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Institute of Clinical Medicine, Clinic of Children´s Diseases

Aimée-Julie Bachmann, Year 6, group 1

INTEGRATED STUDY MASTER'S THESIS

Intraventricular Hemorrhages in Extremely Low Birth Weight and Very Low Birth Weight Babies

Supervisor Professor Dr. Arunas Liubsys

Head of the department Professor Dr. A. Jankauskiene

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aimee-julie.bachmann@mf.stud.vu.lt

Abstract

Background: Intraventricular hemorrhage is a major complication in extremely low birth weight and very low birth weight babies, contributing significantly to neonatal morbidity and mortality. The aim of this study is to provide an overview of current knowledge on the incidence, pathophysiology, risk factors, diagnosis, management, prevention, and long-term outcomes of intraventricular hemorrhage in this vulnerable population and to establish measures to improve the prognosis in affected neonates. A systematic evaluation of recent studies highlights the impact of perinatal care strategies on reducing intraventricular hemorrhage incidence. Despite advancements in neonatal medicine, high grades of intraventricular hemorrhage remain associated with adverse neurodevelopmental outcomes.

Method: A literature review was conducted with a total of 57 studies.

Results: This review included 58 studies published between 2014 and 2025. IVH remains a common complication in ELBW and VLBW infants, with severe cases (Grades III–IV) affecting up to 20% of this population. Key risk factors identified across studies include extreme prematurity, low birth weight, respiratory distress, mechanical ventilation, and fluctuations in cerebral blood flow. Diagnosis is most often made using cranial ultrasound, with MRI providing additional structural details in selected cases. A range of management strategies, such as antenatal corticosteroids, delayed cord clamping, and gentle ventilation, were associated with reduced IVH incidence. Importantly, across the reviewed literature, the most consistent and effective approach to prevention was the implementation of standardized care bundles, evidence-based guidelines, and staff education to reduce clinical variability. Short-term complications included posthemorrhagic ventricular dilation and hydrocephalus, while long-term outcomes often involved neurodevelopmental delay, motor impairments, and cognitive deficits. Because of the interactions between prematurity-related vulnerabilities, the lack of effective treatments, and the possibility of complications, IVH is still difficult to prevent and treat.

Conclusion: Intraventricular hemorrhage remains a serious complication in preterm neonates, particularly those with extremely low birth weight and very low birth weight. Long-term neurological deficits and high morbidity are linked to this condition. The incidence of intraventricular hemorrhage in preterm newborns remains a major concern, even with advancements in neonatal care. The most consistent prevention strategy identified in the literature was the implementation of structured care bundles, standardized guidelines, and ongoing staff education. These approaches reduce variability in care and offer the best potential. To further improve outcomes in this susceptible population, future research should place a high priority on the early identification of high-risk neonates and the creation

of innovative neuroprotective techniques. To develop more individualized and efficient treatment plans, future research should also examine the influence of environmental and genetic factors on the development of intraventricular hemorrhage. More research should be focused on novel preventive and therapeutic approaches to improve prognosis in affected neonates. Enhancing intraventricular hemorrhage management and prevention continues to be a top priority for neonatal care of preterm infants.

Methodology

This paper investigates intraventricular hemorrhages in extremely low birth weight and very low birth weight babies. It was conducted as a literature review analyzing existing research based on the latest literature and publications from articles, journals, and books, especially from "Volpe's Neurology of the Newborn – chapter 28". The publications investigated were found on the following online websites: PubMed, Elsevier, Google Scholar, ClinicalKey, ScienceDirect, and Access Medicine. To limit the extent and select the most relevant data, the inclusion criteria include language, English, and an age maximum of 11 years between 2014-2025. To ensure that the selected literature is from primary resources, the following selection criteria were included: randomized controlled studies, cohort studies, retrospective studies, systematic review articles, and meta-analyses. Exclusion occurs for case reports and publications published more than 11 years ago, to ensure the selection of the most recent literature. Under the search in PubMed, 8349 articles were suitable. However, applying the exclusion criteria, 918 remained. Of these, 868 were individually assessed for potential use in this literature review, and in total 58 studies were selected. The algorithm for the search on PubMed can be visualized in Figure 1. In total, 58 studies were included in this literature review to assess intraventricular hemorrhages in extremely low birth weight and very low birth weight babies.

Keywords: intraventricular hemorrhage, ELBW, VLBW, preterm infant, pathogenesis, risk factors, diagnosis, neurodevelopmental outcomes, treatment

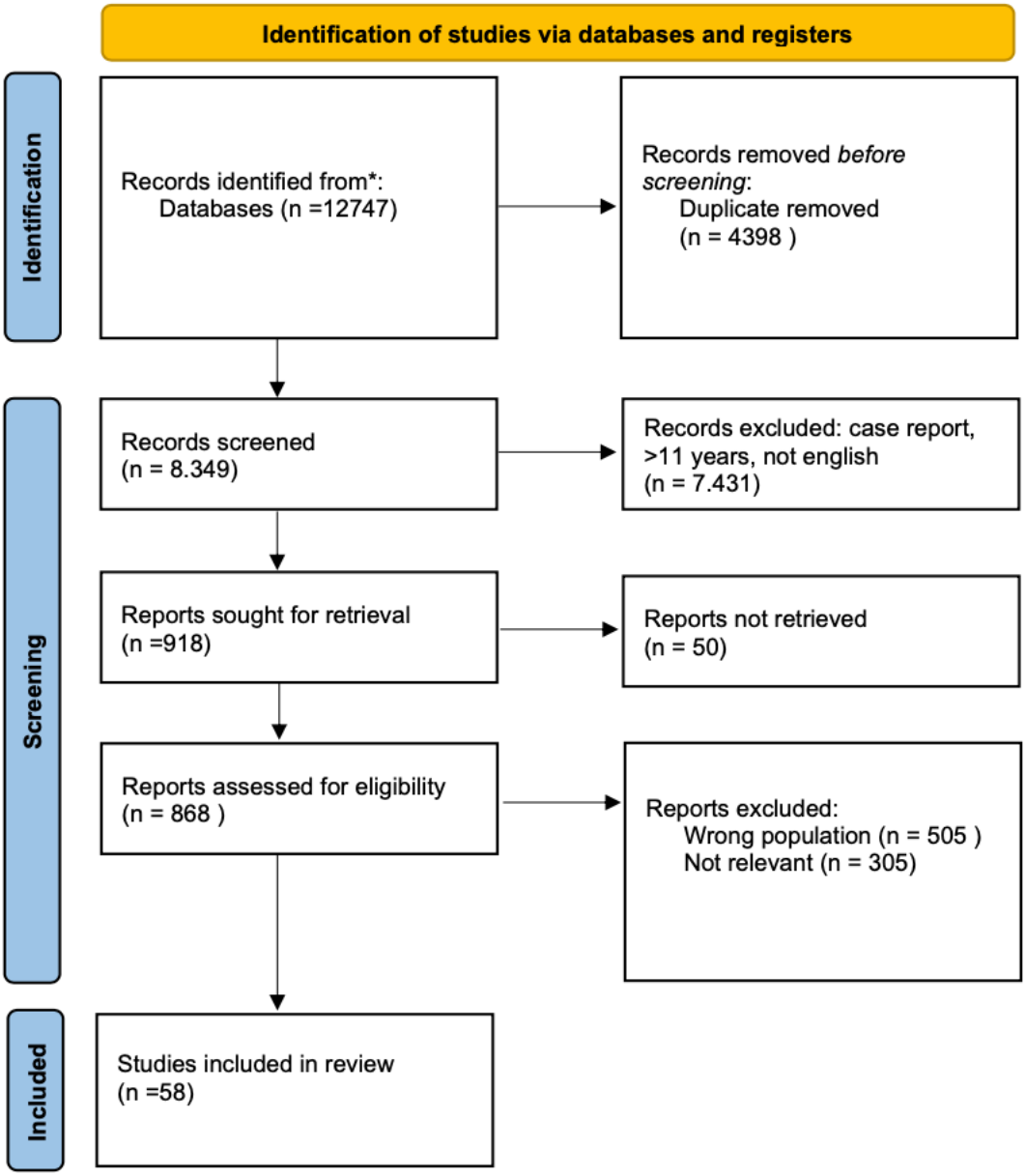

Figure 1. Source: Page MJ, et al. BMJ 2021;372:n71. doi: 10.1136/bmj.n71.

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List of Abbreviations

ANGPT-2	angiopoietin-2
C-section	caesarean section
CBF	cerebral blood flow
CP	cerebral palsy
CSF	cranial spinal fluid
CT	computer tomography
CUS	cranial ultrasound
ELBW	extremely low birth weight
GA	gestational age
GCs	glucocorticosteroids
GFAP	glial fibrillary acidic protein
GM	germinal matrix
GM-IVH	germinal matrix intraventricular hemorrhage
HOL	hours of life
ICP	intracranial pressure
IVH	Intraventricular hemorrhage
MRI	magnetic resonance image
NDI	neurodevelopmental impairment
NICU	neonatal intensive care unit
PDA	persistent ductus arteriosus
PHH	posthemorrhagic hydrocephalus
PHVD	post-hemorrhagic ventricular dilatation
PHVI	periventricular hemorrhagic infarction
PVL	periventricular leukomalacia
TGF-ß	transforming growth factor beta
TNP	temporizing neurosurgical procedures
US	ultrasound
VEGF	vascular endothelial growth factor
VLBW	very low birth weight
wGA	weeks of gestational age
MAP	mean arterial pressure

1. Introduction

Intraventricular hemorrhage (IVH) is one of the leading causes of complications in preterm newborns and extremely and very low birth weight newborns during the neonatal period (1). In preterm infants, IVH is the most common type of intracranial hemorrhage and brain injury (2).

IVH in preterm infants is defined as a hemorrhage of the germinal matrix that ruptures through the ependyma and enters the lateral ventricle (3). This complication occurs in 25-30% of VLBW newborns and up to 45% of ELBW newborns (4).

Future neurodevelopmental abnormalities are strongly predicted by the presence of IVH in preterm infants, especially as the severity of IVH increases (2).

The mortality rate for premature babies has decreased in recent decades, however, this has been accompanied by an increase in the absolute number of children who survive with morbidity. Improvements in neonatal intensive care have improved the survival of extremely preterm infants, leading to an increase in the number of infants who are at high risk of developing IVH (3). IVH occurs in approximately 3 live births per 1.000 (5).

