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A systematic review of pre- and postnatal ultrasound measurements for assessing brain growth: Reliability and implications for clinical practice

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ABSTRACT

Background and aim: The aim of this systematic review was to identify and assess the reliability of pre- and postnatal ultrasound measurements for evaluating early longitudinal brain growth. The secondary aim was to provide a reliable and feasible set of pre- and postnatal ultrasound measurements for clinical practice and future research.

Methods: This review was conducted according to PRISMA guidelines and used the validated QAREL scale to assess the risk of bias in the included studies. We included studies assessing the reliability of prenatal and/or postnatal ultrasound measurements. Articles were excluded if intraclass correlation coefficients for intra- or interobserver agreement were not provided. The primary outcome was the intraclass correlation coefficient (ICC) of the intra- and inter-observer agreement.

Results: A total of twenty-two studies were included, in which one study assessed both pre- and postnatal brain growth measurements, eleven studies focused on prenatal measurements, and ten on postnatal measurements. In these studies, twenty-seven prenatal and thirty-two postnatal ultrasound measurements were used to assess brain growth, showing predominantly good or excellent intra- and interobserver reliability.

Conclusions: This review highlighted a significant gap in studies assessing longitudinal brain growth from the pre- to the postnatal period. Therefore, collaboration between obstetricians, radiologists and neonatologists is important for assessing longitudinal brain growth, which could help identify infants at risk of abnormal brain growth and potential neurodevelopmental impairment. We propose a set of ultrasound measurements of total brain size, ventricles, cerebellum, and corpus callosum to monitor early brain growth.

1. Introduction

The fetal brain undergoes exponential growth from 20 weeks' gestational age (GA) to term age [1]. This growth occurs primarily during the third trimester, including major organizational events, cortical folding, and myelination [2]. Brain growth is an important predictor of neurodevelopmental outcome and is therefore important to assess longitudinally across different GAs and standardized postnatal time points [3–7]. Fetal and neonatal magnetic resonance imaging (MRI) enables accurate measurement of brain growth; however bedside availability is limited restricting routine and longitudinal evaluation. In contrast, fetal and neonatal ultrasound, due to its bedside availability and noninvasiveness, is an ideal method for assessing brain growth longitudinally during both the pre- and postnatal period. Recently, van Von and colleagues demonstrated a robust correlation between several postnatal cranial ultrasound (CUS) and MRI measurements, underscoring the feasibility of using CUS for longitudinal assessment of brain development [8].

Previous research has shown that the corpus callosum (CC) and corpus callosum–fastigium (CCF) length are reliable markers for monitoring brain growth from the pre- to postnatal period [2,9]. The use of consistent and longitudinal ultrasound measurements has the potential to serve as a surrogate quantitative marker for abnormal brain growth and long-term neurodevelopmental impairment [2]. This enables early identification of fetuses and infants at risk for abnormal brain growth and may eventually lead to the development of management and

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treatment options.

Pre- and postnatal ultrasound measurements are mainly focused on specific brain structures, lacking consistent measurements due to varying protocols and the absence of corresponding standard ultrasound planes [2]. Furthermore, there are no integrated growth charts to monitor brain growth between the second trimester and the neonatal period. In clinical practice, there is a need for simple and reproducible ultrasound measurements based on well-defined anatomical landmarks of standard imaging planes, that can be used both pre- and postnatally. However, there is limited information in the current literature regarding the reliability and feasibility of ultrasound measurements for longitudinal quantification of brain growth longitudinally in both the prenatal and postnatal period.

Therefore, the aim of this systematic review was to evaluate the existing evidence on intra- and inter-observer reliability of ultrasound measurements for assessing longitudinal brain growth during both the pre- and postnatal period. The secondary aim was to identify reliable and feasible ultrasound measurements for assessing brain growth longitudinally spanning both the pre- and postnatal period.

2. Materials and methods

2.1. Search strategy

This systematic review followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. We searched the electronic databases of the Cochrane Library, Embase, PubMed, and Web of Science in May 2024 for relevant studies published between 1 January 2000 to 16 May 2024. A scientific information specialist was consulted to develop the search terms. The search strategy consisted of four important keywords: ultrasound, prenatal, postnatal and brain growth. Additionally, a variety of synonyms were added as free-text words and Medical Subject Headings (MESH) terms (Supplementary Material 1). The reference lists of the reviewed articles were manually searched to identify relevant articles that were missed.

