

## Perinatal Factors Preceding Neonatal Hypoxic-Ischemic Encephalopathy in El-Minia Locality

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### Abstract

**Objectives:** We investigated the risk factors of birth asphyxia in neonates in EL-Minia University Hospital from 1 January to 31 December 2015, to identify leading perinatal risk factors causing birth asphyxia in our locality in order to prevent it. Study design this was a retrospective case - control study.

**Setting:** Neonatal Intensive Care Unit (NICU) of Minia University Hospital. We studied 160 neonates. 80 neonates of them full filled the criteria of hypoxic ischemic encephalopathy delivered at 28-41 weeks of gestation from 1 January to 31 December 2015 and admitted to Neonatal Intensive Care Unit (NICU) of El-Minia University Hospitals. In addition to the other 80, neurologically free neonates delivered in the same period included as a control group. Data collected include information about the prenatal period, peripartum period, demographic characteristics, admission and evolution during NICU stay.

**Results:** We found that antepartum, intrapartum and postpartum factors are important risks leading to neonatal encephalopathy. Intrapartum factors were highly associated with birth asphyxia as prolonged 2nd stage first then meconium-stained amniotic fluid and prenatal visits < 4 show a statistical significance.

**Conclusion:** The identified risk factors may be useful indicators for defining children at risk of developing hypoxic ischemic encephalopathy, and helpful for targeting individuals for early intervention programmes.

**Keywords:** Hypoxic ischemic encephalopathy; Birth asphyxia; Antepartum factors; Intrapartum factors

### Introduction

Perinatal hypoxic-ischemic encephalopathy (HIE) is a syndrome of disturbed neurological function in the early life characterized by clinical and laboratory proof of acute or subacute brain injury [1].

Perinatal asphyxia is the major cause of HIE in neonates. All pathological conditions that result in prenatal, perinatal, or postnatal hypoxia and tissue hypoperfusion are etiologic factors of HIE [2].

Birth asphyxia is a leading reason of neonatal mortality and morbidity in developing countries with an incidence of 100-250/1000 live births compared to 5-10/1000 live births in the developed world [3]. Infections, preterm births and birth asphyxia were the leading causes of neonatal deaths globally [4].

Several hazard elements associated with HIE. These include low birth weight, low Apgar score, low pH and hemoglobin level [5], as well as delivery by unskilled birth attendants, prolonged second stage of labor, delivery in nongovernmental hospitals, bad antenatal care [6], post-term gestation, vacuum extraction, male sex, and prolapsed cord [7].

### Method

#### Study design

Authors performed a retrospective study of all new borns with HIE admitted at Neonatal intensive care unit (NICU) in El Minia University hospital. This unit is a tertiary centre. This study conducted from 1 January to 31 December 2015. We studied 160 neonates, 80 neonates of them included as a:

**Group 1:** Who delivered from 1 January to 31 December 2015 with low Apgar scores diagnosed as perinatal asphyxia and admitted

to the Neonatal Intensive Care Unit (NICU) of El-Minia University Hospitals, fulfilling the following criteria:

**Inclusion criteria:** New borns suffering from perinatal asphyxia diagnosed in the presence of at least 2 of the following factors and admitted to the neonatal intensive care unit within 6 hours of birth.

- The first cry delayed for 5 minutes.
- Apgar scores at 5 minutes of age < 5 and didn't improve to more than 7/10 at 20 minutes of age.
- Post asphyxial seizures (seizures identified by means of medical observation) within first 48 hours after birth (diagnosis of perinatal asphyxia in preterm neonates has similar criteria as full-term including suboptimal Apgar scores, a need for respiratory support, and an inability to suck-feed).

#### Exclusion criteria:

- Neonates with major congenital malformations.
- Intrauterine fetal death or stillbirth infants.
- Other causes of central nervous system encephalopathy (infectious, metabolic).

