Ultrasound measurements of the lateral ventricles in neonates: why, how and when? A systematic review

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ABSTRACT
Germinal matrix-intraventricular haemorrhage and subsequent post-haemorrhagic ventricular dilatation (PHVD) are frequently encountered complications in preterm neonates. As progressive dilatation of the lateral ventricles may be associated with elevated intracranial pressure, ultrasound measurements of ventricular size play a major role in the evaluation of neonates at risk of ventricular dilatation as well as in assessing the effect of intervention for PHVD. A systematic search was carried out in Medline and Embase to identify neonatal and foetal ultrasound studies on lateral ventricular size. This review presents an overview of the available data concerning neonatal reference values for lateral ventricular size, the influence of gender, ventricular asymmetry and the effect of the mode of delivery on the phenomenon of ventricular reopening following birth.

Conclusion: Serial cranial ultrasound measurements of the lateral ventricles play a key role in the early recognition and therapeutic evaluation of post-haemorrhagic ventricular dilation and can be of prognostic value in neonates with ventricular dilatation.

INTRODUCTION
Germinal matrix-intraventricular haemorrhage (GMH-IVH) is a frequently encountered complication in the preterm neonate. The incidence of GMH-IVH is inversely related to gestational age (GA) (1) and despite a gradual decline during the last decades, still 20–25% among very low birth weight (VLBW) infants (2,3). For term neonates incidence rates around 1% have been reported, the haemorrhage being mainly restricted to the germinal matrix (4).

Especially after a severe haemorrhage [GMH-IVH grade IIb/III according to Levene et al.(5) and de Vries et al.(6) or grade III/IV according to Papile et al.(7)] the risk of developing post-haemorrhagic ventricular dilatation (PHVD) is considerable. PHVD – defined as ventricular enlargement above the 97th centile for GA (8) – is recognized in about one-third of infants with GMH-IVH (9).

Progressive ventricular dilatation can be associated with elevated intracranial pressure (ICP) (10). Raised ICP may lead to alterations in cerebral hemodynamics and tissue damage (3), and was found to correlate with delayed myelination and neurodevelopment in infantile hydrocephalus (11). Intervention with drainage of cerebrospinal fluid (CSF) improves cerebral perfusion and oxygenation in neonates with PHVD (12,13) and may thus prevent further damage to the brain tissue. This underlines the need for sequential cranial ultrasonography following a diagnosis of GMH-IVH to timely diagnose subsequent PHVD. In this review, an outline will be given of the role of sonographic evaluation of cerebral ventricular size in neonates at risk for PHVD.

METHODS
A systematic literature search was performed in Medline and Embase in December 2009 to identify foetal and neonatal ultrasound studies on lateral ventricular size (detailed search strategy available upon request). The papers with abstracts meeting the predefined in- and exclusion criteria were evaluated for potential inclusion in the review. The references of these studies were screened for additional relevant studies. Foetal and neonatal series were included if frontal and/or occipital horn dimensions had been investigated. Studies on intra- and interobserver variability, ventricular asymmetry, the influence of gender or the effect of

Abbreviations
CSF, cerebrospinal fluid; cUS, cranial ultrasound; ELBW, extremely low birth weight; GA, gestational age; GMH-IVH, germinal matrix-intraventricular haemorrhage; ICP, intracranial pressure; PHVD, post-haemorrhagic ventricular dilatation; VLBW, very low birth weight; VP, ventriculoperitoneal.
Ventricular parameters: AHW, anterior horn width; FHR, frontal horn ratio; HW, hemispheric width; TOD, thalamo-occipital distance; VA, ventricular axis; VH, ventricular height; VI, ventricular index.
the mode of delivery on ventricular size were included as well. Applied language restrictions were English.

THE IMPORTANCE OF EVALUATION OF VENTRICULAR SIZE IN NEONATES AT RISK OF PHVD

Role of cUS in diagnosis and evaluation of PHVD

To diagnose and evaluate PHVD, measurements of ventricular size on cranial ultrasound (cUS) are superior to any subjective assessments of elevated ICP, like a tense fontanel, sunset phenomena of the eyes or measurements of the head circumference (8,14–17).