2.2. Study selection

All relevant articles were assessed for eligibility by screening the title and abstract after removing duplicates. Next, full-text articles were evaluated. All clinical trials, cohort studies, and case-control studies were eligible for inclusion if the study evaluated the reliability of pre- and/or postnatal ultrasound measurements of brain growth**.** Articles were excluded if they did not report intraclass correlation coefficients for intra- and/or interobserver agreement. In addition, articles were excluded if they were case reports, small case series ($n < 3$), conference abstracts, not written in English, or if the full text was unavailable. The search results were independently assessed by two reviewers (M.R. and B.O.). In case of disagreement, a third reviewer (S·S) was consulted to reach a consensus. The primary outcome was the intraclass correlation coefficient (ICC, with 95 % CI) for both intra- and interobserver reliability of ultrasound measurements.

2.3. Assessment of risk bias

The Quality Appraisal of Reliability Studies (QAREL) scale was used to assess the risk of bias in the included studies [10]. The scale consists of 11 items designed to evaluate external validity, internal validity, and statistical methods in reliability studies (Supplementary Material 2). Each item was scored as 'Yes', 'No', 'Unclear', or 'N/A', with equal weighting across all items. If an item was scored as 'yes' it was assigned 1 point, resulting in a maximum possible score of 11. A score of $\leq$4 represented a high, a score of $\geq$5 to 7 a moderate and a score of $\geq$8 a low risk of bias. Two reviewers (M.R. and B.O.) independently assessed all studies. Disagreements were resolved by discussion until a consensus was reached. In cases of unresolved disagreement, a third reviewer (S.S.) was consulted.

2.4. Data analysis

Data were collected regarding the study characteristics, observer characteristics, number of observers, number of ultrasound measurements examined, ICCs, and ultrasound machine characteristics. We grouped the ultrasound measurements into four categories for the prenatal, postnatal and both pre- and postnatal period: overall brain size, ventricular, brain structures (corpus callosum, cerebellum, posterior, subarachnoid space, interhemispheric fissure, mid- and hindbrain structures), and white/deep gray matter ultrasound measurements. ICC values less than 0.50 are considered indicative of poor reliability, values between 0.50 and 0.75 indicate moderate reliability, values between 0.75 and 0.90 indicate good reliability, and values greater than 0.90 are considered excellent reliability [11]. When multiple studies assessed the reliability of a ultrasound measurement, ICCs were first transformed using the Fisher z-transformation. Standard errors were estimated based on reported confidence intervals or, when not available, approximated from the sample size. A random-effect meta-analysis was conducted on the transformed values using inverse-variance weighting, with between-study heterogeneity estimated using the DerSimonian-Laird method. The pooled estimates and their 95 % confidence intervals were subsequently back-transformed to the ICC scale for interpretation. Statistical analyses were conducted using SPSS (version 28; IBM Corp) and GraphPad Prism (version 10.2.3; GraphPad Software).

3. Results

3.1. Study selection

In total 1386 articles were identified through our search strategy (Supplementary material 1), including seven additional articles found through a manual search of reference lists. After removing 657 duplicates, 736 articles were screened based on their titles and abstracts. The initial screening resulted in the exclusion of 706 articles. Of the remaining 30 articles, eight were excluded following a full-text assessment. Thus, the final analysis included 22 articles (Fig. 1).

3.2. Quality assessment

Of the 22 studies, 4 (18.2 %) were classified as having a low risk of bias, 15 (68.2 %) as having a moderate risk, and 3 (13.6 %) as having a high risk of bias (Supplementary Table 1). The scores ranged from a minimum of 4 to a maximum of 10 points. A common limitation across the studies was the lack of a detailed description of whether observers were blinded to their own previous findings, reference standards, clinical information, or other additional cues. Two studies did not report the number of fetuses or neonates included in the calculation of intra- and inter-observer reliability [1,12]. Furthermore, in 18 out of 22 studies, it was unclear whether measurements were conducted in a randomized order. Additionally, three studies did not provide confidence intervals for the intra-class correlation coefficients, which limits the interpretation of the results and comparability with other studies [8,13,14].

3.3. Study characteristics

Twenty-two studies were analyzed, of which 11 provided information about the reliability of postnatal ultrasound measurements, and 10 studies provided information about the reliability of prenatal measurements (Table 1). Only 1 study provided information about the reliability of ultrasound measurements during both the prenatal and postnatal period [2]. Nine studies (41 %) were published in the last five years [1,8,15–18]. The oldest articles ($n = 2$) were published in 2005 [12,19].