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**Group 2:** 80 neurologically free neonates delivered from 1 January to 31 December 2015 and admitted to the Neonatal Intensive Care Unit (NICU). They were included as a control group. They were age and sex matched. We collected the data from medical records and included information about individual characteristics of the mother and prenatal period (mother's age, complications during pregnancy such as diabetes mellitus, preeclampsia and cholestasis), peripartum period (rupture of membranes, cardiotocography tracing, acute intrapartum events, delivery method, Apgar score at the first and fifth minute) demographic characteristics (gestational age, sex, birth weight, place of labor) and admission and evolution during NICU stay (clinical seizures and antiepileptic drugs). This study approved by the ethical committee of Minia faculty of medicine.

**Statistical analysis:** The collected data were coded, tabulated, and analyzed using SPSS program (Statistical Package for Social Sciences) software version 20.

Descriptive statistics were done for numerical data by mean, standard deviation, and minimum and maximum of the range, while they were done for categorical data by number and percentage. The analytical analysis was done for quantitative variables using t-test in cases of two groups with parametric data and Mann -Whitney U in cases of two groups with non-parametric. Analytical analyses were done for qualitative data using Chi -square test for cases more than 5 in the variable, and Fisher's exact test for cases less than 5 in the variable.

The level of significance at P value<0.050.

## Results

In this study group 1 included 80 neonates with asphyxia or Apgar score ≤ 6 (case group) 57 male and 23 females compared to group 2, which included 80 neurologically free neonates (control group) 42 male and 38 female.

Table 1 showing the demographic data of the asphyxiated group is shown in Term babies represent a great percentage about 66.3%. Male gender occupies a large percentage about 71.3% (Table 1).

Comparison between the asphyxiated group and control group as regarding the antepartum risk factors is shown in Table 2. We found that inappropriate antenatal care (ANC) was significantly higher in cases than a control group (p value<0.001). Bronchial asthma and anemia were significantly higher in mothers of cases than controls (p value=0.04), (p value=0.02) respectively. Also, hypertension in pregnancy was significantly higher in cases when compared with control (Table 2).

Comparison between the asphyxiated group and control group as regarding the intrapartum risk factors is shown in Table 3. Meconium-stained amniotic fluid recorded a higher percentage in cases than a control group (p value<0.001). Also, prolonged 2nd stage was significantly higher in cases than a control group (p value<0.001). PROM ≥12 h occurred more frequent in mothers of asphyxiated neonates than the control group, as regard placenta previa, abruption placenta, and cord prolapse they recorded a significantly higher percentage in cases than control also, chorioamnionitis and oxytocin use were significantly higher in cases than control.

As regards polyhydramnios it was greater in mothers of cases than the control with a statistically significant difference. Place of delivery and anesthesia did not affect the outcome.

The significant risk factors of birth asphyxia were further analyzed by multiple logistic regression models as shown in Table 4 in which

intrapartum factors associated with birth asphyxia as prolonged 2nd stage first then meconium-stained amniotic fluid and preeclampsia. Also, prenatal visits<4 show a statistical significance (Figures 1-4).

## Discussion

Despite the important advances in perinatal care in the past decades, asphyxia remains a severe condition leading to significant mortality and morbidity. The term "asphyxia" is derived from the Greek and means "stopping of the pulse". Perinatal asphyxia is a condition characterized by an impairment of exchange of the respiratory gasses (oxygen and carbon dioxide) resulting in hypoxemia and hypercapnia, accompanied by metabolic acidosis [8]. The asphyxial injury may involve body systems, but hypoxic-ischemic encephalopathy (HIE) remains the most studied serious sequelae.

HIE associated with many risk factors such as severe preeclampsia, peripartum fever, acute intrapartum event, meconium staining of amniotic fluid, nonspontaneous vaginal delivery and male sex [9]. Actually, we found most of these risks in our locality so we aim in

The variability	The asphyxiated group (N=80)
<b>Gestational age (week)</b>	
Mean ± SD	37.2 ± 3.3 w
Range	30-42 w
Fullterm 37-42 w	53(66.3%)
Preterm<37 w	18(22.5%)
Postterm>42 w	9(11.3%)
<b>Birth weight (kg)</b>	
Mean ± SD	2.9 ± 0.5 kg
Rang	1.4-4 kg
Birth weight 2.5-3.5	54(67.5%)
Low ≤ 2.5	20(25%)
High ≥ 3.5	6(7.5%)
<b>Sex</b>	
Male	57(71.3%)
Female	23(28.8%)
<b>Maternal age(year)</b>	
Mean ± SD	24.4 ± 4.9 y
Rang	15-40 y
<b>Parity</b>	
Primigravida	38(47.5%)
Multigravida	42(52.5%)

Table 1: Demographic data of the asphyxiated group.

