

# Maternal Morbidities and Occurrence of Intraventricular Hemorrhage in Preterm Infants

Arash Bordbar<sup>1</sup> Mahgol Farjadnia<sup>1</sup>

<sup>1</sup>Department of Neonatology, Akbarabadi Hospital, Iran University of Medical Sciences, Tehran, Iran

Address for correspondence Mahgol Farjadnia, MD, Department of Neonatology, Akbarabadi Hospital, Iran University of Medical Sciences, Tehran, Iran (e-mail: mahgolfarjadnia@gmail.com).

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## Abstract

Intraventricular hemorrhage (IVH) is one of the most serious neurological morbidities in preterm infants. Several prenatal, intrapartum, and neonatal risk factors have been detected in different studies. However, maternal conditions that may render the neonates to IVH have been the subject of very few studies. Preterm infants with and without IVH were included in the study, and maternal obstetrics and general health clinical files were reviewed for any kind of morbidity. Data were then analyzed with statistical software to assess the association between maternal conditions and IVH. A total of 115 neonates with IVH and 120 infants without IVH were recruited. Among all maternal conditions, prolonged rupture of membrane ( $p = 0.00$ ), laparoscopic surgery for infertility ( $p = 0.001$ ), and in vitro fertilization (IVF) ( $p = 0.00$ ) increased the risk of IVH in neonates significantly. IVF remained strongly associated with IVH even after controlling for confounding variables (odds ratio: 9.75; confidence interval: 2.66–35.75;  $p = 0.001$ ). Based on our findings, prolonged rupture of membrane and IVF were maternal conditions that increased the risk of IVH. Laparoscopic surgery for infertility was also associated with an increased risk of IVH.

## Keywords

- ▶ intraventricular hemorrhage
- ▶ maternal morbidity
- ▶ in vitro fertilization
- ▶ prolonged rupture of membrane
- ▶ infertility

## Introduction

Intraventricular hemorrhage (IVH) is among the most devastating morbidities in preterm neonates. Independent of other comorbidities, IVH increases the mortality among preterm infants and survivors will likely suffer from neurological sequels ranging from poor school performance to complete cerebral palsy.<sup>1–6</sup> Although several researchers have reported a higher incidence of morbidity and mortality among children with higher grades of IVH, those with lower grades of IVH are in fairly noticeable risk of disability. Any grade of IVH in neonates raises concerns over appropriate neurological development and possible sequels.<sup>7,8</sup> Several prenatal and postnatal risk factors have been implicated in the IVH. Nevertheless, the association between maternal morbidities and IVH has been the issue of very few studies.

This study was aimed to investigate the possible association between these maternal morbidities and the occurrence of any grade of IVH.

## Materials and Methods

In this case–control study, we reviewed the medical charts and considered preterm infants with less than 34 weeks of gestational age from January 2010 to October 2014. All 115 preterm infants with any grade of IVH were recruited. From the total number of 2,980 preterm neonates, 120 (sample size calculated through the formula adjusted for correlation model) were selected randomly. To match the two groups for weight and age, the mean age and weight were calculated in both groups. The older and heavier neonates than average were excluded from the control group and younger and lighter preterm infants were included in the study. The

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process continued until the mean age and weight in both groups did not differ significantly.

Review of the clinical files with respect to the confidentiality of the patients' information does not require ethical approval in our center.

Maternal obstetrics and general health files were retrieved from the hospital data center, and demographic data including age, weight at the time of delivery, weight gain during pregnancy, cigarette smoking, or drug abuse besides the history of any kind of morbidity both during and before the pregnancy were extracted. Surgical history and type and time of the operations were also recorded.

Neonatal files were reviewed for gestational age, gender, birth weight, single or multiple gestation history of a traumatized delivery, and IVH grading (in neonates with IVH) as well.

Cranial ultrasound is performed for all neonates less than 30 weeks of gestational age or in case of clinical suspicion of an intracranial event. These clinical clues include cardiopulmonary instability, acidosis, and anemia with unknown etiology as well as bulging fontanel, abnormal movements, and seizure.

Sonography is done through the anterior fontanel in the coronal and sagittal planes with a portable ultrasound machine (SonoSite, FUJIFILM SonoSite Corporation, Japan). Intracranial space is examined with both 5 and 7.5 MHz transducers.

IVH is then classified as follows<sup>9</sup>: (grade I) germinal matrix hemorrhage, (grade II) IVH without ventricular dilation, (grade III) IVH with acute ventricular dilation, (grade IV) hemorrhage expanding from the ventricles to parenchyma.