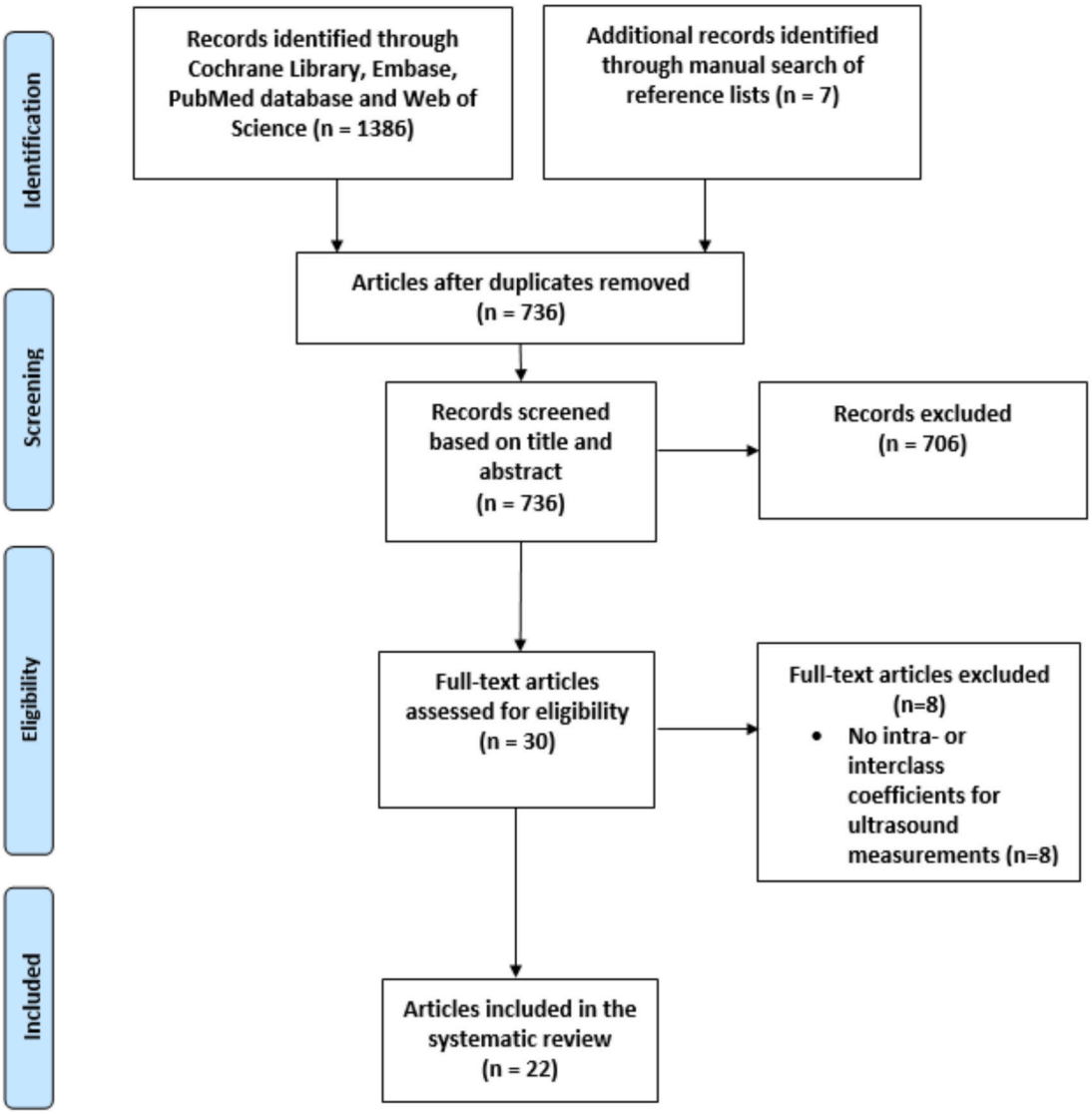

Fig. 1. Flow diagram.

3.4. Intra- and interobserver reliability of prenatal ultrasound measurements

Eleven studies described the reliability of 27 different ultrasound measurements performed during the prenatal period (Supplementary Table 2). The most frequent assessed ultrasound measurement was CC length in three studies with an excellent intra- and interobserver ICC of >0.95.

