

## Perinatal Stroke; Risk Factors and Outcome. A Study from Aga Khan University Hospital Karachi

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### ABSTRACT

**Objective:** To determine the frequency, risk factors and the outcomes of a perinatal stroke.

**Study Design:** Cross-sectional study.

**Place and Duration of Study:** Neonatal Intensive Care Unit, Department of Pediatrics, Aga Khan University Hospital, Karachi Pakistan, from Jan to Dec 2019.

**Methodology:** Neonates with perinatal stroke confirmed on the neuroimaging, were included in the study. The primary outcomes were risk factors, divided into 3 groups, maternal, placental and neonatal. The secondary outcome was the condition at the time of the discharge.

**Results:** A total of 58 patients were included in the study. Maternal risk factors identified in the study, were intrauterine infections 10 (17.2%), anti-phospholipid syndrome, gestational diabetes 8 (13.8%) and preeclampsia 7 (12.1%). Chorioamnionitis 9 (15.5%), antepartum hemorrhage 6 (10.3%), and placenta previa 4 (6.9%) were the placental risk factors. Neonatal risk factors were birth asphyxia 35 (60.3%), sepsis/meningitis 8 (13.8%), premature birth 6 (10.3%) and fetal bradycardia 4 (6.9%). Resuscitation was needed in 35 (60.3%) neonates with birth asphyxia. Haemorrhagic stroke was observed in 38 (65.5%) cases, ischemic stroke in 14 (24.1%) cases and mixed type of stroke was found in 6 (10.3%) patients. The total mortality rate in our study was 13.8%.

**Conclusion:** Haemorrhagic stroke was more common than ischemic or mixed stroke among the patients of perinatal stroke at our healthcare facility. Patients with low APGAR score at 5 minutes, birth asphyxia and male gender, were most affected.

**Keywords:** Neonatal ischemic stroke, Neonatal stroke, Perinatal hemorrhagic stroke, Perinatal stroke.

**How to Cite This Article:** Baloch F, Abro F, Khalid QUA, Chand P. Perinatal Stroke; Risk Factors and Outcome. A Study from Aga Khan University Hospital Karachi. *Pak Armed Forces Med J* 2022; 72(1): 215-219. Doi: <https://doi.org/10.51253/pafmj.v72i1.4863>

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### INTRODUCTION

Perinatal Stroke (PS) is a well-known group of cerebrovascular events that damage the brain early in the life.<sup>1</sup> It is one of the leading causes of Cerebral Palsy (CP) and causes lifelong neurological morbidity.<sup>2</sup> PS is defined as any vascular event causing interruption in the blood supply of the brain, occurring between 20 weeks of gestation through 28<sup>th</sup> day postnatal life and confirmed by neuroimaging studies.<sup>1</sup> It is classified into two major subtypes, ischemic and hemorrhagic stroke.<sup>3</sup> The incidence of PS is probably underestimated due to the variation in presentation, evaluation and diagnosis. Recent advances in diagnostic imaging have shown that strokes in the perinatal period are common with an incidence of at least 1:1578 (including ischemic stroke and hemorrhagic stroke).<sup>4</sup>

PS has complex and multifactorial risk factors including maternal, placental, and neonatal respectively. Maternal risk factors include autoimmune diseases such as antiphospholipid syndrome, gestational

diabetes, any systemic illness, infertility and its treatment, thrombophilia (acquired or inherited), pre-eclampsia, infection, smoking, and drug abuse.<sup>5-6</sup> Placental risk factors include placental abruption, fetomaternal hemorrhage and twin to twin transfusion. Neonatal risk factors include trauma, congenital heart disease, perinatal asphyxia, hypoglycemia in the preterm, male gender, catheter-related infections, polycythemia and dehydration.<sup>5</sup>

Children who suffer PS develop long-term disabilities including motor deficits, cognitive disorders and seizures.<sup>7</sup> Children with PS, having arterial lesions carry the highest risk of epilepsy.<sup>1,8</sup> A previous study showed around 30% children with hemiplegic CP had a PS.<sup>6</sup> Another study showed 54% children with hemiplegic CP due to PS had epilepsy.<sup>9</sup>

There is a paucity of data on PS from the developing countries and very few from Pakistan. The objective of this study was to describe the clinical presentations and outcomes of PS. This will help us to identify modifiable risk factors in patients which will lead to prompt recognition and immediate management of PS leading to reduce future morbidity and mortality.