The International Classification of Disease, 10th edition, Clinical Modification diagnostic codes were applied to determine maternal morbidity (**Appendixes 1 and 5**).<sup>10</sup> All data entered the commercially available biostatistical software (SPSS v.18, IBM SPSS, New York, United States) and underwent univariate and multivariate analyses. The maternal morbidities and neonatal IVH were defined as 2-point scales (1: suffer from the morbidity or afflicted by IVH; and 2: does not suffer from the morbidity/is not afflicted by IVH). Data then underwent analysis using Pearson correlation coefficient which was calculated to measure the strength of relationships. The variables that were significantly associated with IVH entered a logistic regression model to eliminate the probable confounding effects. *P* value was considered to be significant at level  $\leq 0.05$ .

## Results

We evaluated 120 infants without IVH and 115 infants with IVH. The mean age of the neonates with and without IVH was  $29.50 \pm 2.9$  weeks and  $30.74 \pm 1.9$  weeks, respectively ( $p = 0.1$ ). The mean weight of the neonates with IVH was less than those without IVH ( $1,978 \pm 644$  g vs.  $2,188 \pm 864$  g;  $p = 0.2$ ). The mean age of the mothers with an infant with IVH was more than those with a child without IVH ( $30.4 \pm 53$  years vs.  $24.5 \pm 6.8$  years, respectively;

$p = 0.00$ ) and have gained less weight during pregnancy ( $9.65 \pm 5.7$  kg vs.  $10.80 \pm 6.45$  kg).

All collected maternal morbidities were categorized as follows:

### A. Pregnancy and its complications in the alphabetic order

History of abortion, abruptio placentae, antepartum hemorrhage, assisted pregnancy, chorioamnionitis, gestational diabetes mellitus, gestational hypertension, hemorrhage in early pregnancy, malpresentation, multiple gestation, oligohydramnios, placental disorders, polyhydramnios, pre-eclampsia, premature rupture of membrane, preterm labor, and prolonged rupture of membrane. Rupture of membrane was considered prolonged if the interval between the rupture and labor took more than 48 hours (prolonged rupture of membrane is not directly addressed in International Classification of Disease, 10th edition) and traumatized labor.

### B. General health conditions in the alphabetic order

Alopecia areata, asthma, anemia, cardiovascular disorder, collagen vascular disease, dermatitis, diabetes mellitus, epilepsy, hypertension, mood disorders, peptic ulcer disease, personality and behavior disorders, thyroid dysfunction, tuberculosis, and viral hepatitis.

Overall, 41 patients had a history of different kinds of surgery in both groups. From the first category, prolonged rupture of membrane ( $p = 0.00$ ), multiple gestation ( $p = 0.001$ ), and assisted pregnancy ( $p = 0.00$ ) were associated with IVH.

In vitro fertilization (IVF) remained strongly associated with IVH even after controlling for age, weight, and multiple gestation and maternal age (odds ratio: 9.75; confidence interval: 2.66–35.75;  $p = 0.001$ ).

In the second category, none of the maternal morbidities were related to IVH. Maternal morbidities, habits, and their association with IVH are expressed in **Tables 1 and 2**. Among different types of surgery, laparoscopic surgery for unexplained infertility was significantly associated with IVH in preterm infants ( $p = 0.001$ ) (**Table 3**).

## Discussion

IVH, as a cause of significant neurological morbidity and mortality among preterm infants, has always been an issue worth discussing. Several studies have been conducted to find the probable underlying etiologies and to establish preventive strategies. Unlike neonatal morbidities, maternal conditions have been investigated in extremely rare studies. Some studies have directly found a connection between maternal issues and IVH,<sup>11–14</sup> while some have indirectly provided clues to the importance of maternal health state. In our study, only a few variables were found to be related with increased risk of IVH.

Prolonged rupture of membrane was one of the obstetric events that were associated with IVH. In other investigations, researchers have proposed an inflammatory/ infectious basis that may make the infants susceptible to IVH. Researchers have reported an increased level of inflammatory cytokines and elevation in the leukocyte count in blood samples of neonates with IVH.<sup>15–17</sup> This increase in the