Notably, the risk of IVH in infants is inversely connected with the infant's maturity level and rises as GA or birth weight declines (6). Despite changes in routine neonatal care leading to survival rates increasing to approximately 70%, IVH takes an essential place in mortality and morbidity (7).

As IVH plays a decisive role in cognitive and motor development and therefore has a relevant impact on the life of the child and the associated family, premature infant care should continue to prioritize lowering the incidence of intraventricular hemorrhage. Current diagnostic methods and management strategies to reduce the incidence and severity of intraventricular hemorrhage are assessed in this literature review.

The aim of this thesis is to evaluate and summarize current literature focused on intraventricular hemorrhage in extremely low birth weight and very low birth weight babies in order to identify strategies to improve the prognosis. Current knowledge on the incidence, timing, pathophysiology, risk factors, diagnosis, management, prevention, and outcomes were observed. The literature review evaluates risk factors that contribute to the development in this vulnerable population. Furthermore, it assesses current diagnostic methods and management strategies to reduce the incidence and severity of intraventricular hemorrhage. Finally, this thesis identifies approaches to prevent and improve long-term neurodevelopmental outcomes, based on the underlying pathophysiology and risk factors.

1.1 Definition

Abraham Towbin discovered intraventricular hemorrhage in 1968 (8).

Intraventricular hemorrhage is mainly caused by disruption of cerebral blood flow and the vulnerability of the germinal matrix vasculature. The severity of IVH is correlated with the occurrence of complications like brain parenchymal lesions and post-hemorrhagic ventricular dilatation (PHVD) (2).

IVH occurs more frequently the younger and more immature the infants are, whereby the immaturity and extent of asphyxia and severity of the bleeding are correlated (9). According to the World Health Organization, preterm infants are defined as those who are born alive before reaching 37 weeks of gestation. Prematurity is further subdivided into low birth weight, very low birth weight, and extremely low birth weight. The first weight recorded within hours after birth below 2500g is defined as low birth weight (LBW). A weight below 1500g at birth is classified as a very low birth weight (VLBW) and below 1000g as an extremely low birth weight (ELBW) (10).

Nearly one-half of the four million live births in the United States each year are ELWB, and about 55.000 are VLBW infants. Despite a decrease in mortality rates, the number of VLBW and ELBW infants born has remained constant over the last two decades (9). In the year 2020, around 19.8 million newborns were born with low birth weight globally, an estimated 14.7 percent of all babies born that year. These infants were more likely to die during their first month of life, and those who survived face lifelong consequences, including impaired growth, a lower IQ, and chronic conditions like diabetes and obesity that develop in adulthood (11).

1.2 Incidence

The incidence rate of IVH has been significantly impacted by an increase in preterm delivery brought on by improved assisted reproductive technology-mediated pregnancy (3). In the last decades, there have been crucial changes to routine neonatal care. As medical technology continues to advance, survival rates for preterm infants are rising, and the gestational age at which very low birth weight (VLBW) infants can survive has declined. Due to significant medical advancements, high-risk infants who would not have survived otherwise now have a chance to survive because the age of viability has been lowered to 22–24 weeks of gestation (2).

Because of the new positive pressure mechanical ventilation, the incidence of GM-IVH in neonatal intensive care units (NICUs) increased from 4.7% before the 1960s to 50% between 1975 and 1980. Then, in 2005, it dropped by three-quarters to 12.5%, most likely because of ventilator advancements and the introduction of surfactants and corticosteroids (12).

The occurrence of IVH events in the first six hours of life has decreased to less than 10%, even though the incidence of IVH is rising along with the survival of infants with low GA (13). The incidence of IVH ranges from 20-25%. In preterm newborns younger than 25 weeks, IVH occurs in up to 40% (14). IVH occurs in about 20-30% of infants suffering from a very low birth weight (15). According to a meta-analysis from Lai et al. (2022), newborns with a gestational age (GA) of less than 28 weeks had a 15% incidence of severe IVH and a 34.3% incidence of any grade of IVH (16). In the United States, 12.000 infants are born with intraventricular hemorrhage every year. Preterm infants born before 30 weeks of GA have an IVH frequency of 10-20%. In those infants weighing less than 750g at birth, the incidence of severe IVH accounts for up to 35-45% (2).

1.3 Timing of IVH

The vast majority of intraventricular hemorrhage in preterm newborns happens during the first three days of life. Of those, about 70% happen within the first 24 hours of life, and about 50% happen within the first 5 hours. 95% of IVH will have happened by 7 days, with a tiny percentage showing up between 7 and 10 days later (17).

Wu et al. report that 8.2% of preterm neonates (less than 32 weeks) with grades II-III GM-IVH worsen to grade III-IV GM-IVH within 7 days (12).

1.4 Classification

As demonstrated in Table 1, IVH can be detected and diagnosed by cerebral ultrasound and magnetic resonance imaging, using two different grading systems. These systems communicate the extent of harm, which predicts the infant's future results.

In 1978, Dr. Lu-Ann Papile classified intraventricular hemorrhages into 4 grades, based on the severity assessed by CT findings in newborns, which clinicians and researchers have used for decades (6).

Joseph J. Volpe modified Papile’s classification based on ultrasound findings. Grade I is defined as an isolated bleeding confined to the GM or as a ventricle filled with blood is <10%, while Grade II is an IVH with approximately 10 to 50% filling of the ventricular area. Grade III is an IVH affecting

more than 50% of the ventricular area, tending to expand into the lateral ventricle. He graded IVH IV separately as PVHI, as it results from IVH but is not a distention of IVH. PVHI is defined as periventricular hemorrhagic infarction. Grade I or II can be defined as mild IVH, while grade III or IV is termed severe IVH (8). Nowadays, Papiles' grading system is used for any form of neuroimaging to classify the severity of IVH (6).

Table 1. GM-IVH grading system

Severity	Papile	Volpe
Grade I	subependymal bleeding, confined to the GM	Germinal matrix hemorrhage with or without IVH (< 10% of ventricle filled with blood)
Grade II	bleeding extends into lateral ventricles without ventricular dilation	IVH (10%–50% of ventricle filled with blood) typically without ventricular dilation
Grade III	bleeding extends into lateral ventricles with dilation of the ventricles	IVH (>50% of ventricle filled with blood) typically with ventricular dilation
Grade IV	includes grades 1-3 with parenchyma bleeding	Periventricular hemorrhagic infarction

2. The preterm newborn

2.1. Etiology and consequences of prematurity

13.4 million babies were born prematurely in 2020, meaning they were born before 37 full weeks of pregnancy (10).

Premature births can occur naturally or as a result of medical conditions. In one out of five cases, a higher gestational age could have been achieved with fewer complications later on (18). Intrauterine infections, maternal smoking, adverse economic circumstances, and multiple gestations account for the majority of spontaneous preterm births. As the use of assisted reproductive techniques has increased in recent years, up to 50% of the resulting births occur prematurely. High economic and societal costs are linked to complications from premature birth that can persist into adulthood. Furthermore, preterm newborns are more likely to develop related pathologies, primarily pulmonary, cardiovascular, and neurodevelopmental conditions. Necrotizing enterocolitis, RDS, and severe germinal matrix IVH are the most pertinent morbidities linked to an increased risk of mortality in extremely preterm newborns (18).

2.2. Neurological Complications of preterm newborns

Despite a decrease in preterm newborn mortality, neurological problems such as neurodevelopmental and functional impairments are more common in extremely preterm newborns, due to their greater survival rates. In practical terms, babies born very early and very underweight are at a crucial stage of brain development, and it is still challenging to improve neurological development outcomes. The total brain volume of a normally growing fetus increases by 230% between 25 and 37 weeks of gestation. The volume of the cerebellum rises by 384%, whereas the volume of the brain stem grows by 134%. Between weeks 24 and 40, the cerebellum's volume increases fivefold (18).

Additionally, after 24 weeks of pregnancy, the radial glia disappear, the cortical gray matter grows, the connections get more intricate, and the cortical folding and gyrification become more complicated. Axons, glial cells, and oligodendrocytes are all developing significantly in the white matter. The significance of an impaired development, size, structure, connectivity, and function in the preterm newborn brain at this stage is highlighted by these data taken together. The central nervous system (CNS) is immature due to a number of factors, including the fragile vascular structure of the germinal matrix (GM), low neuronal migration, poor white matter myelination, and exponential growth of the grey matter (18).

Atienza-Navarro (2020) states that these restrictions lead to various brain lesions in preterm newborns, such as intracranial hemorrhages (including GM, intraventricular, and intraparenchymal), cerebellar injury, periventricular leukomalacia, periventricular hemorrhagic infarction later developing posthemorrhagic hydrocephalus, or posthemorrhagic ventriculomegaly (18).

2.3 Normal brain development

During the earliest fetal period, neuronal proliferation and cellular differentiation are the primary neurogenic events. Within the ventricular and subventricular zones, neuronal proliferation starts at 5–6 weeks of gestational age (wGA) and lasts until 26–30 wGA. About 8 wGA is when the first synapses appear. While neurogenesis continues after 17 wGA, at 5–6 weeks of gestational age, tangential neuronal migration begins and continues past birth (19).

Between 13–15 wGA, synapses begin to form within the cortical subplate, a crucial transient structure in corticogenesis. This subplate emerges at 13–15 wGA and continues to expand until 26–28 wGA, reaching a thickness four to five times greater than that of the cortical plate. By 23–25

weeks of gestation, subplate neurons establish interactions with afferent fibers from the thalamus, a process essential for cortical development. After 26 weeks of gestation, thalamocortical fibers migrate toward the cortical plate, marking a critical step in the maturation of the fetal brain (19).

The most frequent cerebral hemorrhages in neonates may be categorized into five kinds based on where they occur: parenchymal hemorrhage, intraventricular hemorrhage, intracerebellar hemorrhage, primary subarachnoid hemorrhage, and subdural hemorrhage. The most prevalent kind of intracerebral hemorrhage in preterm newborns is intraventricular hemorrhage (IVH), which originates in the subependymal germinal matrix (9).