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Received: 28 Jul 2020; revision received: 10 Sep 2020; accepted: 16 Sep 2020

## METHODOLOGY

This cross-sectional study was conducted at the Neonatal Intensive Care Unit (NICU) of Aga Khan University Hospital Karachi, from January 2009 to December 2019. After approval from the Institutional Review Board was obtained (ERC-2020-3427-8770). All the medical record charts were reviewed.

**Inclusion Criteria:** Neonates with any gestational age from birth to 28<sup>th</sup> days of life of either gender, with a confirmed diagnosis of PS on neuroimaging were included in the study.

**Exclusion Criteria:** Neonates presenting with the focal deficit or seizures due to any congenital structural anomalies were excluded from the study.

Data were collected using a structured proforma. Basic demographic characteristics were evaluated, i.e. age of baby at the time of admission, age at the time of discharge or death, gestational week, maternal age, birth weight, neuroimaging findings, outcome at the time of discharge. Maternal risk factors included in the study were; gestational diabetes, pre-eclampsia, thrombophilia, antiphospholipid syndrome, intrauterine infections, use of infertility medication or treatments, drug abuse. Placental risk factors included in the study were; placenta previa, placental abruption, chorioamnionitis, and fetal risk factors were; any infection, birth asphyxia, fetal distress, congenital heart disease, congenital anomalies, umbilical catheterization and dehydration.

The data were analyzed by using Statistical Package for Social Sciences (SPSS) version 22. The numerical variables were summarized as mean with standard deviation. Quantitative variables were summarized as frequencies and percentages.

## RESULTS

A total of 58 patients were included in the study. Maternal mean age was  $27.79 \pm 4.28$  years and the mean neonatal age was  $4.96 \pm 6.35$  days, while the average gestational age was  $35.82 \pm 4.63$  weeks. The average neonatal birth weight was  $2.27 \pm 0.81$  kg. Association of stroke with the mode of delivery was shown in the Table-I. Most of women, 24 (41.4%), underwent

emergency lower segmental cesarean section while 22 (37.9%) women underwent elective cesarean section. Spontaneous vaginal delivery was carried out in 8 (13.8%) women while 4 (6.9%) women underwent vacuum assisted spontaneous vaginal delivery. Out of 58 patients, 40 (69.0%) neonates were males and 18 (31%) were females.

According to the maternal risk factors, infections were seen in 10 (17.2%) cases, antiphospholipid syndrome was observed in 8 (13.1%) patients and gestational diabetes was found in 8 (13.8%) patients. Seven (12.1%) patients had pre-eclampsia, while 2 (3.4%) patients had hypothyroidism. On the assessment of placental risk factors, chorioamnionitis was present in 9 (15.5%) cases while antepartum hemorrhage was observed in 6 (10.3%) patients. Placenta previa was seen in 4 (6.9%) cases and premature rupture of the membrane was found in 2 (03.4%) patients. According to neonatal risk factors, birth asphyxia was found in 35 (60.3%) patients, sepsis/meningitis in 8 (13.8%) patients, pre-mature birth and fetal bradycardia in 4 (6.9%) cases each, dehydration in 3 (5.1%) cases, catheter-related infection and antenatal dilated ventricles were found in 2 (3.4%) cases each (Table-II). In this study, we found that resuscitation was performed in 35 (60.3%) patients.

**Table-II: Risk factors of perinatal stroke.**

Risk Factors (n=58)	n (%)
Emergency Lower Segment Cesarean Section	24 (41.4%)
Lower Segment Cesarean Section	22 (37.9%)
Intrauterine Infections	10 (17.2%)
Gestational Diabetes	8 (13.8%)
Hypothyroidism	2 (3.4%)
Antiphospholipid Syndrome	8 (13.8%)
Birth Asphyxia	35 (60.3%)
Sepsis/Meningitis	8 (13.8%)
Chorioamnionitis	9 (15.5%)
Premature Rupture Of Membranes	2 (3.4%)
5 min APGAR score $\leq 7$	38 (65.5%)
Preeclampsia	7 (12.1%)
Resuscitation At Birth	35 (60.3%)
Dehydration	3 (5.1%)

Hemorrhagic stroke was the most common and was found in 38 (65.5%) patients, ischemic stroke was

**Table-I: Association of Stroke with the mode of delivery.**

Type of Stroke	Mode of Delivery				Total	p-value
	Lower Segment Cesarean Section	Emergency Lower Segment Cesarean Section	Spontaneous Vaginal Delivery	Spontaneous Vaginal Delivery; Vacuumed		
Hemorrhagic	11 (52.3)	19 (70.3)	2 (28.6)	3 (100)	38 (65.5)	0.041
Ischemic	4 (19.1)	8 (29.7)	2 (28.6)	-	14 (24.2)	
Mixed	6 (28.6)	-	3 (42.8)	-	6 (10.3)	

identified in 14 (24.1%) cases, while mixed type of stroke was observed in 6 (10.3%) patients (Figure).