In clinical practice, the ventricular index (VI) of the lateral ventricles as measured on cUS (Fig. 1A) is most frequently used for monitoring ventricular size following GMH-IVH. In some studies (18–20), measurements of the VI are expressed as a ratio to the hemispheric width (HW). The use of a ratio is however considered to be less useful for detecting ventricular dilatation according to some articles (8,21). Absolute measurements of the VI are therefore used in our centre.

Although a rise in ICP may be accompanied by an increase in VI (10), often the VI only starts to enlarge in more severe hydrocephalus and consequently may fail to identify neonates with mild dilatation (22,23). The first sign of an increase in ICP is more frequently a change in ventricular shape with rounding of the frontal horns and an increase in anterior horn width (AHW, Fig. 1A) (15,22) – a phenomenon referred to as ‘ballooning’ (24) (Fig. 2). Hence, the AHW has been suggested to be a more sensitive marker for early or mild ventricular enlargement than the VI (22,23).

The depth of the occipital horn of the lateral ventricle [thalamo-occipital distance (TOD), Fig. 1B] has also been recommended as a valuable addition for the evaluation of ventricular size following GMH-IVH. Occipital horn enlargement is often visible before any increase in frontal horn dimensions (19,25–30). The occipital horns are usually dilated to a greater extent than the frontal horns and may represent the only site of ventricular dilatation (19,25–27,30). Isolated occipital horn dilatation is mainly recognized in extremely low birth weight (ELBW) infants with, but also without GMH-IVH. Whether it needs intervention, even if the VI and AHW are normal, or whether it is justified to wait, still has to be evaluated.

The occipital horns, as well as the atria, also appear to dilate prior to other parts of the lateral ventricles in early congenital hydrocephalus (31,32). The underlying mechanism of this phenomenon has not been identified so far. Sauerbrei et al. (22) observed that in neonates with GMH-IVH, small intraventricular collections of blood tended to accumulate in the occipital horns while large collections of blood were distributed uniformly throughout the ventricles. Whether this finding plays a role, remains speculative.

Visualizing the occipital horn may however be challenging however and more prone to measurement errors (28,30,33). Nevertheless, non-visualization of the occipital horn...
Ventricular size and timing of treatment

About 35% of the neonates who develop PHVD require some form of intervention (9). The decision whether to initiate treatment or not tends to be based on measurements of ventricular size.

Cerebrospinal fluid drainage has a central role in the treatment of PHVD. It can be achieved by repeat lumbar punctures, ventricular taps or the placement of a subcutaneous reservoir, subgaleal shunt or ventriculoperitoneal (VP) shunt. Optimal timing for CSF drainage in infants with PHVD is still a matter of debate (35). It has been described that when the VI in neonates with progressive ventricular enlargement exceeds 4 mm above the 97th centile for GA (8), PHVD carries a poor prognosis with about 40–60% of the children being shunt dependent, and over 60% of the infants being deceased or either disabled or impaired at the age of 1 year (37–39). Whether early intervention decreases the need for shunting and improves long-term neurodevelopmental outcome is still uncertain (9,38–40). In a retrospective study in five Dutch neonatal intensive care units, low threshold intervention – initiated when the VI crossed the p97 line – was associated with a significant reduced risk of VP-shunting and a lower number of infants with a moderate or severe handicap compared with high threshold intervention – started after crossing the p97 + 4 mm line (9). A randomized multicentre intervention study (Early versus Late Ventricular Intervention Study, ELVIS) is carried out at the moment to explore whether there is a beneficial role for low compared with high-threshold intervention in neonates with PHVD with regard to both the risk of VP-shunting and neurodevelopmental outcome.

When treatment for PHVD is initiated, serial cUS measurements of the lateral ventricles still play an important role. Monitoring ventricular size enables us to assess the effect of the intervention and the need for other therapeutic options.

Relevance of ventricular dilatation for long-term outcome

Evaluation of ventricular size is also of prognostic value. In addition to concomitant mortality and shunt dependency, PHVD is often associated with impaired neurodevelopmental outcome in preterm neonates (9,37–40). Several studies have demonstrated that ventricular dilatation is predictive of cognitive impairment (41,42) as well as cerebral palsy (41,43) in (V)LBW infants. Often though, it is hard to distinguish the mechanisms underlying the origin of ventriculomegaly – either post-haemorrhagic resulting from increased ICP or atrophic resulting from white matter loss (or a combination) – what makes it difficult to judge the impact of mild or moderate PHVD. The extent of parenchymal involvement and associated white matter injury may be the main predictor for neurodevelopmental outcome in infants with PHVD, especially with regard to motor outcome (6,40,44).