3. Pathogenesis and risk factors

3.1 Anatomy of GM

The origin site of intraventricular hemorrhage is the subependymal germinal matrix. The subependymal region of the ventricle walls contains the germinal matrix (GM). It´s responsible for generating excitatory neuronal precursors in the brain from about 10 to 20 weeks of gestation. Later, it also produces neuroglial precursors that develop into oligodendrocytes and astrocytes, along with late-migrating GABAergic neurons destined for the cerebral cortex. The germinal matrix is vascularized by capillaries that are poorly supported by collagen or muscle and very cellular and gelatinous (9).

Between weeks 10 and 20, the subependymal GM, a metabolically highly active layer of neuroepithelial origin situated ventrolaterally of the lateral ventricles, provides a source of neuronal precursor cells. During the third trimester, these give rise to oligodendroglia cells and astrocytes. The germinative matrix starts to increase from the 23rd to the 24th week of pregnancy, and by the 36th week, it is hardly noticeable. Between weeks 28 and 32 of pregnancy, the germinal matrix is most noticeable adjacent to or behind the foramen Monroi and the caudate nucleus head. This is in line with where the premature infant's intracerebral hemorrhages are usually observed (9).

Bleeding can also happen in the corpus of the caudate nucleus, particularly in premature infants who are still immature, because the GM still covers this area before the 28th week of pregnancy.

It is not surprising that the GM has a large blood supply because, as previously mentioned, it is crucial to the formation and maturation of neuronal structures. The GM has the highest vascular density in premature infants, followed by the gray and white matter of the fetal brain, according to anatomical studies conducted on the brains of deceased premature infants by Ballabh et al (20).

As seen in Figure 2, derived from the internal carotid artery through the anterior choroidal artery, the anterior cerebral artery via the Heubner artery, the middle cerebral artery via the deep lateral striate branches, and penetrating branches from the surface meningeal branches provide the blood supply to the subependymal germinal matrix. In the GM, a capillary bed is nourished by this arterial supply. This arterial supply's terminal branches are vulnerable to ischemic injury because they most likely constitute a vascular end zone (9).

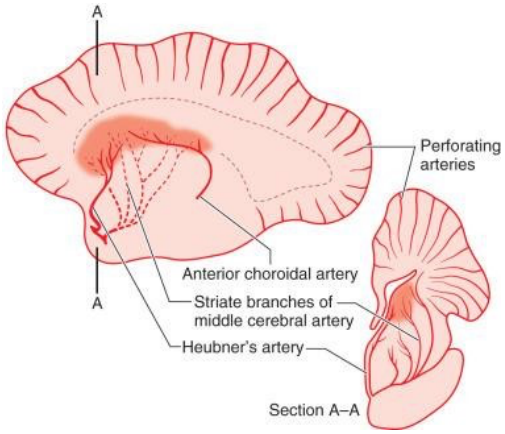

Figure 2. Arterial supply to the subependymal matrix at 29 weeks of gestation (9)

Numerous distinctive features of these germinal matrix vessels could be the cause of their brittleness and inclination to bleed. Some of these features include regulated vascular wall expression phenomena, such as discontinuous glial endfeet of the blood-brain barrier, exuberant angiogenesis, and features of immature basal lamina (9).

The venous drainage of the GM occurs via V. terminalis into V. cerebri interna. The great cerebral vein of Galen is where this venous drainage ultimately comes to an end (9). Venous blood is drawn from the cerebral white matter, choroid plexus, striatum, and thalamus via the medullary, choroidal, thalamostriate, and terminal veins in addition to the matrix area. The medullary, choroidal, and thalamostriate veins all essentially terminate in the terminal vein, which runs inside the germinal matrix. At the level of the caudate nucleus, the last three arteries mostly go anteriorly to a point of confluence where they form the terminal veins. These veins empty into the internal cerebral vein, which travels directly posteriorly to join the vein of Galen (9). The venous drainage is shown in Figure 3.

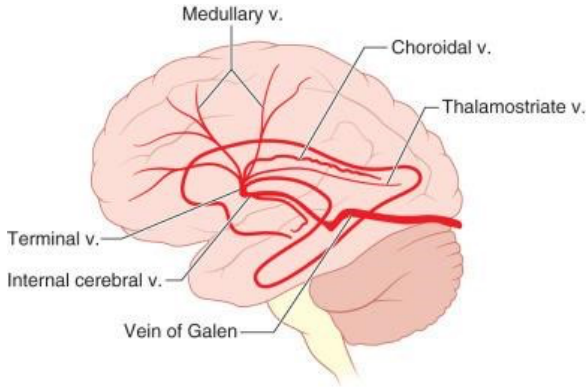

Figure 3. Veins of the Galenic system (9)

The GM begins to vascularize around week seven or eight of pregnancy and continues to do so until the start of the third trimester. The GM starts to get thinner after 24 weeks of pregnancy and nearly vanishes by 36–37 weeks. Between weeks 28 and 32 of pregnancy, the GM is most visible along the anterior caudothalamic groove. At 23 weeks of gestational age (GA), its width reaches 2.5 mm at 32 weeks, it decreases to 1.4 mm, and by 36 weeks, it is nearly completely involuted. The germinal matrix is an ideal site for bleeding because of these thin-walled vessels. Approximately half of infants with IVH have choroid plexus bleeding (9).

In around 80% of germinal matrix hemorrhage instances, blood that penetrates the lateral ventricles tends to disseminate throughout the ventricular system. This blood typically gathers in the posterior fossa's basilar cisterns after passing through the Magendie and Luschka foramina. Over days to weeks, a substantial accumulation may result in obliterative arachnoiditis, which would obstruct the flow of cerebrospinal fluid (CSF) (9). The subependymal germinal matrix's microvasculature is delicate. Around week 34–36 of postconceptional age, the natural maturation and involution of the germinal matrix begin to take place during the gestational period. After that, this embryonic structure disappears. Cellular maturation and angiogenesis slow down after this delicate time of vulnerability. Consequently, there is a higher chance of germinal matrix-associated IVH in preterm infants. Cell migration to cortical areas of the brain and cellular maturation may be impacted by damage to the germinal matrix. The structural integrity of the endothelial tissue surrounding the microvasculature is maintained by a subset of neural cells known as pericytes. Weakness and bleeding can be avoided when the endothelium is intact. When pericytes are absent, the brain tissue's integrity is diminished, which can result in ruptures and breakdowns. It has been noted that the density of pericytes in the germinal matrix is lower in preterm infants. A decrease in pericyte action could make vessels more prone to rupture (9).

3.2 Pathogenesis and risk factors

Vascular rupture in the area of the germinal matrix is caused by 3 main factors: (20)

1. High vascularization and vascular fragility of the GM due to
   a. relative hypoxia
   b. decreased TGF-ß, decreased amount of pericytes, fibronectin, and GFAP in astrocyte endfeet
2. impaired autoregulation of cerebral perfusion in preterm infants
3. postnatal blood pressure fluctuations

The pathophysiology of IVH primarily is ascribed to the fragility of the primitive GM vasculature and fluctuations in cerebral blood flow brought on by low mean arterial pressure (MAP), and impaired cerebral autoregulation, all of which raise the risk of vascular rupture and a hemorrhage that is either limited to the GM or spreads to the nearby lateral ventricle. Angiogenesis is induced by hypoxia in the GM, which also causes VEGF and angiopoietin-2 (ANGPT-2) to be expressed and upregulated. Fragile vessels with no pericytes, immature basal lamina low in fibronectin, and astrocyte end-feet coverage lacking in glial fibrillary acidic protein are the result of this. It is believed that hemorrhagic parenchymal infarction happens when periventricular white matter perfusion is compromised by venous occlusion from a hematoma (12).

The most crucial factors in the development of IVH are cerebral blood flow, arterial blood pressure, and arterial carbon dioxide partial pressure. Even upon blood pressure fluctuations, a constant cerebral blood flow (CBF) is guaranteed by intact cerebrovascular autoregulation in the mature brain. However, autoregulation systems in preterm infants are still immature and unable to compensate for these fluctuations, therefore ischemia or hyperperfusion may cause the delicate germinal matrix arteries to burst (21).

Intraventricular hemorrhages in very low birth weight and extremely low birth weight infants are multifactorial and caused by an interaction of prenatal, perinatal, and postnatal risk factors, all leading to the vulnerability of the germinal matrix.

According to a meta-analysis from 2014, in neonates weighing 1500g or less, 48% of all IVH events occurred during the first 0 to 6 hours of life (13). Therefore, recognizing the risk factors linked to early IVH is crucial (22).

IVH is associated with risk factors including low birth weight, low gestational age, unsatisfactory APGAR score, respiratory distress syndrome, neonatal intensive care unit (NICU) environment, as well as invasive procedures (23).

As described in 1.2, the GA and birth weight are linked to the occurrence of IVH.

The Neonatal Research Network of the National Institute of Child Health and Human Development (NICHD) discovered in 2016 that IVH appeared in 23.7% of the sonograms of very low gestational age (GA) and VLBW babies, with severe IVH making up 31.6% of these instances (24). Severe IVH can occur in up to 35-45% of newborns weighing less than 750g (6). Furthermore, there is an inverse relationship between birth weight and the risk of IVH on the first day of life. As demonstrated in Figure 4, there is a strong correlation between birth weight and occurrence as well as the severity of IVH.

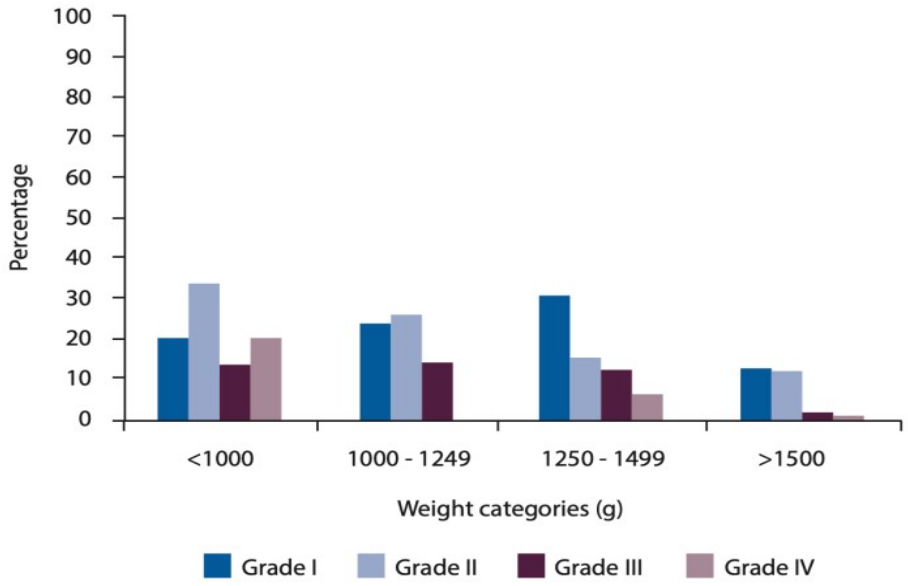

Figure 4. Prevalence of IVH related to the birth weight (25)

A more recent research from 2022 states that IVH affects 25% to 30% of all very low birth weight preterm newborns, with a reported incidence of up to 45% in these infants (15).

