients with any of the risk factors identified in this preliminary analysis should be given careful consideration to ensure the prevention of PAIS. In infants with risk factors and clinical symptoms (such as seizures), magnetic resonance imaging scanning should be used as the first line imaging modality for detection of PAIS. In the future, large scale prospective clinical studies are required to better understand the pathophysiological mechanisms of PAIS and to identify potential therapies.

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Disclosure of conflicts of interest

The funders/sponsors had no role in the design and conduct of the study; collection, management, analysis or interpretation of the data; preparation, review or approval of the manuscript; and decision to submit the manuscript for publication. The authors declare that they have no competing interests.

Supporting Information

Additional Supporting Information may be found in the online version of this article:

Appendix S1. PRISMA checklist.

References