Importance of accurate reference ranges

With a better understanding of normal and abnormal size of the neonatal lateral ventricles, it may be possible to improve both the diagnostic and therapeutic evaluation of neonates with GMH-IVH/PHVD. Infants with ventriculomegaly at high risk of neurodevelopmental impairment may be identified with greater accuracy.

An overview on neonatal reference ranges for the lateral ventricles, including several variables influencing those values, will be provided in the following sections.

(AB) NORMAL VENTRICULAR SIZE ON CUS: NEONATAL REFERENCE VALUES

Six studies (8,15,20,21,30,34) which met the selection criteria, reported cross-sectional reference ranges for lateral ventricular size on cUS in neonates (Table 1). Data are available for both term and preterm infants, although reference values for ELBW infants are scarce and based on small numbers in most studies.

Considerable variation exists between the studies with respect to sample size, patient characteristics, timing of the first cUS and measured parameters. In the study of Levene (8) ultrasound measurements of the VI were performed through the temporoparietal bone, which correlated well with measurements through the anterior fontanel according to the author.

Most commonly measured parameters

Several dimensions of the lateral ventricles have been investigated. Levene (8) was the first to publish a reference curve for the VI – the distance between the falx and the lateral wall of the anterior horn in the coronal plane at the level of the third ventricle (Fig. 1A). The VI has also been expressed as a ratio to the width of the corresponding hemisphere, referred to as the frontal horn ratio (FHR, Fig. 1A) (20). Because ratios are considered to be less useful for monitoring ventricular size (8,21), as outlined before, the FHR is left out of consideration. Another parameter that can be measured in the coronal plane is the maximal diagonal width of the third ventricle in a neonate with an easily accessible fontanel is an important negative finding (28).

The clinical value of measurements of the third and fourth ventricle is unclear. When combined with the dimensions of the lateral ventricles, assessment of the size of the third and fourth ventricular size may help in differentiating between communicating and non-communicating hydrocephalus (34). Enlarged third and fourth ventricular size may also contribute to distinguishing PHVD from ex-vacuo dilatation, which has important therapeutic implications (35). The observation of isolated dilatation of the third and/or fourth ventricle can be associated with posterior fossa haemorrhage and may provide the clue to the proper diagnosis. Dimensions of both ventricles are, however, not easy to determine on cUS and reference values are scarce (20,34). The third ventricle is usually not visible in the coronal plane and must be dilated to perform measurements (36), while the fourth ventricle has a quite complex shape resulting in a higher interobserver variability (34). Therefore evaluation of third- and fourth ventricular size is not included in this review.
Ventricular Index. In addition to Levene (8), Liao et al. (15) also published a nomogram for the VI in newborns (Fig. 3A). Both demonstrated that the upper limit for the VI depends on GA. The reference values of these studies correlate well for term neonates, while those for preterm newborns show more variation. This may be attributable to the fact that the lower the post-menstrual age the fewer infants were included, making the results more prone to variation. For premature newborns below 26 weeks of gestation, who are most at risk of developing GMH-IVH and subsequent PHVD, only the study of Liao et al. (15) is applicable. Therefore more data are needed for ELBW infants.

Anterior Horn Width. Whether normal values for the width of the anterior horn correlate with GA is controversial. While several authors (15,21,34) reported no or just minimal change in AHW with GA, an evident increase in AHW was demonstrated with ongoing maturity by Sondhi et al. (20) (Fig. 3B). Remarkable is the small standard deviation in the last study in comparison with previously published data. Whether this can be completely explained by the large sample size and the fact that all neonates were examined on the third day post-partum in Sondhi’s study (20), remains uncertain.

In the majority of neonates, the AHW is less than 3 mm (15,20,21,34). The clinical significance of an AHW above 3 mm in the absence of GMH-IVH is not clear. An AHW exceeding 6 mm, however, is associated with ventricular ballooning and suggest the need for treatment according to Govaert et al. (24).