The APGAR score evaluates an infant's appearance, pulse, grimace response, activity, and respiratory effort immediately after birth, serving as a crucial standardized indicator of health at this vital time. A consistently low APGAR score measured at 1 and 5 minutes post-birth signals an increased risk for IVH (26).

The leading cause of childhood mortality is premature birth. One in ten live births, or roughly 13.4 million babies, in 2020 were born prematurely (27). Prematurity can significantly affect the function of multiple organ systems, particularly the lungs. Lung development begins in the first trimester, and full alveolar maturation typically occurs around the 35th week of gestation. As a result, respiratory challenges are mainly seen in premature infants, although term infants can also experience complications. Conditions such as respiratory distress syndrome and apnea can arise directly due to prematurity. Extremely preterm infants often require advanced life-saving interventions, such as resuscitation, endotracheal intubation, and mechanical ventilation due to compromised lung capacity. These infants usually need supplemental oxygen within the first 24 hours of life, delivered through either invasive or non-invasive methods to ensure adequate tissue oxygenation. Inadequate lung function can lead to hypoxic injuries in the developing brain, resulting in potential acid-base imbalances due to fluctuating systemic blood flow. Thus, maintaining proper respiratory function is vital in mitigating the risk of IVH, particularly as these infants often exhibit significant physiological instability that necessitates continuous medical support. Several studies have shown a direct correlation between intubation and IVH. Preterm infants require early intubation, often as they are severely sick and at higher risk of IVH (23). It is unclear if the intubation process itself or the associated critical state of the preterm infant contributes to the occurrence of IVH (23). Intubated infants often also undergo suctioning to maintain airway patency. In addition to disrupting cerebral blood flow, this procedure raises the risk of IVH and microvascular damage (28).

The germinal matrix, a highly vascularized and fragile region in preterm infants, is particularly susceptible to ischemic injury, increasing the risk of hemorrhage. In the initial ischemic phase, occurring within the first 12 hours, several hemodynamic factors contribute to decreased cardiac output and, consequently, reduced cerebral perfusion (9). Hemodynamic variability refers to changes in blood flow and perfusion levels associated with the cardiopulmonary system (12). One of the key factors is myocardial dysfunction and immaturity. The underdeveloped myocardium of preterm neonates has a limited ability to adapt to hemodynamic changes, leading to instability in cardiac output due to impaired preload and afterload regulation. Additionally, decreased intravascular volume and anemia further compromise oxygen delivery to the brain, exacerbating the risk of ischemic injury (9). Premature infants often present with anemia, characterized by low red blood cell counts, as well as thrombocytopenia, which involves reduced platelet counts stemming from coagulation issues. Insufficient red blood cell production directly affects tissue oxygenation, as these cells are essential for transporting oxygen throughout the body. To address anemia, these infants frequently receive blood transfusions. However, this can lead to hypervolemia, or excess blood volume, which may disrupt systemic blood flow and exacerbate hemodynamic instability (12).

Another major contributor is a persistent patent ductus arteriosus (PDA) with a left-to-right shunt, which diverts blood away from the systemic circulation, leading to systemic hypoperfusion and worsening cerebral ischemia (9).

40% of premature births are attributed to antenatal infections (29). Recent research indicates that intrauterine infections and inflammation lead not only to preterm delivery but are also associated with neonatal sepsis, PDA, and bronchopulmonary dysplasia. According to earlier studies, inflammatory factors may be important in the development of intraventricular hemorrhage by causing immune responses, rupturing brain barriers, and raising cerebral oxygen consumption. Additionally, the development of IVH may also be influenced by the effect of infections on the stability of blood pressure in the brain. Premature infants are especially at risk in this area because of their immature cerebral blood pressure autoregulation. Unusual blood pressure swings brought on by infections and sepsis can increase the risk of IVH and cause unstable cerebral blood pressure (5). Ventilatory instability, particularly fluctuations in CO_2 levels caused by mechanical ventilation and surfactant therapy, can also have a detrimental effect. Hypocapnia, a condition in which CO_2 levels drop too low, induces cerebral vasoconstriction, further reducing cerebral perfusion. As a result of these factors, cerebral venous drainage is impaired, and cerebral perfusion is significantly reduced (9). Following this initial ischemic phase, between 12 and 72 hours after birth, hemodynamic stabilization can lead to a secondary phase of reperfusion injury. During this period, cerebral venous congestion may occur, often exacerbated by increased intrathoracic pressure due to mechanical ventilation, which impairs venous return. Cardiac preload dysfunction further contributes to venous stasis within the brain. Additionally, as cerebral perfusion is restored, abrupt increases in systolic blood pressure and MAP can overwhelm the fragile vessels of the germinal matrix. Hypercapnia, characterized by elevated CO_2 levels, induces cerebral vasodilation, further amplifying the risk of vessel rupture (9). The diagnosis of hypotension can be made in 20-45% of premature infants, while hypertension is not so common (9). Variations in cerebral blood flow velocity have been linked to restlessness, patent ductus arteriosus, hypoglycemia, hypovolemia, hypotension, hypercarbia, hypoxia, and relatively high inspired oxygen concentrations. These variations cause cerebral vasodilation and raise the risk of IVH (7, 9). Multiple studies showed that vaginal delivery and emergency C-section are linked with preterm infants developing IVH. A cohort study of preterm infants weighing less than 1500g has shown that elective cesarean deliveries in preterm infants of less than 30 weeks GA have a decreased risk of developing IVH (31). In multiple studies, it was found that delivery via caesarian section is associated with a lower IVH grade in infants born at 24–27 weeks of gestation. While other studies found out that vaginal delivery is linked to an increased risk of IVH in infants born weighing less than 1500 g (24).

To summarize, the occurrence of IVH (grade I-IV) is shown to be lower when preterm babies are delivered via cesarean delivery, as depicted in Figure 5. But Nagy Z. (2024) stated that there is no significant difference in the occurrence of severe IVH. In preterm deliveries of less than 32 weeks of gestation and breech pregnancies, Cesarean delivery should be preferred (31).

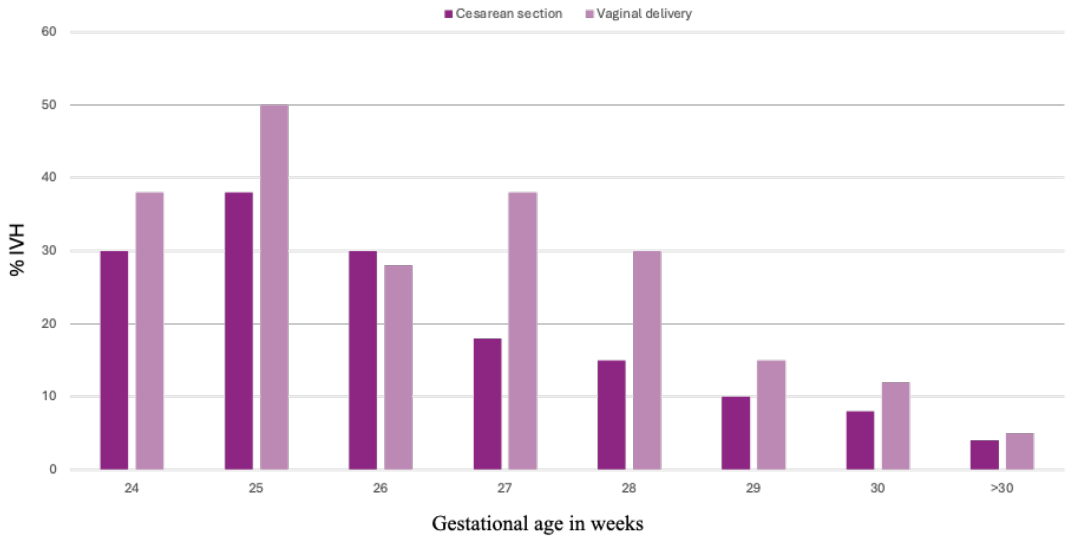

Figure 5. The percentage of intraventricular hemorrhage in infants correlates with gestational age and mode of delivery (30)

The hypothalamic-pituitary-adrenal axis, cerebral autoregulation, and the autonomic nervous system can all be affected by prolonged and repeated stressors, according to the neonatal stress embedding model. Variations in blood flow and oxygenation may result from this, which may lead to IVH and microvessel rupture (28).

Also, severe brain injury, adverse neurodevelopmental outcomes, and increased mortality rates were higher in outborn than inborn infants (9).

4. Diagnosis

4.1 Clinical manifestation

While infants with lower-grade intraventricular hemorrhage often exhibit no or only mild clinical symptoms, patients with severe hemorrhages experience a sudden deterioration in their overall condition. Volpe & Darras categorize the clinical manifestations of IVH into three distinct types (32).

The rare "Catastrophic Syndrome," which occurs in preterm infants with high-grade IVH, leads to seizures, coma, apnea, and fixed pupils within a very short period. The "Saltatory Syndrome" and "Clinically Silent Syndrome" are significantly more common. Affected infants may present with altered consciousness, hypotension, reduced spontaneous movements, and ocular abnormalities. A decrease in hematocrit may serve as a key indicator, though some infants remain entirely asymptomatic, known as "Clinically Silent Syndrome" (32). A healthy growth in head circumference is defined as an increase of 1 mm per day in the 26th to 32nd postnatal week and 0.7 mm per day in the 32nd to 40th postnatal week. Conversely, a sustained growth rate of 2 mm per day in head circumference may raise concern for abnormality. Furthermore, an increase of 4 mm within two days serves as a significant warning sign, aiding in treatment decisions, as detecting a subtle variation of just 2 mm can be challenging. Lastly, an increase of 14 mm within one week is classified as abnormal (7).