3.4.1. Overall brain size measurements

The intra- and interobserver ICCs for both the fronto-occipital diameter (FOD) and frontal antero-posterior diameter (FAPD) were excellent in the trans-ventricle view. FOD showed intraobserver and interobserver ICC of both 0.98 (95 % CI, 0.97–0.99, $n = 2$) [20,21]. For FAPD, the ICCs were 0.98 (95 % CI, 0.97–0.99) and 0.97 (95 % CI, 0.95–0.99) [21].

3.4.2. Ventricular measurements

Both anterior horn width (AHW), ventricular atrium width (VAW), ventricular index (VI) and thalamo-occipital distance (TOD) showed an excellent intra- and interobserver ICC, all being ≥ 0.99 [22].

3.4.3. Brain structures measurements

In the included studies, the intra- and interobserver reliability of eighteen different brain structures measurements have been assessed. Seven measurements were used to assess the corpus callosum: CC length, CCF length, corpus callosum genu width (CCgw), corpus callosum splenium width (CCsw), corpus callosum height (CCh), corpus callosum rostrum width (CCrw) and corpus callosum inner-inner border (CCi). Each measurement of the corpus callosum showed an intra- and inter-observer ICC >0.95 [2,23,24].

Seven measurements of the mid- and hindbrain were performed: anterior posterior pons diameter (APPD), aqueductal thickness (ADT), Blake's pouch neck height (BPNH), tectal thickness (TcT), tectal length (TL), tegmental laterolateral width (TLW) and tegmental thickness (TmT). Both BPNH and TLW showed excellent intraobserver reliability (0.97, 95 % CI 0.92–0.1.0, $n = 1$; and 0.99, 95 % CI 0.97–1.00, n = 1) [18]. Interobserver reliability was good for BPNH (0.89, 95 % CI 0.56–0.975, n = 1) and excellent for APPD (0.98, 95 % CI 0.97–0.99, $n = 2$) and TLW (0.99, 95 % CI 0.97–1.00, $n = 1$) [18,25]. The TcT, TL, TLW and TmT exhibited moderate to good intra-and interobserver reliability [18].

The cerebellum was assessed using three different measurements: trans cerebellar diameter (TCD), vermis width (VW) and vermis height (VH). The measurement of TCD showed an excellent intraobserver ICC

Table 1
Baseline characteristics of the included studies.

First author (year)	Country	Study design	Study period	Number of fetuses (N)	Population	Risk of bias
Prenatal studies						
Weissbach et al. (2023) [24]	Israel	P	2020–2022	187	Singleton uncomplicated pregnancies	Moderate
Gerbino et al. (2022) [22]	Italy	R	2015–2021	182	Singleton uncomplicated pregnancies	Moderate
Peng et al. (2022) [21]	China	R	2020–2021	440	Singleton uncomplicated pregnancies (n = 352) and fetal growth restricted fetuses (n = 88)	Low
Birnbaum et al. (2021) [18]	Israel	R	2018–2019	60	Singleton uncomplicated pregnancies	Moderate
Albers et al. (2018) [20]	The Netherlands	P	2015	80	Singleton uncomplicated pregnancies	Moderate
Koning et al. (2017) [26]	The Netherlands	P	2013–2015	213	Congenital heart disease fetuses (n = 20) and controls (n = 193)	Moderate
Koning et al. (2017) [2]	The Netherlands	P	2013–2015	199	Fetuses with fetal growth retardation (n = 22), with congenital heart defects (n = 20), and controls	Moderate
Alves et al. (2013) [27]	Brazil	P	2010–2012	393	Singleton uncomplicated pregnancies	Moderate
Pashaj et al. (2013) [23]	Albania	P	2010–2012	466	Singleton uncomplicated pregnancies	Moderate
Mirlesse et al. (2010) [25]	France	P	NR	913	Singleton uncomplicated pregnancies	Moderate
Viñals et al. (2005) [12]	Chile	P	NR	203	Singleton uncomplicated pregnancies	High
Postnatal studies						
Arena et al. (2024) [1]	Italy	P	2016–2018	80	Preterm born with GA less than 32 weeks.	Moderate
Fernandez et al. (2023) [16]	United Kingdom	R	NR	30	Term-born neonates with hypoxic-ischemic encephalopathy	Moderate
Vo Van et al. (2022) [8]	France	P	2013–2014	102	Neonates born at <32 weeks GA	Moderate
Groene et al. (2022) [17]	The Netherlands	R	2010–2020	116	Monochorionic twin pairs with selective fetal growth restriction	Moderate
Boswinkel et al. (2021) [15]	The Netherlands	P	2014–2016	150	Moderate preterm (GA: 32 + 0–33 + 6wks, n = 44), late preterm (GA: 34 + 0–36 + 6wks, n = 54) and full term (n = 52)	Low
Cuzilla et al. (2018) [28]	Australia	P	2011–2013	144	Neonates born at <30 weeks GA	Low
Roelants et al. (2016) [9]	The Netherlands	P	2010–2012	140	Preterm infants born <29 weeks of GA	Low
Sancak et al. (2016) [14]	Turkey	P	2013	78	Preterm between 27 and 32 weeks	Moderate
Graça et al. (2013) [13]	Portugal	P	NR	126	Preterm (n = 70) and term-born neonates (n = 56)	High
Hagmann et al. (2011) [29]	United Kingdom	P	2007	106	Term-born neonates	Moderate
Anderson et al. (2005) [19]	New Zealand	P	1998–2000	100	Very low birthweight neonates	High