Thalamo-Occipital Distance. No explicit conclusions can be drawn from data on occipital horn size. Controversy also exists whether normal values of occipital horn size depend on GA. Furthermore, the variation in reported reference curves is considerable (Fig. 3C). Reeder et al. (30) compared occipital horn measurements in normal premature infants and in premature neonates with intracranial haemorrhage or neural tube defects and concluded that, regardless of the degree of prematurity, an occipital horn length exceeding 16 mm suggests intracranial pathology in preterms. Davies et al. (34) reported much higher reference values for the TOD in preterm neonates, with an upper limit of 24.7 mm. Neonates with a GMH-IVH grade I/II were, however, not excluded in the latter study, which may have resulted in higher values. A smaller occipital horn size was measured in premature newborns by Sondhi et al. (20) Again the small range in this study is remarkable.

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and does not agree with the other studies (30,34) and our own experience.

Reliability of ventricular measurements
To develop reliable reference ranges for clinical practice, ventricular measurements need to be reproducible for subsequent measurements with good interobserver agreement. The few studies (8,20,34) which reported data on intra- and interobserver variability for several ventricular parameters are reassuring. For all above mentioned ventricular dimensions (VI, AHW and TOD) good intra- (8,34) and interobserver (8,20,34) correlation could be achieved.

Figure 3 Overview of the reference curves for the (A) ventricular index, (B) anterior horn width and (C) thalamo-occipital distance according to Davies et al. (34) (regression line with 95% confidence interval), Levene (8) (p3, p50, p97), Liao et al. (15) (mean ± 2 SD), Perry et al. (21) (p97), Reeder et al. (30) (mean ± 2 SD) and Sondhi et al. (20) (p5, p50, p95). Adapted from Davies et al. (34), Levene (8), Liao et al. (15) and Sondhi et al. (20).
With respect to assessment of occipital horn size, it has been our experience that reproducible measurements of the TOD are harder to obtain in some neonates because of difficulties in visualizing the occipital horn and obliquity of the transducer.

Subjective assessment of ventricular size is less reproducible, especially in case of ventricular enlargement (45,46).

The use of cross-sectional data for follow up

Compared with term-born infants, preterm infants tend to have increased volumes of lateral ventricles and CSF on MRI at term-equivalent age (47–49). This phenomenon has been demonstrated during infancy (50,51) and adolescence (52) as well and may be due to cerebral atrophy. Hence it is questionable whether cross-sectional reference ranges for ventricular size can be used for the follow up of premature neonates, especially in neonates with PHVD. Longitudinal data on neonatal ventricular size are nevertheless scarce and only available for the VI and AHW. While an increase in VI was demonstrated in both preterm and term infants postnatally (8,15), the AHW remained stable in preterm infants during the first 6 weeks of life (15).

VENTRICULAR SIZE: DOES GENDER MATTER?

In foetuses ventricular size seems to be correlated to gender. Normal male foetuses appear to have slightly larger atria than female foetuses throughout the second and third trimester (53–56). Although statistically significant, reported mean differences are small, ranging from 0.1 to 0.6 mm.

 Less is known about the relationship between gender and ventricular size in neonates. A good correlation has been observed between male and female newborns for the FHR (20), AHW (20,34) and TOD (20).

Volumetric MRI-measurements demonstrated larger mean ventricular volumes in boys during the first 6 years of life (57). The difference disappeared however when corrected for intracranial volume. No difference in ventricular volume between both sexes could be demonstrated with further growth (51,57,58).

According to these data gender seems to play only a minor role in determining neonatal ventricular size. Male neonates may have slightly larger ventricles than female neonates, but if present, the difference does not seem to be clinically significant.

ASYMMETRY OF THE LATERAL VENTRICLES

The phenomenon of lateral ventricular asymmetry on cUS was first described in the 1980s (59). Since then it was demonstrated by others as well (30,33,34,60; 61–64 in Supporting Information). Reported prevalence rates range from 12 to 77% and this wide range was partly explained by the definition which was used.