**Table 1** Pregnancy-related complications and their association with intraventricular hemorrhage

Pregnancy-related complications	Presence of intraventricular hemorrhage, <i>n</i> (%)	Absence of intraventricular hemorrhage, <i>n</i> (%)	Pearson correlation coefficient ( <i>r</i> )	<i>P</i> value
History of abortion	6 (5.2)	2 (1.6)	0.097	Not significant
Abruptio placentae	3 (2.6)	5 (4.1)	0.044	Not significant
Antepartum hemorrhage	3 (2.6)	6 (5)	0.063	Not significant
Chorioamnionitis	4 (3.4)	1 (0.8)	0.091	Not significant
Gestational diabetes mellitus	4 (3.4)	8 (6.6)	0.074	Not significant
Gestational hypertension	17 (14.7)	13 (10.8)	0.058	Not significant
Hemorrhage in early pregnancy	25 (20.8)	16 (13.3)	0.109	Not significant
In vitro fertilization	23 (20)	2 (1.6)	0.296	< 0.001
Malpresentation	5 (4.3)	9 (7.5)	0.068	Not significant
Multiple gestation	33 (27.8)	13 (10.8)	0.224	0.001
Oligohydramnios	9 (7.8)	5 (4.1)	0.076	Not significant
Placental disorder	3 (2.6)	2 (1.6)	0.027	Not significant
Polyhydramnios	0 (0)	1 (0.8)	0.064	Not significant
Preeclampsia	12 (10.4%)	13 (10.8%)	0.006	Not significant
Premature rupture of membrane	34 (29.5)	51 (42.5)	0.138	Not significant
Prolonged rupture of membrane	20 (17.3)	2 (1.6)	0.269	< 0.00
Traumatized labor	3 (26)	4 (33.3)	0.022	Not significant

**Table 2** Maternal health conditions and habits and their association with intraventricular hemorrhage

Maternal morbidities and habits	Presence of intraventricular hemorrhage <i>n</i> (%)	Absence of intraventricular hemorrhage <i>n</i> (%)	Pearson correlation coefficient ( <i>r</i> )	<i>P</i> value
History of abortion	2 (1.7)	3 (2.5)	0.027	Not significant
Asthma	7 (6.0)	4 (3.3)	0.064	Not significant
Anemia	6 (5.2)	2 (1.6)	0.097	Not significant
Cigarette smoking	4 (3.4)	6 (5)	0.039	Not significant
Cardiovascular disease	7 (6.0)	3 (2.5)	0.088	Not significant
Collagen vascular disease	0 (0)	1(0.8)	0.064	Not significant
Dermatitis	4 (3.4)	8 (6.6)	0.074	Not significant
Drug abuse	3 (2.6)	4 (3.3)	0.022	Not significant
Diabetes mellitus	3 (2.6)	5 (4.1)	0.044	Not significant
Epilepsy	2 (1.7)	2 (1.6)	0.002	Not significant
Hypertension	7 (6)	4 (3.3)	0.064	Not significant
Mood disorders	5 (4.3)	3 (2.5)	0.050	Not significant
Peptic ulcer disease	2 (1.7)	3 (2.5)	0.027	Not significant
Personality disorders	2 (1.7)	1 (0.8)	0.040	Not significant
Thyroid dysfunction	3 (2.6)	4 (3.3)	0.022	Not significant
Tuberculosis	2 (1.7)	2 (1.6)	0.002	Not significant
Viral hepatitis	2 (1.7)	1 (0.8)	0.040	Not significant

**Table 3** Association between surgical procedures and infantile intraventricular hemorrhage

Type of surgery	Presence of intraventricular hemorrhage <i>n</i> (%)	Absence of intraventricular hemorrhage <i>n</i> (%)	Pearson correlation coefficient ( <i>r</i> )	<i>P</i> value
Appendectomy (open)	9 (7.8)	11 (9.1)	0.025	Not significant
Cholecystectomy (open)	2 (1.7)	3 (2.5)	0.027	Not significant
Cholecystectomy (laparoscopic)	3 (2.6)	4(3.3)	0.022	Not significant
Infertility workup (laparoscopic)	12 (10.4)	1 (0.8)	0.209	< 0. 001
Intestinal resection/anastomosis obstruction due to tuberculosis (open)	0 (0)	1 (0.8)	0.064	Not significant

cytokine level and leukocyte count was independently associated with IVH after eliminating the effect of confounding variables. In a study by DiSalvo,<sup>14</sup> the sign of amniotic infection that was confirmed by histological findings was associated with IVH. Findings of our study support the probable role of an underlying infection or inflammation. How the inflammation (and/or infection) apart from the ensuing shock makes the neonates susceptible to IVH is not yet clear. Whether these cytokines impair the autoregulation of cerebral vasculature or interfere with the integrity of endothelial cells should be investigated in further studies. Although chorioamnionitis was diagnosed more commonly in mothers with babies afflicted with IVH, it did not significantly increase the risk of IVH. This observation might be attributed to very few cases of proved chorioamnionitis in this study.

Assisted pregnancy was another variable that was strongly associated with IVH in neonates. IVF is assumed to increase the odds of multiple gestation and consequently the risk of preterm labor and complications of prematurity. However, IVF remained strongly associated with IVH even after controlling for age, weight and multiple gestation, and maternal age (because mothers with an infant with IVH were in average older than those with an infant without IVH, maternal age [as a probable risk factor for infertility and other comorbidities] entered the regression model as well).