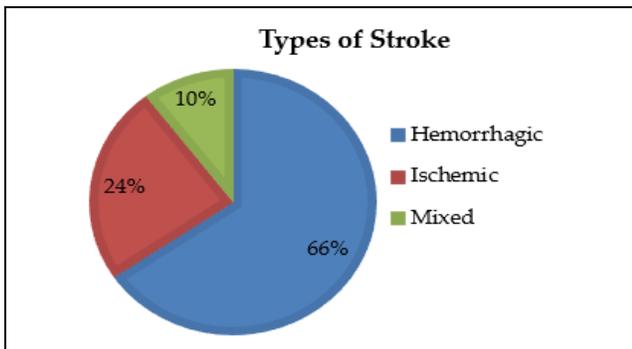


Figure: Frequency of perinatal stroke in a tertiary care hospital of Karachi.

APGAR score >7 was observed in 26 (44.8%) patients and APGAR score 1-3 in 14 (24.1%) cases, while 18 (31%) patients were found with APGAR score of 4-6. APGAR score of less than 7 at 5 minutes was associated with a high risk of hemorrhagic stroke. There was no significant difference in the mean APGAR score between different types of stroke (Table-III). Out of 58 patients, there were 8 deaths, 25 were stable without focal deficit and 25 were stable with focal deficit. There was a significant difference in the outcomes between different types of stroke ( $p$ -value=0.008) as shown in Table-IV.

Table-III: APGAR score at 5 minutes and its association with different type of strokes.

	Hemorrhagic (n=38)	Ischemic (n=14)	Mixed (n=6)	$p$ -value
Type of Stroke	6.92 ± 1.96	7.42 ± 1.55	8.33 ± 0.82	0.37

Table-IV: Outcome of perinatal stroke.

Type of Stroke	Death	Stable with focal deficit	Stable without focal deficit	$p$ -value
Hemorrhagic	4 (6.9)	21 (36.2)	13 (22.4)	0.008
Ischemic	1 (1.7)	3 (5.2)	10 (17.3)	
Mixed	3 (5.2)	1 (1.7)	2 (3.4)	

## DISCUSSION

Stroke is an uncommon but increasingly recognized cause of mortality and long-term neurological morbidity in children.<sup>10</sup> Although several risk factors have been identified, many questions regarding causes and clinical outcomes remain unanswered.<sup>11-12</sup> The identified risk factors including maternal, neonatal and placental conditions, but most of them are with a focus on specific conditions and do not necessarily reflect a causal relation. In this study, several maternal conditions were taken as risk factors such as

intrauterine infections, autoimmune diseases (anti-phospholipid syndrome), gestational diabetes and pre-eclampsia, while infertility treatment, hypothyroidism, and vitamin D deficiency were also found in few cases. The study by Cole *et al*,<sup>13</sup> described the association between maternal factors including age, primiparity and abortion inconsistent in the perinatal ischemic stroke. Additional possible risk factors were not supported by our data like gestational age and birth trauma. Previous studies have suggested increased rate of assisted deliveries in neonatal hemorrhagic stroke, but we did not observe this in our study. Our results support long-standing evidence dissociating routine birth trauma, assisted delivery, and neonatal hemorrhage. Study by Stamboul *et al*,<sup>14</sup> reported that gestational diabetes, fetal heart rate, and smoking were associated with an increase in peri-natal arterial ischemic stroke. It was claimed that diabetes could increase the risk of perinatal arterial ischemic stroke by increasing the hemoglobin concentration in blood and the size of the fetus, a condition favoring a difficult birth. The study by Munoz *et al*,<sup>12</sup> showed consistent findings, as maternal infection (12.5%), pre-term labor (12.5%) and prolonged rupture of membranes (2.5%).