When asymmetry is present, the left ventricle is usually larger than the right ventricle (33,34,60; 61–63 in Supporting Information). The same trend has been noted in the foetus (65 in Supporting Information). Volumetric cUS- and MRI measurements in neonates (66–70 in Supporting Information) as well as children and adolescents (58) also showed that left ventricular volumes tend to be larger than right ventricular volumes. Asymmetry tends to be more pronounced in the occipital horns than in the anterior part of the lateral ventricle (33; 62,64 in Supporting Information) and side to side differences exceeding 5 mm have been described (34). The frontal horns may show some asymmetry, but reported differences in left- and right frontal horn dimensions are small and unlikely to be of clinical relevance (20,34).

The clinical significance of ventricular asymmetry is not clear. Observations in some studies (30,33; 61 in Supporting Information) suggest that there might be a relationship with intracranial pathology. A higher percentage of GMH-IVH was found in neonates with asymmetrical ventricles raising the possibility that intracranial haemorrhage (in utero) may lead to ventricular asymmetry in some infants (33; 61 in Supporting Information). However, the GMH-IVH was more commonly seen on the side of the smaller ventricle (61 in Supporting Information) and the majority of neonates with asymmetry did not have any evidence of a haemorrhage (33; 61 in Supporting Information). Other investigators also demonstrated that asymmetry is not necessarily a pathological entity, because of GMH-IVH or impaired liquor drainage, but exists in the normal population and may represent normal physiological variation (63,64 in Supporting Information). This is consistent with observations in utero where asymmetry of the lateral ventricles also was observed, although less frequently, and was considered to be a normal variant after excluding underlying pathology (65 in Supporting Information).

Ventricular asymmetry may be influenced by genetic factors or environmental events that occur during brain growth (71 in Supporting Information). It has also been reported that in case of asymmetry, the enlarged ventricle is often associated with a larger ipsilateral choroid plexus (62 in Supporting Information). No relationship was found between ventricular asymmetry and gender, mode of delivery or the infants age at the time of the ultrasound (61,64 in Supporting Information).

There appears to be an effect of head position at the time of scanning on ventricular asymmetry. In preterm neonates as well as in term newborns with brain damage, the depth of the anterior horn clearly changed with head position within 3 h after turning the head. While the upper frontal horn increased in size, the depth of lower frontal horn decreased. (71 in Supporting Information) Area (63 in Supporting Information) and volume measurements (70 in Supporting Information) in preterm and term infants also showed that head position plays a role. Its influence seems to depend on the time interval between changing the position of the head, for turning the head did not significantly alter ventricular asymmetry within 1 h (61 in Supporting Information). The influence of head position on ventricular size appears to diminish with increasing GA, which contributes to the idea
that maturation of the brain plays a role. It has been suggested that the structure of the brain of preterm infants might be less firm when compared with term infants, making it more sensitive to the effect of gravity. (71 in Supporting Information)

DIFFERENCES IN ANTENATAL AND POSTNATAL VENTRICULAR SIZE

Foetal reference curves

Both abdominal and transvaginal ultrasonography are used for monitoring foetal ventricular size during intra-uterine development to detect congenital hydrocephalus. Like in neonates, the foetal atria and occipital horns appear to be more sensitive for early ventricular enlargement than the frontal horns and midbody of the lateral ventricles (31,32). Because reference values for the occipital horn are harder to obtain (72,73 in Supporting Information) most studies (56; 74–80 in Supporting Information) have focussed on the size of the atria. Foetal ventriculomegaly has been defined as an atrial size exceeding 10 mm, which represents 2.5–4 standard deviations above the mean. Less data are available with respect to foetal dimensions of the frontal (31; 72,73,81–83 in Supporting Information) and occipital horn (83,84 in Supporting Information).

Foetal ventricular size has mainly been determined in the axial plane. Monteagudo et al. (83 in Supporting Information), however, performed frontal horn measurements in the coronal plane and occipital horn measurements in the parasagittal plane, thus enabling comparison with neonatal data. Differences between intra-uterine and extra-uterine reference ranges are remarkable, especially with regard to the AHW and TOD. Upper limits for the foetal AHW and TOD are 7.5 mm and 25–30 mm (depending on GA) respectively (83 in Supporting Information), which is higher than neonatal measurements for those parameters (15,20,21,30,34) (Fig. 3B–C). This raises the question what happens with ventricular size during and following birth.