IVH symptoms are nonspecific and vary depending on the disease's severity. Pale skin, acute anemia, respiratory dysfunction, temperature instability, and fontanel bulge are some of the symptoms that can appear in severe and acute IVH cases.

4.2 Imaging techniques

Neuroimaging plays a significant role in the early diagnosis and monitoring of suspected cases of IVH. Nowadays, cranial ultrasound (CUS) or magnetic resonance imaging (MRI) is done during the first three days of life and is repeated two or three times to determine the severity of the condition (33).

In a study of 1105 premature babies, Panet et al. discovered that within the first five hours of life, 40% of the infants with IVH (roughly 25% of the entire group) had visible bleeding (7).

Additionally, it should be noted that in 20–40% of cases, an existing hemorrhage may continue to expand 3–5 days after diagnosis, which should be taken into consideration when determining a

reasonable time for screening. About 90% of hemorrhages can be seen at their worst by the end of the first week of life, regardless of the GA (9).

Brain MRI and cranial ultrasound are crucial in the early detection of IVH and neurological injuries. Between 25 and 50 percent of preterm infants with mild GMH-IVH in clinical settings are asymptomatic, although they can be identified through routine screening (6).

4.2.1 Cranial Ultrasound (CUS)

Since the late 1970s, the cornerstone in diagnosing IVH has been high-resolution cranial ultrasound, showing a sensitivity of 96% and specificity of 94% (12). CUS continues to be the most accessible and popular neuroimaging technique in NICUs worldwide (34).

Serial CUS can identify 80% of IVH when it is carried out during the first two weeks of life. In addition to detecting brain damage, CUS is widely accessible, reasonably priced, and noninvasive. Also, the portability of this imaging modality allows diagnostic approaches with minimal disturbances to the infant. CUS depicts GMHs larger than 5mm, with a sensitivity of nearly 100% and specificity of 91% (34).

The anterior, posterior, and mastoid fontanelles are used as acoustic windows in CUS to visualize the brain. All views must be used as they each offer important details that might not be visible in the other windows. The posterior fontanelle view allows for a more thorough assessment of the occipital lobes and periventricular white matter. Both left and right angulation in the sagittal plane and anterior and posterior views in the coronal plane should be used throughout the ultrasonography (34).

GM hemorrhages appear as a region with increased medial echogenicity to the head of the caudate nucleus and inferolateral to the floor of the frontal horns on CUS coronal images. Known as the caudothalamic groove, it is visible on the parasagittal view between the thalamus and the caudate head. The floor of the lateral ventricles is elevated in cases of large hemorrhage, resulting in effacement of the frontal horn or body. The ventricular system may be affected by a hemorrhage that starts in the GM. IVH can be classified according to US findings as described earlier in 1.4 and depicted in Table 1. Ultrasound findings are demonstrated in Figure 6.

Common findings of IVH grade I, when bleeding is restricted to the GM, is a subependymal hyperechoic globular thickening in the first few weeks. Grade II hemorrhages, which are defined as IVH without ventricular enlargement, are still categorized as having a slight degree of severity. In advanced stages of IVH the third and fourth ventricles may be filled with blood. Because of the clot forming, this will show up as homogeneously echogenic on imaging. However, as the bleeding

progresses, the retraction and lysis of the clot will cause it to appear more irregular. A rupture of the GM hemorrhage through the lateral ependymal wall causes these hemorrhages, which fill the ventricular system but do not dilate it by more than 50%. When the IVH causes ventricular enlargement, the hemorrhage is classified as Grade III, and its severity rises to moderate. Lastly, Grade IV hemorrhages, which are defined as IVH with parenchymal hemorrhage and are categorized as having a severe degree of severity, may be linked to venous infarction. These will appear vividly echogenic on imaging in the periventricular white matter located ipsilateral to the IVH (36).

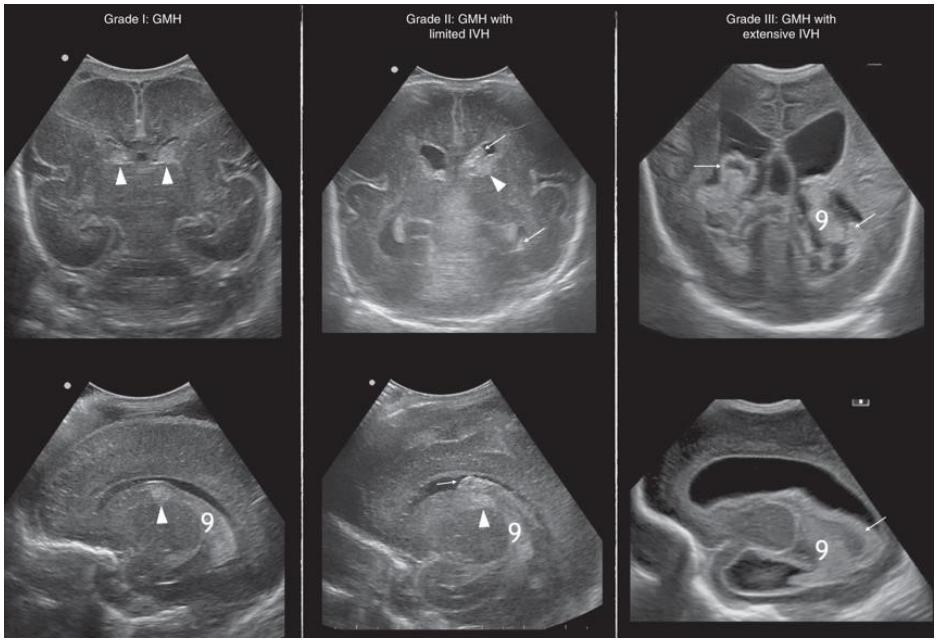

Figure 6. CUS grading of IVH (34)

arrowheads point to GMH, arrows to the presence of clot in the ventricle cavity; asterisk is choroid plexus

Unilateral GMH is strongly suggested by asymmetric hyperechoic thickening in coronal planes during the first postnatal days at the caudothalamic groove, which is the most frequently observed site for GMH. Of course, bilateral GMH is also possible. The cauda-thalamic region is where most GMHs develop, according to postmortem studies, though GMH has also been reported in the occipital and temporal horns, it should be closely monitored during cranial ultrasound (34).

After IVH, hyperechoic ependymal alterations start to show up two to four weeks later. By scanning via the mastoid fontanelle, clots of supratentorial origin can be located in the fourth ventricle. It is important to differentiate PHVD, which appears days or weeks later as a result of distal restriction

of CSF circulation and maybe later owing to poor resorption, from ventricular dilatation caused by a big clot (according to Papiles and Volpes classification - grade III) (34).

It's crucial to always consider how the clot's ultrasonographic features evolve over time to suspect an IVH as soon as possible. Hyperechogenicity, which results from the formation of fibrin at the end of the clotting cascade, is the main characteristic of the clot between 4 - 6 hours and 3 days after the bleeding. During the first, acute phase, fresh intraventricular hemorrhage may stay hypo- or isoechoic, and particulate CSF motion may occasionally be observed inside the ventricles (34). During the subacute phase, the clot shows hyperechoic margins after an initial retraction and a progressive hypoechoic change in the central region. Intraventricular fibrin strands encircle the clot. Intraventricular clot fragments can sometimes be detected even months later (chronic phase). The discovery of clot remnants on the 1st day of life indicates antenatal origin (34).

4.2.2 Other imaging modalities

Notwithstanding these benefits, using CUS has several drawbacks and difficulties. Although mastoid views can identify hemorrhages, they cannot identify cerebellar microhemorrhages, which require MRI visualization. Furthermore, certain white matter abnormalities, such as ventricular enlargement, hyperechoic and hypoechoic lesions, brain periphery, and posterior fossa, are not well demonstrated on CUS (34).

MRI is another modality that is commonly used to visualize the brain of preterm, as it provides more detailed imaging compared to CUS, but without radiation, in contrast to CT (17). Neuroimaging studies have shown that the magnetic resonance-susceptibility weighted imaging sequence, which is thought to be the most sensitive method for detecting subtle hemorrhage, has a higher diagnostic accuracy than CUS for minor forms of GMH-IVH (34). CT is no longer used as a standard modality in premature infants due to its high radiation risk (34).

4.3 Other diagnostic methods

Regular monitoring of the CBF level and observation of CBF changes brought on by pressure-passive cerebral circulation are necessary to prevent complications. Despite the existence of several non-invasive methods to determine the cerebral blood flow, such as transcranial Doppler ultrasound and near-infrared spectroscopy, neither of these approaches is frequently used routinely in clinical

settings. In the management of preterm infants, numerical assessment of CBF appears to be a promising strategy (21).

5. Outcome and Prognosis

5.1. Short-term outcomes

As depicted in Figure 5, mortality rates were 4%, 10%, 18%, and 40%, respectively, for grades I, II, III, and IV IVH during initial hospitalization (5).

5.1.2 PHVD and Hydrocephalus

Posthemorrhagic ventricular dilation (PHVD) refers to the progressive dilatation of the ventricles brought on by IVH and includes other terms like post-hemorrhagic hydrocephalus (35). PHVD usually can be seen one to two weeks after the occurrence of IVH (36).

The emergence of PHVD is the most dangerous complication of IVH. After severe GMH-IVH (grade III or IV GMH-IVH), there is an increased risk of PHVD of about 30-50%. It usually occurs after the cerebellum's liquor pathways are blocked. An imbalance between the production, circulation, and/or resorption of CSF results in post-hemorrhagic ventricular dilatation (38). A high risk of later poor motor and cognitive neurodevelopmental outcomes is linked to PHVD. The best way to treat PHVD remains a matter of debate among neonatologists, pediatric neurologists, and pediatric neurosurgeons despite decades of research (35).

About 25% of babies with GMH-IVH go on to develop progressive PHVD. Although very rare cases have been documented where it develops after term-equivalent age, it typically occurs a few days to a few weeks after the initial IVH. There are two types of PHVD, obstructive and communicating hydrocephalus (37).

The incidence of VLBW babies with IVH of grade II or higher developing PHH is demonstrated in Figure 7.