Abbreviations: GA, gestational age, NR, not reported, P, prospective, R, retrospective.

(0.91, 95 % CI, 0.86–0.94, n = 1) and a good interobserver ICC (0.86, 95 % CI 0.78–0.91, n = 1) [20]. The VH and VW showed an excellent intra-observer reliability ICC, however the interobserver reliability was not reported [12,25].

3.4.4. White/deep gray matter measurements

The reliability of the sylvian-, insula-, parieto-occipital fissure (POF), hippocampal-, calcarine fissure length, and the thalamus width (TW) were assessed [20,26,27]. All fissure length measurements showed excellent intraobserver reliability, with ICCs >0.9 [26,27]. The hippocampal fissure length showed an excellent interobserver ICC (0.97, 95 % CI 0.94–0.98, n = 1) [27]. Both sylvian-, insula-, POF and calcarine fissure showed a good intra- and interobserver reliability [26,27]. The TW showed a poor reliability of the intra- and interobserver ICC, both <0.5 [20].

3.5. Intra- and interobserver reliability of postnatal ultrasound measurements

Eleven studies described the reliability of 32 different ultrasound measurements during the postnatal period (Supplementary Table 3) [1,8,9,13–17,19,28–30]. These measurements are illustrated in Fig. 2. The most frequently assessed measurement was the CC length in 8/11 (73 %) studies with excellent intra- and interobserver reliability of 0.96 (95 % CI, 0.96–0.97) and 0.96 (95 % CI, 0.96–0.96) [1,8,9,15,17,19,28,29]. The intra- and interobserver reliability of the ten most often assessed postnatal ultrasound measurements in the literature are shown in Fig. 3.

3.5.1. Overall brain size measurements

In total, 6 different ultrasound measurements were evaluated for their reliability in assessing overall brain size: the bone biparietal diameter (BBD), bifrontal diameter (BFD), biparietal diameter (BPD), FOD, intracranial height (ICH) and total brain surface (TBS). Among these, the BPD was the most frequently assessed (n = 4), demonstrating an intraobserver ICC of 0.96 (95 % CI, 0.96–0.96) and a interobserver ICC of 0.95 (95 % CI, 0.95–0.95) [8,15,17,28]. The BBD, BFD, FOD, ICH, and TBS also exhibited excellent reliability, with both intraobserver and interobserver ICCs exceeding 0.93 [1,8,17].