The association between IVF and IVH has already been reported. In a study by Linder et al<sup>18</sup> on 36 infants with IVH, IVF was expressed to increase the risk of cranial hemorrhage, independent of the interfering factors (age, weight, and multiple gestation). In the current study with the number of cases approximately three times more than that study's we found the same. The pathogenesis of this finding is largely unknown and both maternal and environmental factors are postulated to be important. Pathologic research on placental abnormality, cerebral vasculature, and scaffolding matrix besides molecular research on the type and quantity of receptors for vasoactive agents on the endothelial cells could probably be enlightening.

Among different types of surgery, laparoscopic surgery for unexplained infertility was found to increase the risk of IVH. As far as we know, this is the first time in the literature that laparoscopic surgery for workup and treatment of infertility has been found to be related with infantile IVH.

Researchers have found that placental abruption and placental abnormalities could increase the risk of IVH and cerebral palsy.<sup>13</sup> Manipulation of the pelvic structures, especially the uterus, that can further affect the uteroplacental interaction and combat an integrated implantation may seem justifying. Nevertheless, histological confirmation is necessary to prove the hypothesis. Moreover, we could not detect any association between antenatal vaginal bleeding and documented placental abnormalities such as placental abruption and placenta previa with IVH. No association between other maternal conditions and IVH was found in this study.

In 1992, Kuban et al<sup>11</sup> concluded that maternal preeclampsia acted as a protective factor against IVH in preterm newborns. However, in another study by Paul et al<sup>19</sup> no association was found between maternal preeclampsia and IVH after multivariate modeling. In our study, we did not find any difference in the rate of IVH between neonates born to mothers with and without preeclampsia.

Thyroid hormones play a fundamental role in neurodevelopment of the fetus and neonate. A complicated interplay between the level of thyroid hormones, thyroid receptor expressions at precise points, modulating pathways, transporters, and transcription factors defines the final expression of thyroid hormone-responsive target genes. It has been shown that T3 modulates the neural differentiation from embryonic stem cells and neural migrations are also under control of thyroid hormone-regulated genes.<sup>20,21</sup> The association between the level of thyroid hormones and the occurrence of IVH has been investigated in some studies.<sup>22</sup> Nevertheless, the level of maternal thyroid hormones, as the major source of fetal thyroid hormones in the first trimester, and its association with IVH has not been sought in any study. In our study, we did not observe any significant differences between these two groups. Mothers with thyroid dysfunction who were recruited to this study were all under treatment and the level of thyroid hormones was normalized months before the pregnancy. It can thus be concluded that at least maternal thyroid dysfunction that are under treatment do not increase the risk of IVH.

The retrospective nature of the study limited the possibility to investigate a causal relationship between maternal conditions and the occurrence of IVH. To increase the sensitivity of the study, we had to enlist some very rare morbidities under one major entity.

In conclusion, among all maternal morbidities and habits that were investigated in this study, prolonged rupture of membrane, IVF, and laparoscopic surgery were associated with an increased risk of IVH. IVF remained significant after controlling for confounding variables.

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**Appendix 1** Pregnancy-related complications and their codes from International Classification of Disease, 10th edition

Diseases	Applied codes
History of abortion	O03–07
Gestational hypertension	O13
Preeclampsia	O14, O14.1
Gestational diabetes mellitus	O24
Multiple gestation	O30.0, O30.1, O30.2, O30.8, O30.9
Polyhydramnios	O40
Oligohydramnios	O41.0
Chorioamnionitis	O41.1
Premature rupture of membrane	O42
Placental disorder	O43, O44
Abruptio placentae	O45
Antepartum hemorrhage	O46
Ectopic pregnancy	O00
Traumatized delivery	O81, O81.4, P12, P114
Hemorrhage in early pregnancy	O20
Preterm labor	O60.0
Failed medical induction of labor	O61.0
Malpresentation	O64, O32

**Appendix 2** General health conditions and the applied codes from International Classification of Disease, 10th edition

Diseases	Applied codes
Cardiovascular disease	I01, I02, I05–09, I20–I25, I30–52
Hypertension	I10, I15, I15.0, O10, O11
Thyroid disorder	E00–E07, E35, E89
Diabetes mellitus	E10–14
Peptic ulcer disease	K25, K26, K29
Collagen vascular disease	M30–36, M05–14, M60–63
Tuberculosis	A15–19
Viral hepatitis	B15, B16, B18
Anemia	D50–52
Personality and behavior disorders	F60–69
Mood disorders	F30–39
Dermatitis	L20–30
Alopecia areata	L63
Asthma	J45
Epilepsy	G40