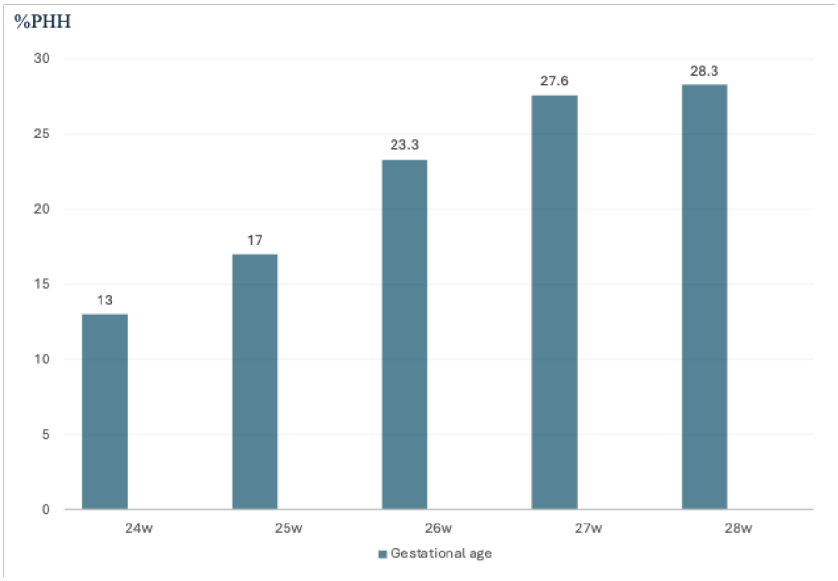

Figure 7. Percentage of VLBW infants of 24 to 28 weeks of gestation with IVH grade II or higher that developed PHH (38)

Depending on the location of the obstruction, the patient may experience complete internal hydrocephalus after obstruction of the fourth ventricle outlets (foramina of Luschka and Magendi), unilateral PHVD after unilateral obstruction at the foramen of Monro, supratentorial PHVD after aqueduct obstruction, or combined internal and external hydrocephalus (also known as communicating hydrocephalus) after impairment of CSF reabsorption in the peri tentorial arachnoid spaces (34).

Hydrocephalus is defined as a progressive ventricular dilatation brought on by a disruption in CSF dynamics that raises intracranial pressure. Posthemorrhagic hydrocephalus may occur within days (acute process) or weeks (subacute-chronic). Regretfully, it takes days or weeks after ventricular dilatation has already occurred for the classic clinical signs of developing hydrocephalus, including, for example rapid head growth, full/bulging anterior fontanelle, irritability, and separated cranial sutures, to manifest (9). Communicating posthemorrhagic hydrocephalus (PHH) accounts for most cases, with the obstruction to CSF outflow, which occurs outside the ventricular system (in comparison to noncommunicating), typically located distal to the fourth ventricle. It is believed that mechanisms like impaired CSF reabsorption, which occurs when microthrombi obliterate the arachnoid villi and cause inflammation and fibrosis, are the cause of communicating PHH. Another factor contributing to vulnerability is the apparent lack of fibrinolysis in premature infants (caused by extremely low plasminogen levels). It is hypothesized that subependymal scarring or an acute

blood clot blockage of the foramen of Monro causes noncommunicating hydrocephalus (12). US findings of communicating hydrocephalus are shown in Figure 8.

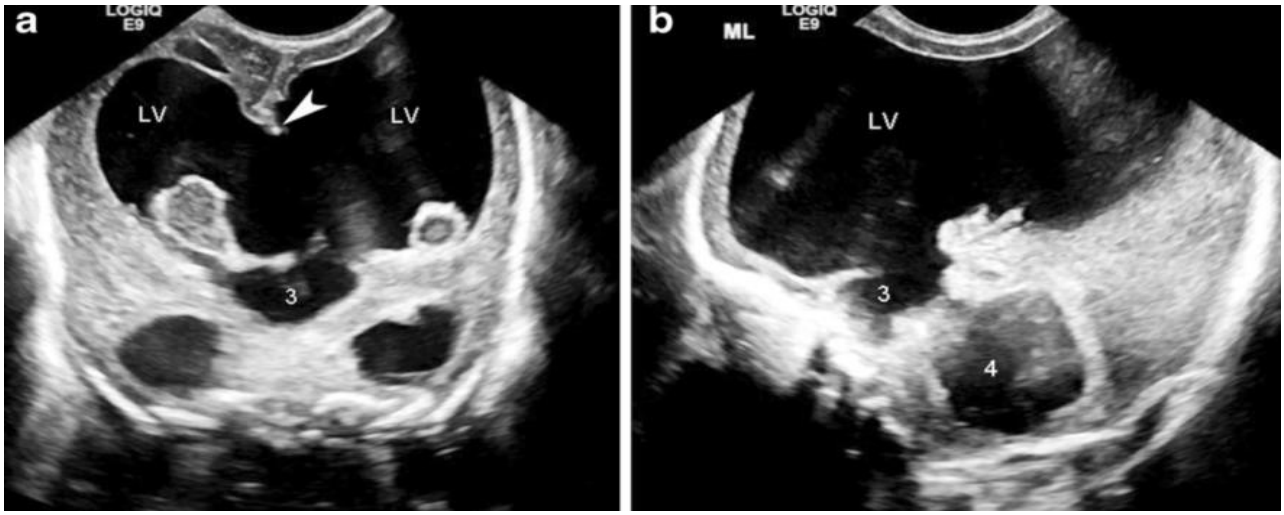

Figure 8. Communicating post-hemorrhagic hydrocephalus, 3rd ventricle -3, 4th ventricle – 4, left ventricle – LV (39)

a. Coronal plane US showing dilated temporal horns and the lateral ventricles being dilated and containing residual aging clot. Dilated frontal horns extending via the foramen of Monro into a dilated 3rd ventricle.

b. Sagittal plane US showing the dilated lateral, 3rd, and 4th ventricle.

Clinically, the daily head circumference measurement should be monitored, and the anterior fontanel examined. A hydrocephalus can be tracked by using the Evans ratio or measuring the ratio of the frontal and occipital horns (8).

Cranial ultrasound is used to monitor and decide which infants require a shunt. A ventricular shunt is necessary in about 25% of cases, but the majority of ventricular enlargement resolves on its own (40).

Temporizing neurosurgical procedures (TNPs) for CSF removal are a standard procedure to treat hydrocephalus. If this method fails, VP shunts will be placed, which are considered to be the most promising treatment. Complications may include shunt obstruction, shunt infections, and abdominal skin ulcers. By inserting a shunt under the skin, the excess fluid can be drained into the chest cavity or abdomen, and the body can absorb it. Shunts require monitoring and regular check-ups. After

shunt placement, cranial US monitoring should be continued to determine ventricular decompression (9).

Motor dysfunction, intellectual disability, behavioral issues, memory deficiencies, emotional problems, including depression and anxiety, attention deficit hyperactivity disorder, and impairments in vision are among the neurodevelopmental abnormalities that PHH may cause.

PHH may lead to a series of neurodevelopmental disorders: motor dysfunction, intellectual disability, behavioral problems, memory and executive deficits, emotional problems such as anxiety and depression, attention deficit hyperactivity disorder, and visual impairment (41).

Management of PHH and PHVD aims to prevent secondary damage caused by increased intracranial pressure (ICP) and to avoid the need for a permanent shunt, as a shunt may be associated with complications like blockage and infection (12). Even after decades of intensive research, PHVD treatment is still difficult. Several options were examined, including permanent ventriculoperitoneal shunting, surgically inserting an external drain, lumbar or ventricular tapping, cerebrospinal fluid (CSF) drainage and fibrinolytic treatment, and a subcutaneous reservoir (12).

5.2. Long-term outcomes

5.2.1 Periventricular hemorrhagic infarction

Periventricular hemorrhagic infarction (PVHI) is a major determinant for long-term outcomes in preterm newborns suffering from IVH. Each grade of GMH-IVH can be complicated by periventricular hemorrhagic infarction, also known as parenchymal hemorrhagic infarction, periventricular venous infarction, or intraparenchymal lesion. About 15% of GMH-IVH cases are complicated by PVHI, the likelihood increasing with GMH-IVH grade. Venous blockage brought on by GMH-IVH results in PVHI. Ischemia and secondary hemorrhagic infarction are caused by venous congestion. It appears to happen a few hours to a few days after the initial bleeding. A triangular, fan-shaped echo density in the periventricular white matter, ipsilateral to GMH-IVH, is the distinctive ultrasonographic feature. Infants with PVHI frequently experience severe cognitive impairment and cerebral palsy. The location and extent have a significant impact on the prognosis (34).

5.2.2 Neurodevelopmental Impairment

IVH is a major predictor of neurodevelopmental impairment, including cerebral palsy (CP), cognitive deficits, and motor disabilities. The gestational age and severity of IVH independently correlate with the extent of brain damage and subsequent impairment (42).

Neurodevelopmental impairment (NDI) can be defined as any of the following: severe visual impairment (visual acuity ≤ 20/200 (metric scale), cognitive delay (scores on standardized cognitive tests that were one standard deviation below the mean), severe hearing impairment (neither bilateral nor unilateral cochlear implants or hearing aids are required), or moderate to severe cerebral palsy (a score of ≥ 2 on the Gross Motor Functional Classification System) (6).

CP develops in approximately 10-20% of preterm newborns with IVH. With almost 60-100% of grade IV IVH developing CP, caused by white matter injury and disruption of motor pathways. Intraventricular hemorrhages associated with parenchymal injury are highly linked to CP (2).

According to the Surveillance of Cerebral Palsy in Europe, CP can be defined as a group of permanent disorders of movement, posture, and motor functions. CP is caused by a nonprogressive interference/abnormality in the developing and immature brain and can be classified into 3 groups: spastic, dyskinetic, and ataxic (43).

Several other neuropathological consequences of IVH may occur. Germinal matrix destruction, as GM hemorrhages lead to the destruction of the germinal matrix, which influences later brain development. During the third trimester, oligodendrocyte precursor cells migrate in the cerebral white matter, differentiate, and produce myelin. In preterm infants, this process is disrupted, which can impair myelination and lead to altered cerebral development. Cerebellar dysmaturation may occur, which can impact motor coordination and cognitive function.