Changes in ventricular size following birth

While the lateral ventricles are open in most foetuses (83 in Supporting Information), nearly or completely closed ventricles are quite a common phenomenon in term and preterm neonates in the first week post-partum and not necessarily related to cerebral ischaemia (33,36; 85–87 in Supporting Information).

A rapid increase in ventricular area (36; 63 in Supporting Information) and volume (69 in Supporting Information) at the end of the first week and in the second week of life has been reported. Nelson et al. (85 in Supporting Information) investigated the postnatal change in ventricular size in a population of healthy term newborns following a vaginal delivery. By combining cross-sectional and longitudinal classifications of the lateral ventricles, it was assessed that within 12 h of birth the ventricles were completely closed in 80%, partially opened in 18%, and completely open in only 1% of the newborns. Gradual reopening was seen over the following days. The estimated median time to partially open ventricles following a vaginal delivery was 2.5–3 days.

The effect of the mode of delivery

The difference in ante- and postnatal ventricular size and the process of reopening seen postnatally may be partly explained by the effect of a vaginal delivery (33; 85 in Supporting Information). It has been suggested that the compression on the skull of the baby during its passage through the birth canal possibly forces the CSF out of the ventricles. (85 in Supporting Information) For term infants, a statistically significant correlation between the mode of delivery and the visibility of CSF in the lateral ventricles was reported by Winchester et al (33). While open ventricles were found in two out of 16 neonates born by caesarean section within the first 6 days of life, it was seen in only two out of 28 infants born vaginally. For preterm infants, the association between compressed ventricles and mode of delivery is less clear.

The optimal study design for demonstrating a possible effect of the mode of delivery on ventricular size would be a longitudinal study with antenatal and postnatal ventricular measurements in neonates born after a vaginal delivery or primary caesarean section. In addition to Nelson’s research in term infants (85 in Supporting Information), it would be interesting to investigate whether the phenomenon of reopening can also be observed in preterm infants.

Other hypotheses

Postnatal changes in ventricular size can not exclusively be explained by the mode of delivery as compressed ventricles may persist after the first week after birth (85 in Supporting Information) and can also be seen following a caesarean section (33; 86 in Supporting Information). Another factor that at least partly may be responsible for the difference in ante- and postnatal ventricular size, is the mild degree of dehydration of the newborn during the first days of life, which is also considered to explain the smaller renal pyela in neonates compared with foetal pyelum size (88,89 in Supporting Information). Dehydration may lead to a reduced CSF production and hence to a smaller ventricular size.

The transition from the foetal low pressure to the neonatal high pressure circulatory state, probably accompanied by changes in the secretion or reabsorption of CSF, has also been proposed as an explanation for the changes in ventricular size following birth (36).

CONCLUSION

Evaluation of the size of the lateral ventricles is important for the early detection of PHVD in neonates, which may have important therapeutic and prognostic implications. During the last three decades, cUS played a key role in the diagnosis and evaluation of ventricular dilatation. Reference values were established for several ventricular dimensions. Furthermore, several variables influencing ventricular size have been investigated.

The main conclusions are that, while reference values for the VI increase with ongoing maturity, the correlation with GA remains controversial for measurements of the AHW and TOD. Asymmetry between the lateral ventricles is a
common phenomenon and appears to represent a normal physiological variation rather than a sign of cerebral pathology in most neonates. The difference in foetal and neonatal reference curves is remarkable, the ventricular size appearing larger in foetuses. This may partly be explained by the effect of a vaginal delivery.

Several questions remain unanswered. There is still a need for more cross-sectional as well as longitudinal data on normal ventricular size, especially for ELBW infants. Some studies have been carried out with only a small study population or were performed quite a long time ago with less advanced techniques. No data are available with respect to reopening of the ventricles in premature infants or neonates born by primary caesarean section, so the effect of the mode of delivery on postnatal ventricular size is still not clear.

The main question, however, which needs to be answered is which ventricular parameter gives the most accurate reflection of intracranial pressure in neonates with PHVD. To our knowledge, this has only been investigated for the VI(10). As important therapeutic decisions are based on ventricular size measurements, there still remains a need for prospective studies.

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References


**Supporting Information**

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

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