	Cases (N=80)	Controls (N=80)	P
<b>Maternal age</b>			
18-35 years	68(85%)	76(95%)	0.1
Teenager(<18)	8(10%)	3(3.8%)	0.3
Elderly(>35)	4(5%)	1(1.3%)	0.5
Inappropriate ANC ≤ 4 visits	62(77.5%)	20(25%)	<0.001*
DM	6(7.5%)	2(2.5%)	0.1
Anemia	11(13.8%)	3(3.8%)	0.02
Bronchial asthma	4(5%)	0(0%)	0.04
Renal disease	2(2.5%)	0(0%)	0.1
<b>Blood pressure</b>			
Hypotension	5(6.3%)	2(2.5%)	0.4
Hypertension	17(21.3%)	2(2.5%)	0.001

Table 2: Comparison between asphyxiated group and control group as regarding the maternal factors (Antepartum factors).

	Cases (N=80)	Controls (N=80)	P
Meconium stain AF	40(50%)	0(0%)	<0.001*
Prolonged 2 <sup>nd</sup> stage	63(78.8%)	2(2.5%)	<0.001*
PROM ≥ 12 h	14(17.5%)	0(0%)	<0.001*
Cord prolapsed	21(26.3%)	0(0%)	<0.001*
Placenta previa	54(67.5%)	0(0%)	<0.001*
AbruptioPlacenta	19(23.8%)	0(0%)	<0.001*
Twins	7(8.8%)	2(2.5%)	0.09
Chorioamnionitis	19(23.8%)	0(0%)	<0.001*
Oligohydraminios	11(13.8%)	3(3.8%)	0.05
Polyhydraminios	16(20%)	3(3.8%)	0.003
<b>Place of delivery</b>			
Home	35(43.8%)	29(36.3%)	0.4
Clinic	38(47.5%)	41(51.3%)	0.7
Hospital	7(8.8%)	10(12.5%)	0.6
Oxytocin use	55(68.8%)	16(20%)	<0.001*
<b>Mode of delivery</b>			
Vaginal-SVD	33(41.3%)	39(48.8%)	0.4
ABD	1(1.3%)	2(2.5%)	0.9
<b>Instrumental</b>			
Forceps	18(22.5%)	3(3.8%)	0.001*
Ventose	6(7.5%)	1(1.3%)	0.1
-CS	22(27.5%)	35(43.8%)	0.05
<b>Anesthesia</b>			
Spinal	20(25%)	30(37.5%)	0.6
General	2(2.5%)	5(6.25%)	0.7
Preeclampsia	17(21.3%)	2(2.5%)	0.001*

**Abbreviations:** AF: Amniotic Fluid; PROM: Premature Rupture Of Membranes; SVD: Spontaneous Vaginal Delivery; ABD: Assisted Breech Delivery; CS: Cesarean Section

**Table 3:** Comparison between the asphyxiated and control groups as regarding the intrapartum factors.

Model	Standardized Coefficients Beta	T	Sig.
Constant		-1.247	0.214
Instrumental delivery	-0.094	-1.698	0.092
Prolonged 2 <sup>nd</sup> stage	0.388	5.4	0
Prenatal visits<4	0.242	3.921	0
Polyhydraminos	-0.018	-0.326	0.745
PROM ≥ 12 h	0.093	1.617	0.108
Cord prolapsed	-0.009	-0.136	0.892
Bleeding	-0.044	-0.75	0.454
Chorioaminionitis	-0.063	-1	0.319
Meconiam stain	0.227	3.147	0.002
Preeclampsia	0.185	3.258	0.001
Male sex	0.075	1.454	0.148
Oxytocin use	0.134	2.313	0.022
Gest. Age	-0.155	-2.722	0.007
Birth weight	0.031	0.602	0.548
Outcome	0.165	2.374	0.019
Anemia	-0.054	-0.929	0.354
Bronchial asthma	0.007	0.141	0.888