About 75% of infants who died with the diagnosis of IVH had periventricular leukomalacia (PVL). PVL can be defined as a symmetrical, non-hemorrhagic, ischemic white matter injury of the premature infant (9). PVL is an abnormality occurring in the premature brain as a result of ischemic insult to the white matter tracts. In preterm infants born before 32 weeks of gestational age, deep penetrating arteries of the periventricular white matter have not yet developed. PVL is most observed in the white matter lateral to the frontal horns and next to the trigone of the lateral ventricles. Compared to the mature oligodendrocytes of the term brain, pre-oligodendrocytes, which make up the majority of the cerebral white matter of the immature brain, are more vulnerable to hypoxic injury. Visual, auditory, and motor impairments accompanied by spastic diplegia or quadriplegia are long-term consequences of PVL (39).

The severity and incidence of IVH in preterm or LBW newborns were strongly linked to adverse neurodevelopmental outcomes in later life (5). Even in cases of mild IVH, long-term cognitive and behavioral challenges are observed, and the risk of neuropsychiatric disorders is greatly increased when IVH occurs. Children with IVH have a 3 times higher probability of developing psychiatric disorders (2). As a result, adolescents with IVH who were born prematurely have higher rates of ADHD, poor social skills, anxiety disorders, and depression than adolescents without IVH. Although the exact causes of psychiatric disorders in infants with IVH are unknown, both white matter and cortical injury may be involved (42).

A retrospective cohort study showed that differences between preterm infants with mild IVH and those without in cognitive, motor, and academic outcomes at school age are not significant (44). According to reports, special education is not needed in about 35% of children with a history of IVH at preterm birth who did not suffer from an injury, whereas up to 76% of children with brain parenchymal injury, referring to grades III-IV IVH, ventriculomegaly or PVL, do (2). Compared to children born preterm but with no ventricular dilatation, children with posthemorrhagic ventricular dilatation had a significantly lower total IQ, particularly those who underwent surgical intervention like external ventricular drainage and ventriculoperitoneal shunt (45).

At two years corrected age, 35.6% of infants with low-grade IVH and 67.2% of infants with high-grade IVH had severe NDI or died. Increasing IVH grade, bilateral as opposed to unilateral, decreasing gestational age, and an increase in the number of other major morbidities were all associated with a lower survival rate without severe NDI. Impairments in expressive communication and gross motor skills were common (46). A cohort study found that survival with severe NDI at 2 years corrected age included severe delays, such as blindness, uncorrectable hearing impairment, or the inability to walk, sit, or use hands, as well as the inability to comprehend or use more than five words or signs. Vision, hearing, receptive and expressive communication, gross and fine motor function, and general developmental progress were secondary outcomes (40). At two to three years of corrected age, Bolisetty et al. found that even children with mild IVH had a higher incidence of neurosensory impairment, developmental delay, cerebral palsy, and deafness (47).

Two potential pathophysiological pathways could account for the anticipated harm caused by an IVH. First, glial precursor cells that migrate to cortical layers are locally destroyed as a result of IVH, which starts in the germinal matrix. A crucial role in postnatal myelination is played by these immature cells. Motor impairment could result from myelination disruption. This loss of cortical organization and growth may be the cause of the reduced grey matter volume observed in studies of premature infants at term after mild IVH. Second, the white matter may be negatively impacted by

the clinical characteristics of preterm birth that resulted in IVH, such as hypotension, poor cerebral perfusion, hypoxia, and acidosis (44).

The long-term consequences of IVH extend beyond the affected infant, impacting families through increased caregiving demands, financial burden, and emotional stress. Families of children with severe neurodevelopmental impairment often require long-term support and specialized care (2).

5.3 Prognosis

Table 2. The prognosis of IVH regarding the correlation with mortality rates and neurodevelopmental outcomes (5)

Grade	Mortality	Neurodevelopmental outcomes
I	4%	15%
II	10%	25%
III	18%	50%
IV	40%	75%

6. Management and Prevention

6.1 Acute management

The initial task is to maintain cerebral perfusion. Cerebral perfusion is related to arterial blood pressure and intracranial pressure therefore, arterial blood pressure must be maintained at adequate levels. This blood pressure control must be carried out carefully to avoid pressure-passive cerebral circulation. The ideal management of blood pressure in preterm infants remains an area of active investigation. The volume bolus followed by dopamine infusion is most commonly used as a treatment. To maintain cerebral perfusion, abrupt increases in cerebral blood flow should also be avoided. Including avoidance of increased arterial blood pressure, hypercarbia, hypoxemia, acidosis, hyperosmolar solutions, rapid volume expansion, and pneumothorax (8).

6.2 Prevention

In a study of infants who needed neurosurgical treatment for posthemorrhagic hydrocephalus, the average age at which IVH developed was two days, and by three days, ventriculomegaly was evident. Therefore, regular monitoring of significant IVH until it resolves or stabilizes will probably enable early detection of ventricular dilatation and the possible need for treatment (17). Serial assessment by US scan of ventricular size should be conducted. A minimum of twice a week is recommended to monitor the bleeding (8). Currently, the American Academy of Pediatrics recommends that all infants born at less than 30 weeks of gestational age undergo ultrasonographic IVH screening by 7-10 days of age. It is advised to repeat the screening before hospital discharge or after 4-6 weeks and by completing 36 weeks of gestational age. In case of abnormal cranial ultrasonography findings, serial and more frequent CUS should be performed. It is not recommended to perform a CT scan for IVH screening and a routine MRI before discharge (8).

Because IVH in preterm infants results from a multifactorial interplay of prenatal, perinatal, and postnatal influences, preventive strategies must target multiple aspects of care, including maternal health, delivery management, and neonatal hemodynamic stabilization.

IVH is associated with factors like those listed above, low gestational age, low APGAR score, low birth weight, respiratory distress syndrome, NICU environment, and invasive procedures. To reduce the incidence of IVH, listed risk factors and stress in the NICU should be minimized.

It has been found that prenatal glucocorticosteroids (GCs) are the most effective intervention to prevent IVH. The beneficial effect of GCs can be seen in stabilizing the germinal matrix´s microvasculature and reducing the CBF disturbances, by inhibiting angiogenesis in the germinal matrix microvasculature and stabilizing the GM blood-brain barrier. When a course of 2 doses of betamethasone or 4 doses of dexamethasone is given a week before delivery of the preterm newborn, good effects have been observed (20).

Intubation attempts should be minimized as much as possible, and intubation should be performed by experienced operators with the highest likelihood of success.

In several studies, the use of postnatal indomethacin starting within 6h after birth has shown a reduction in the incidence and severity of IVH. On the other hand, it is concerning as indomethacin is associated with complications such as acute kidney injury, intestinal perforation, and potential adverse effects on brain development. The beneficial effect of indomethacin was seen in male but not female patients (4).

The most crucial tactics for reducing the incidence of GM-IVH are those that focus on preventing preterm birth. Preterm birth can occur naturally or be caused by conditions like eclampsia. Evidence-based strategies, such as supplementation of antenatal progesterone starting from 16 to 24 weeks through 34 weeks of gestation in women with a current singleton pregnancy and a history of spontaneous delivery, and those with a short cervical length of ≤ 20 mm before 24 weeks of gestation, can postpone preterm birth unless medically indicated. Additional interventions have been used, including tocolytics for preterm labor, cervical cerclage for cervical incompetence, avoiding tobacco use during pregnancy, and specialized preterm birth prevention clinics (12).

In multiple studies, the role of delayed cord clamping and milk clamping played a role in the discussion of preventing the incidence of IVH, with mixed findings (4). The American College of Obstetricians and Gynecologists recommended a delay for at least 30 to 60 seconds in umbilical cord clamping in January 2017 (48).

In several studies conducted during the 1990s, magnesium sulfate was shown to have a promising effect on preterm fetal neuroprotection. In 2015, the WHO announced a strong recommendation for magnesium sulfate use to improve preterm birth outcomes (49). Magnesium sulfate increases the brain's antioxidant properties and protects it against apoptosis, hypoxia, and normalizes platelet aggregation (33). Various studies have found that the application of magnesium sulfate reduces the risk of brain injury in preterm infants, while in contrast, other studies don´t confirm the beneficial effect. Indeed, some studies have shown a harmful effect of Magnesium sulfate in preterm newborns (33).

Although some studies assert that there is not enough data to determine how head tilting and positioning affect preterm infants' cerebral hemodynamics and oxygenation, as well as the incidence of GMH-IVH (50). Others claim that head position during care may have an impact on cerebral hemodynamics and make infants born extremely preterm more susceptible to developing germinal matrix-intraventricular hemorrhage (GM-IVH). Turning the head toward one side may occlude jugular venous outflow while raising intracranial pressure and cerebral blood volume. It is suggested that cerebral venous pressure is reduced and hydrostatic brain drainage is improved if the infant is cared for in the supine 'head midline' position (51).

In addition to cerebral hemodynamics, tilting maneuvers may also affect blood pressure, heart rate, and mechanics of ventilation (52).

Another risk factor for the development of IVH is outborn deliveries, resulting in postpartum transfer to another hospital. Therefore, early transfer of mothers with an increased risk of premature birth to

a perinatal center with an adequate level of care makes postpartum transport unnecessary and reduces the risk of cerebral hemorrhage (9).

For infants suffering from IVH, a comprehensive rehabilitation plan is needed. At birth, it is important to detect the hemorrhage as early as possible and provide early interventions (2).

Tsao (2023) provided the following neonatal bundle of care for the prevention of IVH (53)

1. Maintaining a spine midline with a neutral head position
2. Avoiding a head-down position by tilting the incubator to 10-30 degrees
3. Minimal handling, including suction
4. Avoiding rapid flushes and blood withdrawal via intravenous or arterial routes
5. Avoiding routine endotracheal suction
6. Initiating further interventions for pain or stress reduction in the form of non-nutritive sucking and oral breast milk or sucrose

Notably, IVH should be monitored for in high-risk groups, such as premature low birth weight, very low birth wieght and extremely low birth weight infants, since prompt treatment and early detection can prevent negative consequences in later life. Additionally, since mild IVH has been linked to poor neurological outcomes, medical professionals can advise and inform family members about the risks and post-discharge precautions that should be taken (6).

Management strategies to prevent the occurrence of IVH should be based on risk factors, as summarized in Table 3.