In this study the fetal risk factors; birth asphyxia, sepsis, premature birth, fetal bradycardia, dehydration and catheter-related infections were most common. Perinatal risk factors were chorioamnionitis, antepartum hemorrhage, placenta previa and premature rupture of the membrane. On the other hand, Munoz *et al*,<sup>12</sup> had seen fetal risk factors as meconium-stained amniotic fluid (7.5%), breech presentation (2.5%), fetal heart rate abnormalities (22.5%), early-onset sepsis (17.5%), hyperbilirubinemia (12.5%) and birth asphyxia (15%). These findings were almost inconsistent with our study. Some other studies found risk factors like emergency cesarean section, birth asphyxia and APGAR score 7 after 5 min as often associated with fetal distress and suggested an important role of hypoxia ischemia as one of the possible causes of neonatal stroke.<sup>15-16</sup>

Another study by Lee *et al*,<sup>17</sup> stated that factors significantly associated with perinatal arterial stroke could be identified before delivery like primiparity, infertility, oligohydramnios, pre-eclampsia, chorioamnionitis, prolonged rupture of membranes, decreased fetal movement, the prolonged second stage of labor, and fetal heart rate abnormalities. Machado *et al*,<sup>18</sup> reported neonatal risk factors as primiparity, maternal age ≥35 years old, gestational diabetes, chorioamnionitis,

meconium-stained amniotic fluid, instrumental delivery, need for resuscitation maneuvers, dehydration and umbilical catheter.

The mean neonatal age was  $4.96 \pm 6.35$  days in our study, while the average gestational age was  $35.82 \pm 4.63$  weeks, 40 neonates were males and 18 were females. Similarly, Munoz *et al*,<sup>12</sup> reported that 18 (45%) patients diagnosed with neonatal arterial ischemic stroke, presented with clinical symptoms in the first three days of life, out of those 24 were males and 16 were females and mean gestational age was  $39.1 \pm 2.3$  weeks.

In our study, most of the women, 24 (41.4%), underwent emergency cesarean section, 37.9% women underwent low segment cesarean section; followed by spontaneous vaginal delivery in 13.8% and 6.9% women underwent vacuumed assisted spontaneous vaginal delivery. However, some other studies also stated that emergency C-section and instrumental assisted deliveries could be the cause of neonatal stroke.<sup>17</sup>

In this study hemorrhagic stroke was found in 65.5% cases and ischemic stroke in 24.1% while mixed type of stroke in 10.3% of the patients. Similarly, Lee *et al*,<sup>11</sup> reported that 10 infants had a perinatal arterial ischemic stroke and 20 had a perinatal hemorrhagic stroke. Another study stated that 51 (59%) infants had with neonatal hemorrhagic stroke, out of which 32 (67%) were idiopathic, 30 (35%) were the hemorrhagic transformation of primary ischemic injuries. While 14 cases were with neonatal cerebral venous sinus thrombosis, 11 were with hypoxic-ischemic encephalopathy and 5 with neonatal arterial ischemic stroke) and 5 were presumed perinatal hemorrhagic stroke.<sup>19</sup> Our study revealed that only 8 patients out of 58 died, 25 were stable without focal deficit and 25 were stable with focal deficit. In this study APGAR score  $<7$  in 1 minute was observed in 44.8% patients and  $<3$  in 1 minute was seen in 24.1% cases. In the study by Munoz *et al*,<sup>12</sup> APGAR  $\leq 3$  at 1 min was in observed in 7.5% cases and APGAR  $\leq 7$  at 5 min was seen in 10% cases. In another study by Harteman *et al*,<sup>19</sup> reported APGAR score of (1 min)  $\leq 3$  in 29% cases and APGAR score (5 min)  $<7$  in 25% cases. There is a big confusion regarding risk factors of perinatal stroke, different studies showed different risk factors and it also varies with the population of different ethnic origins.<sup>20</sup>

Our study demonstrated that hemorrhagic stroke was more common than ischemic or mixed stroke among the patients of PS at our healthcare facility. Hemorrhagic stroke was more common in patients who

were born with low APGAR score at 5 minutes and male gender was most vulnerable.

### LIMITATIONS OF STUDY

We have only studied those neonates who underwent neuroimaging studies, there were a lot of neonates who presented with subtle clinical features but did not undergo any extensive screening and could be missed in retrospective studies.

### RECOMMENDATION

Future multicenter and large sample size studies are required to exhibit the perinatal stroke risk factors to decrease the neonatal morbidities.

### CONCLUSION

Haemorrhagic stroke was more common than ischemic or mixed stroke among the patients of PS at our healthcare facility. Patients with low APGAR score at 5 minutes, birth asphyxia and male gender, were most affected.

**Conflict of Interest:** None.

### Authors' Contribution

FB: Intellectual Contributin, FA: Direct contribution, QUAK: PC: Intellectual contribution.

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