**Table 4:** Multiple logistic regression analysis.

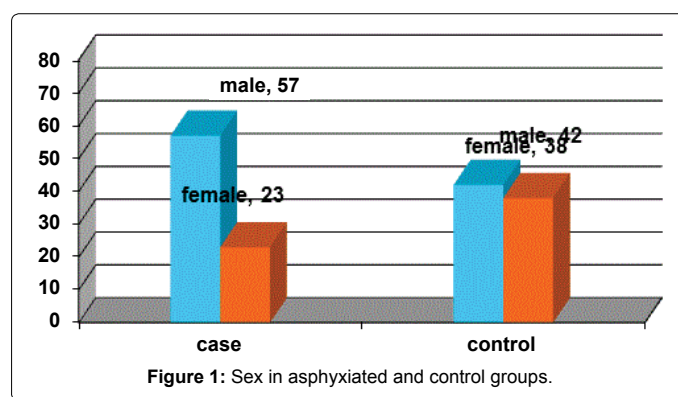
our study to discover the leading perinatal risk factors causing birth asphyxia.

Full terms had a high risk of HIE than premature and postmature, this could be explained by the high percentage of prolonged 2nd stage of labor in the asphyxiated group about 78.8% and usually, the prolonged 2nd stage occurs with term babies.

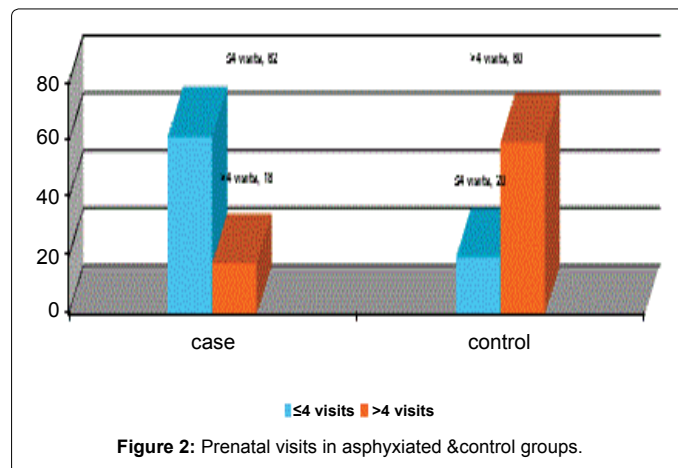
Male sex represents a great proportion of cases than control (71.3%). This is in agreement with the results of Futrakul et al., [7] and Sithivuddhi et al., [10] studies who mentioned that the male gender vulnerable to any threatening factors such as increasing the risk of sepsis, bronchial hyperresponsiveness, atopy, and mortality from RDS etc.

In contrast to Nayeri et al., [11] who found no enormous differences among male and female in their study.

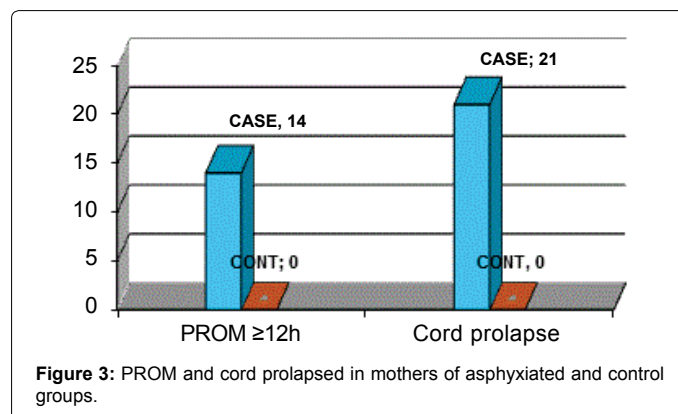
HIE was reported more in males than females [12] and male sex associated with the risk of cerebral palsy, especially in very preterm infants. Although the biological basis of this increased risk of brain injury in male babies is not completely understood, several studies explain the mechanisms of cell death after HIE like:



**Figure 1:** Sex in asphyxiated and control groups.



**Figure 2:** Prenatal visits in asphyxiated & control groups.



**Figure 3:** PROM and cord prolapsed in mothers of asphyxiated and control groups.

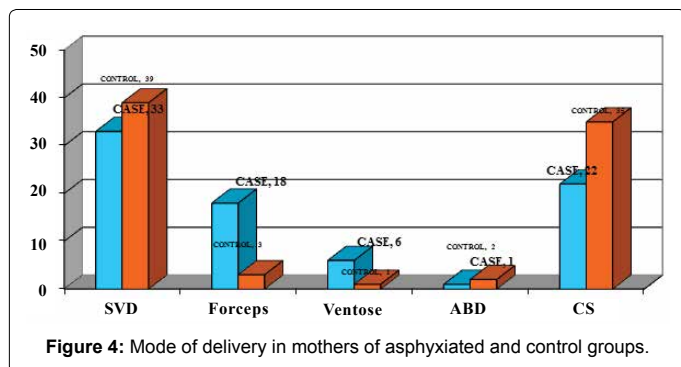


Figure 4: Mode of delivery in mothers of asphyxiated and control groups.

- The nuclear enzyme poly (ADP-ribose) polymerase-1 (PARP), involved in DNA repair, is activated by HIE in both sexes, but contributes to neuronal injury, through depletion in NAD+ stores, only in males [13].
- It was also shown that there is an increase in apoptosis-inducing factor (AIF) in the immature male brain, this is not observed in the female brain after HIE [14].
- Similarly, under conditions of stress *in vitro*, male neurons die via an AIF-mediated pathway, while a more prominent cytochrome c release from the mitochondria occurs in female neurons, suggesting that intrinsic gender differences in the mechanisms of cell death may occur independently of circulating sex hormones [15].
- The elevated circulating levels of dihydrotestosterone in males during the late embryonic period, persisting through the first year of life could be partially responsible for these differences as androgens increase the excitotoxic cell death induced by GABA activation in the developing hippocampus [16].

In our study, we found that the improper antenatal care (ANC) was significantly higher in asphyxiated than control groups. This is coinciding with Gane et al., [17] who found that mothers with antenatal visits less than three had a higher risk for perinatal asphyxia. This finding was a result of poor utilization of health care services in our locality so it is important to establish a safe motherhood policy recommendation of a minimum of three antenatal visits during pregnancy focusing on risk screening, immunization, anemia prophylaxis, and treatment.

Significant risk factors for birth asphyxia analyzed by multiple logistic regression models. Revealing that the leading risks were intrapartum factors which associated with birth asphyxia like prolonged 2nd stage, meconium-stained amniotic fluid.

Prolonged second stage of labor (>2 hours) remained the most important risk factor of birth asphyxia representing 78.8% of asphyxiated group. Similar finding in a study done by Kiyani et al. [18] who reported prolonged second stage of labor in (72%) cases, so early decision of cesarean section could eliminate the great proportion of birth asphyxia resulting from prolonged 2nd stage of labor.

50% of asphyxiated group had meconium-stained amniotic fluid. Similarly, Pitsawong and Panichkul [19] study who found a higher number of asphyxiated group presented with thick meconium-stained amniotic fluid. It might be due to the fact that meconium aspiration syndrome was primarily associated with acute hypoxic events late in labor or related to acute events that occur late in labor or after birth and also depends on increasing consistency of meconium [20].

The major limitation of this study was its design. As it is a

retrospective study, it mainly relies on information from medical records, with possible inaccuracies and loss of data. However, observations made in this study can help in planning larger population-based studies to confirm and target the risk factors of perinatal asphyxia to prevent birth asphyxia.

## Conflict of Interest

We declare no conflict of interest.

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