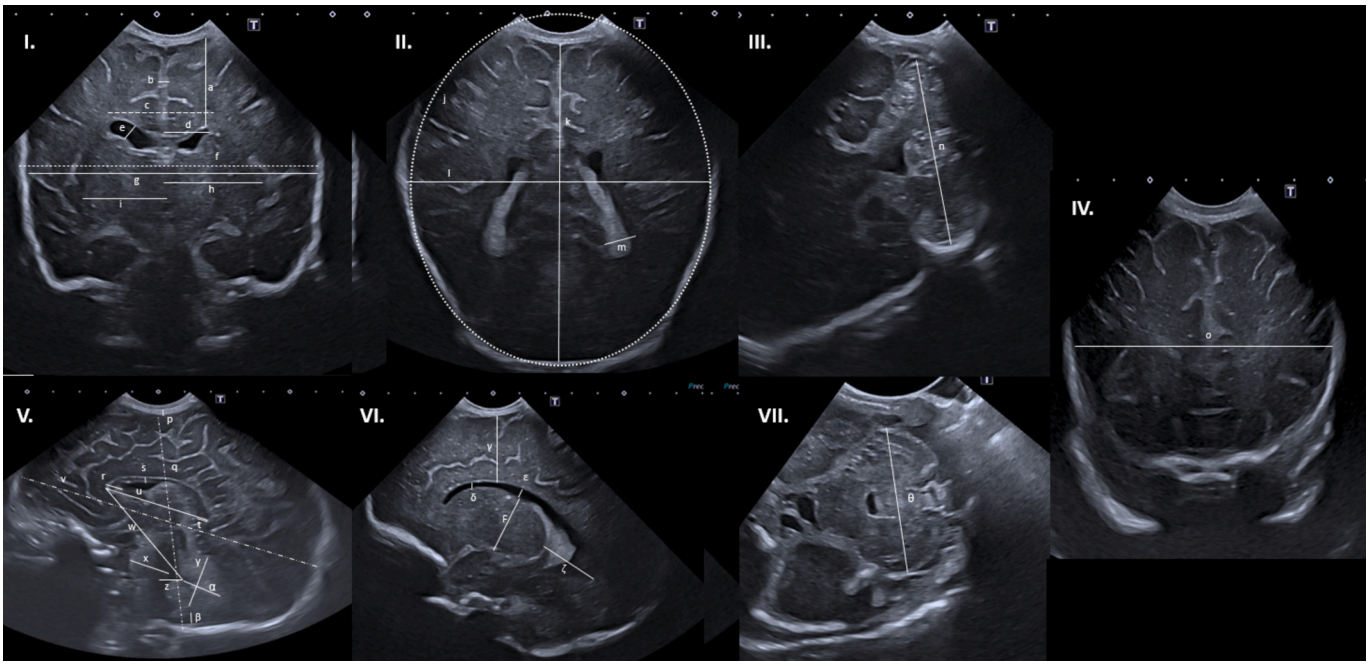

Fig. 2. Overview of postnatal ultrasound measurements of the brain.
FWMH (a), IHF (b), VWL (c), VI (d), AHW (e), BBD (f), BPD (g), BGIW (h), DGMW or BGW (i), TBS (j, based on calculations of k and l), VAW (m), TCDcor (n), BFD (o), SAS (p), ICH (q), CCgw (r), CCh (s), CCsw (t), CC length (u), FOD (v), CCF length (w), APPD (x), VH (y), FVD (z), VW (α), CMH (β), HH (γ), AHH (δ), VMH (ε), DGMH (ϝ), TOD (ζ), TCDax (θ). I (mid-coronal), II, and IV are acquired in the coronal plane via the anterior fontanelle. V (mid-sagittal) and VI (parasagittal) are obtained in the sagittal plane via the anterior fontanelle. III is imaged in the coronal plane through the mastoid fontanelle, while VIII is obtained in the axial plane via the mastoid fontanelle.

3.5.2. *Ventricular measurements*

The reliability of assessing the lateral ventricles or fourth ventricle was evaluated in seven studies using eight different measurements, including AHW, VI, anterior horn height (AHH), fourth ventricle diameter (FVD), VAW, TOD and ventricular midbody height (VMH). The AHW and VI have been the most frequently assessed in the studies reporting on the measurements of ventricles ($n = 4/7$, 57 %). The intra- and interobserver ICC for AHW was excellent (0.98, 95 % CI, 0.95–0.99) and good (0.78, 95 % CI, 0.48–0.92), respectively [1,15,17,28]. For VI, the intra- and interobserver showed both good reliability with 0.81 (95 % CI, 0.57–0.92, $n = 3$) and 0.87 (95 % CI, 0.75–0.94, n = 3), respectively [15,17,28,29]. The FVD, VAW, TOD, and VMH measurements exhibited moderate to excellent intra- and interobserver reliability [8,13,17,28,29].