Table 3. Strategies for prevention of GM-IVH in preterm neonates (12)

Prenatal	Perinatal	Postnatal
Prevent preterm birth Corticosteroids	Delivery at a tertiary hospital Prompt delivery upon recognition of fetal distress Delayed cord clamping	Avoid interhospital transport Elevated midline head positioning Minimize handling and stimulation Fluid therapy for hypotension Near-infrared spectroscopy monitoring of cerebral oxygenation Prevent and treat NEC and sepsis Erythropoiesis stimulation agents (e.g., erythropoietin and darbepoetin)

7. Follow-up

It is important to conduct outpatient follow-ups to detect morbidities and offer suitable guidance and treatment via comprehensive neurorehabilitation programs. In light of the heightened risk of PHH, it is important to keep track of head circumference on an ongoing basis. Children with neuropsychological deficits need special assistance in school concerning writing, reading, and mathematics (12).

8. Comparison: I-II vs. III-IV

Table 4. Summarizing the comparison between Garde I-II vs. III-IV IVH

Comparison	I - II	III - IV
Incidence	More common	Less common
GA	< 32 weeks	< 28 weeks
Severity	Mild, confined to GM / small ventricular involvement	Severe, with parenchymal dilatation and parenchymal injury
Hydrocephalus	Low risk	High risk
Neurodevelopmental outcomes	Normal / mild impairment	High risk of CP & cognitive deficitis
Mortality	Low	High

As presented in Table 4, there are major differences between mild and severe grades of IVH. The incidence of mild IVH grade I-II is more common than the incidence of severe grades (III-IV) of IVH. According to a recent cohort study from the American Journal of Obstetrics and Gynecology (2025), 20.02% of patients had IVH (any grade), with mild/moderate IVH accounting for 16.79% and severe IVH for 3.23% of cases (54).

Most immature preterm neonates have much higher rates of intraventricular hemorrhage (IVH), which is inversely connected with gestational age. As gestational age increases, IVH decreases in

both rate and severity. The most immature infants are also at the highest risk for the more severe types of IVH, with a 10-fold higher chance of developing IVH grade III-IV (9). As explained earlier in section 3. Pathogenesis and risk factors, the developing brain's structural and functional immaturity, are the main causes of this increased vulnerability. The risk of IVH decreases as gestational age rises because the cerebral vasculature matures and the germinal matrix progressively regresses. Because of the physiological and anatomical vulnerabilities associated with early brain development, the chance of IVH increases with the gestational age at birth.
Higher grades of IVH are also associated with increased incidences of morbidity and mortality, as demonstrated in Table 2.

Almost 25–30% of infants with grades III-IV develop post-hemorrhagic hydrocephalus, 25% of survivors have neurological-behavioral problems, and 0.5–2/3 develop intellectual, cerebral palsy, neurosensory, or cognitive deficits (55). Christian et al. (2016) reports that posthemorrhagic hydrocephalus (PHH) develops in 9% of preterm neonates with IVH. 1%, 4%, 25%, and 28% of patients with grades I–IV, respectively (56). The risk of posthemorrhagic hydrocephalus increases with the grade of intraventricular hemorrhage.

Most survivors with IVH grade III will develop progressive ventricular dilation (25). Eighty percent of cases of progressive PHVD occur after IVH III, frequently in conjunction with a PHI (34).

The grade of IVH has a direct correlation with the incidence of CP. The frequency of cerebral palsy in grades III-IV is above 50%, and special education is needed in 75%. While cerebral palsy affects 60-100% of infants with grade IV IVH (7).

Of all the outcomes evaluated, children with severe IVH were more likely than those with mild IVH to experience negative neurodevelopmental outcomes. In contrast to children without IVH, mild IVH was linked to a higher risk of NDI, motor/cognitive delay, hearing impairment, visual impairment, and cerebral palsy (6).
Hong (2022) states that in infants with 5–7 months of corrected age, mild IVH (grade I or II) is linked to adverse effects on cortical vision development and function, according to visually evoked potential. Among infants with severe IVH (grade III or IV), visual-motor coordination dysfunction was more common (2).

When comparing extremely preterm infants with mild IVH to infants without IVH, there is no difference in their neurodevelopmental outcomes at five and eight years on formal developmental testing (44).

The infants with grade I-II IVH have a survival rate of 80%, while in infants with grade III-IV, more than 40-45% survive (42). Severe IVH (Grade III-IV) is strongly associated with increased mortality in preterm infants.

9. Discussion

The comparatively high and consistent prevalence of prematurity, combined with rising survival rates of premature infants, contributes to the ongoing clinical challenge of IVH in neonatal care.

While mortality declined over the previous ten years, IVH rates among ELBW newborns rose sharply. VLBW babies with IVH have shown significant improvements in several neurodevelopmental outcomes and decreases in early morbidities (57). The survival rate of preterm infants has increased due to improvements in clinical management, however, more survivors are at a higher risk of developing IVH, which can cause brain damage and long-term neurological effects (6).

There are many unanswered questions regarding the treatment of posthemorrhagic hydrocephalus. Although there are no recognized methods to prevent a hemorrhage, and it is also not certain what the best treatment procedures are after a hemorrhage has occurred, several strategies based on pathophysiological understanding can guide early care. Based on the knowledge of the pathophysiology of the development of IVH, the following recommendations for therapy and care in the first days of life can be made: “normal” oxygenation and ventilation should be sought as soon as possible postpartum. In addition, normal perfusion of the brain should be achieved and, as far as possible, acidosis should be prevented. If acidosis requires buffering, it should be kept in mind that rapid administration of sodium bicarbonate is associated with an increased risk of bleeding. The aim should therefore be to administer sodium bicarbonate slowly. Synchronized ventilation, rapid closure of a hemodynamically relevant ductus arteriosus, and stable arterial blood flow, as well as PaO2 and PCO2 in the normal range, are considered important preventive measures, as are limiting tracheal suctioning and disruptive medical and nursing measures to a necessary minimum. Careful care (minimal handling) and reduced stimulation of the premature infant lowers the incidence of intraventricular hemorrhage. It should be mentioned that none of these steps might be enough to prevent and eradicate IVH (18).

Currently, not all IVH prevention strategies are well-developed or consistently implemented. Nonetheless, the decrease in early IVH is a positive outcome. This may indicate a more regular application of practices that have demonstrated promising outcomes. Despite this progress, the risk

and vulnerability to IVH persist throughout the early stages of life and may still emerge due to pain, respiratory and circulatory disturbances, or other environmental stressors that remain inadequately managed. Increased cranial ultrasonography in the first few days of life can aid in the accurate and timely diagnosis of IVH. According to World Health Organization guidelines regarding the timing and quantity of ultrasound, screening has led to better outcomes. However, this contradicts the recommendation for minimal handling of infants. Future advancements in neuro-intensive monitoring techniques, including electroencephalography, near-infrared spectroscopy, and the ongoing development of ultrasonographic technology, or a combination of these methods, may enable more precise and timely IVH detection.

According to Nagy Z. (2024), using measures from a care bundle during different time windows (antepartum, intrapartum, and postpartum) has the greatest potential to reduce IVH due to its multifunctionality. Knowing when IVH occurs is crucial to evaluating the effectiveness of these interventions. The majority of IVH happens in the first 3 days of life, however, the exact onset is typically unknown in individual cases. According to a 2014 meta-analysis, in neonates weighing 1500g or less, 48% occurred in the first 0-6 hours of life, and 38% of IVH events happened after 24 hours of life (13).

In general, the enhancement of healthcare provider adherence to an evidence-based IVH prevention bundle correlated with a decrease in the severe IVH rate from 9.8% to 2.4%, resulting in a 76% reduction of severe IVH incidence among infants with a birth weight of ≤1250 g or gestational age of ≤30 weeks. To maximize their effectiveness in preventing adverse health outcomes, it is essential to evaluate and promote adherence to evidence-based guidelines and prevention bundles (58).

Fascinatingly, perinatal and, more importantly, environmental factors may have the biggest impact on future neurodevelopmental delays. These factors include the education and occupation of the mother, whether the parents are caring for the children, exposure to stress during the neonatal intensive care unit stay, and malnutrition.

Given its multifactorial origin, reducing the burden of IVH will require continued interdisciplinary efforts, including at the bedside of newborns, through broader public health and social interventions.

10. Conclusion

Intraventricular hemorrhage is one subtype of intracranial injury and a serious neurological complication in the neonatal intensive care unit. It is the most common form of central nervous system disorder associated with preterm birth and is most likely secondary to prematurity (1).

The combination of ischemic injury, venous congestion, and reperfusion-induced vascular fragility ultimately results in the rupture of the germinal matrix vasculature, leading to intraventricular hemorrhage.

Given the high risk within the first 72 hours of life, early detection and intervention are crucial. Intraventricular hemorrhage symptoms are nonspecific and vary depending on the disease's severity. Pale skin, anemia, respiratory dysfunction, and fontanel bulge are some of the symptoms that can appear in severe and acute cases (33) .

This literature review evaluated 58 recent studies and revealed consistent associations between intraventricular hemorrhage and the most significant risk factors, such as low gestational age, very low and extremely low birth weight, mechanical ventilation, and hemodynamic instability, highlighting the importance of close monitoring and targeted interventions in preterm infants.

Since cranial ultrasound is a marker for long-term neurodevelopment and an early diagnostic tool to reduce adverse outcomes, it is currently the most common modality utilized for imaging premature infants (37). The main advantages of cranial ultrasound are its portability, dependability, affordability, noninvasiveness, lack of radiation, and lack of preparation (34).

The outcomes of intraventricular hemorrhage in preterm infants are diverse and significantly influenced by the severity of the hemorrhage. Children who have more severe intraventricular hemorrhage are at a higher risk of experiencing negative consequences (6). This literature review has shown that, despite technological and clinical advances in neonatal care, intraventricular hemorrhage remains a major determinant of long-term neurodevelopmental and health outcomes.

Although the incidence of intraventricular hemorrhage has decreased due to advancements in neonatal care, more research is required to create more potent treatments.

One of the most significant findings across this literature review is the significance and effectiveness of standardized care bundles, implementation of evidence-based guidelines, and education in reducing intraventricular hemorrhage incidence.

Further research is needed to enhance early prevention, intervention, and management strategies to improve the prognosis for affected infants. Lifelong management is necessary, from early detection and intervention to long-term care (2). A guideline-driven approach supported by multidisciplinary education should be implemented.

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