3.5.3. *Brain structures measurements*

In the included studies, the reliability of thirteen different measurements of brain structures has been assessed. Five measurements were used to assess the corpus callosum: CC length, CCF, corpus callosum genu width (CCgw), corpus callosum splenium width (CCsw) and corpus callosum height (CCh). The reliability of CC and CCF length is most often evaluated (8/11 studies, 73 %) in ultrasound assessments. The CC showed an excellent intra- and interobserver reliability of 0.96 (95 % CI, 0.96–0.97, $n = 8$) and 0.96 (95 % CI, 0.96–0.96, $n = 7$). The CCF showed an excellent intraobserver ICC of 0.94 (95 % CI, 0.84–0.98, $n = 4$) and a good and interobserver ICC of 0.86 (95 % CI, 0.73–0.93, $n = 3$) [1,8,9,15,17,19,28,29]. The CCh, CCgw, CCsw demonstrated poor to good intra- and inter observer reliability [8,17,28].

The cerebellum was assessed using four different measurements: axial (TCDax) or coronal (TCDcor) transverse cerebellar diameter, VH, and VW. The TCDcor showed an excellent reliability, with an intraobserver ICC of 0.99 (95 % CI, 0.98–0.99; $n = 8$) and an interobserver ICC of 0.99 (95 % CI, 0.99–0.99; $n = 7$). The TCDax showed good intraobserver and interobserver reliability [1,8,13–17,28,29]. The VH and VW showed moderate to good intra- and interobserver reliability [8,13–17,28,29].

The other ultrasound measurements of brain structures, the interhemispheric fissure width (IHF) and subarachnoid space (SAS), showed excellent intraobserver ICC of 0.98 (95 % CI, 0.98 to 1.00; $n = 5$) and 0.92 (95 % CI not reported; $n = 1$), respectively. Interobserver reliability was moderate for IHF, with an ICC of 0.68 (95 % CI, 0.40–0.85; $n = 4$), and excellent for SAS, with an ICC of 0.95 (95 % CI not reported; $n = 1$) [1,8,15,17,28] The APPD and CMH showed poor to good intra- and interobserver reliability [13,29].

3.5.4. *White/deep gray matter measurements*

Frontal white matter height (FWMH) and hemisphere height (HH) showed both excellent reliability with an intraobserver ICC of 0.91 (95 % CI, 0.76–0.96; $n = 2$) and 0.98 (95 % CI, 0.98–0.98; n = 1), and a interobserver ICC of 0.96 (95 % CI, 0.96–0.96, n = 1) and 0.97 (95 % CI, 0.96–0.8, n = 1) [1,17]. Deep gray matter height (DGMH), deep gray matter width (DGMW) and basal ganglia insula width (BGIW) were used to assess deep gray matter, with moderate to good intra- and interobserver reliability [1,15].

3.6. *Intra- and interobserver reliability of pre- and postnatal ultrasound measurements*

Koning et al. was the only study to examine ultrasound measurements during the pre- and postnatal period [2]. They investigated the CC and CCF as markers for pre- and postnatal brain growth. Ultrasound measurements were performed at 22, 26 and 32 weeks of GA and postnatally at 42 weeks of postmenstrual age [2,9]. These measurements were performed in fetuses and neonates with fetal growth restriction ($n = 22$), congenital heart defects ($n = 20$) or controls ($n = 157$). The intraobserver ICC for CC and CCF during the prenatal period was >0.99 (95 % CI, not reported). The interobserver ICC for CC and CCF length during the prenatal period was in both cases 0.97 (95 % CI not reported)

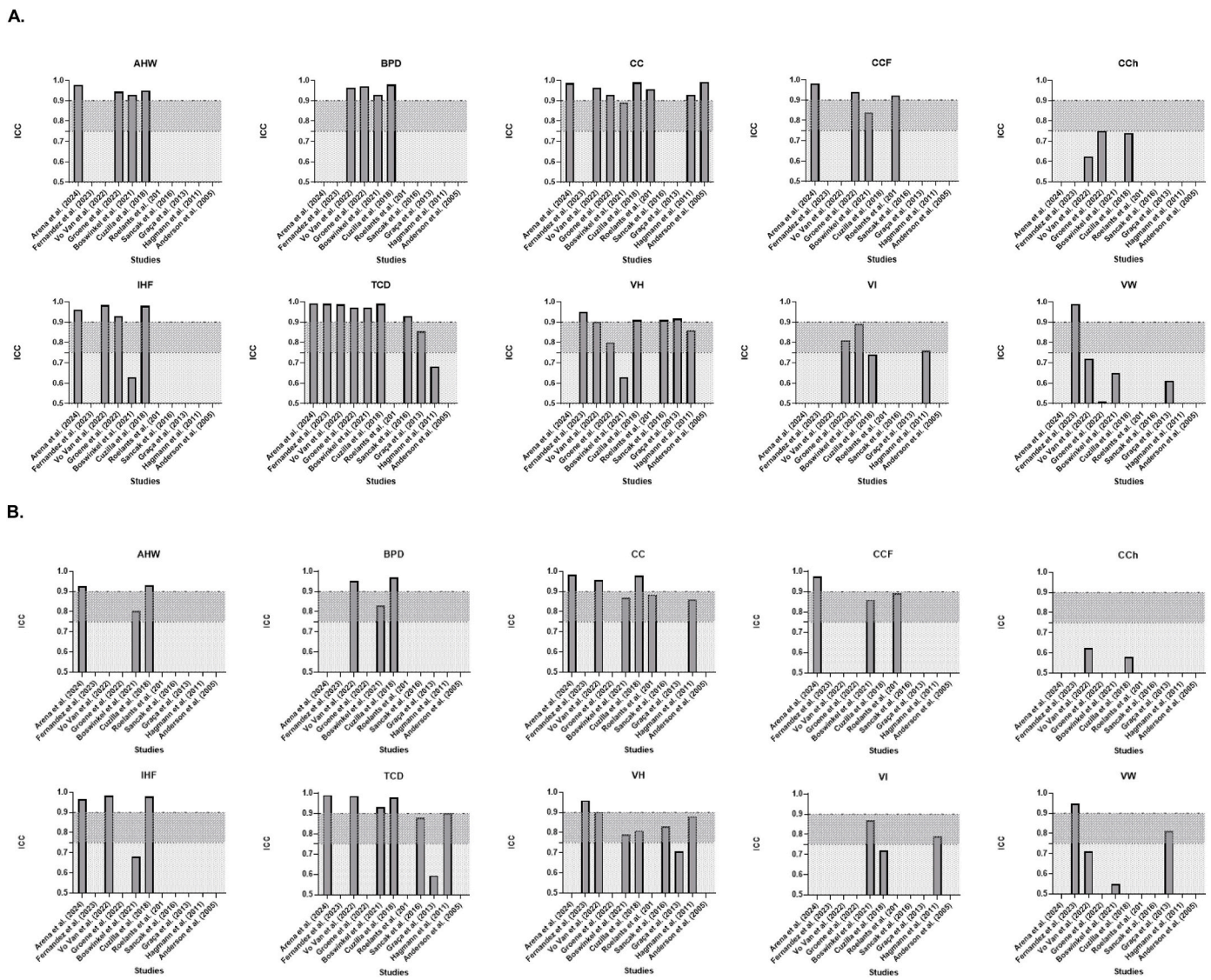

Fig. 3. Intra- and interobserver reliability of the postnatal ultrasound measurements.
The intra (A)- and inter-observer (B) reliability of the ten most frequently used ultrasound measurements during the postnatal period The light gray area indicates moderate reliability (ICC 0.5–0.75), the dark gray area indicates good reliability (ICC 0.75–0.90), and the white area indicates excellent reliability (ICC 0.9–1.0). Abbreviations: AHW, anterior horn width, BPD, biparietal diameter, CC, corpus callosum length, CCF, corpus callosum fastigium length, CCh, corpus callosum height, IHF, interhemispheric fissure, TCD, trans cerebellar diameter, VH, vermis height, VI, ventricular index, VW, vermis width.

[2]. They showed an excellent reliability postnatally, with intraobserver ICC of 0.96 (95 % CI: 0.91–0.98) and 0.92 (95 % CI: 0.84–0.96), and interobserver ICC of 0.89 (95 % CI: 0.77–0.94) and 0.89 (95 % CI: 0.78–0.95) for CCF and CC length, respectively [9].

An overview of the reliability for both intra- and interobserver reliability categorized in excellent, good, moderate and poor in both the pre- and postnatal period is provided in Table 2.

4. Discussion

4.1. Key findings

This systematic review identified 22 studies, reporting on 27 prenatal and 32 postnatal ultrasound measurements currently used to assess brain growth, for which intra- and interobserver reliability were evaluated. At present, only one study has provided data on the reliability and feasibility of ultrasound measurements in both the prenatal and postnatal period, indicating a significant gap in the literature and the need for further research. Most ultrasound measurements showed excellent or good intra- and interobserver reliability. Of note, the majority of studies had a moderate to high risk of bias, as assessed with the QUAREL tool, highlighting the need for standardized and detailed methods to assess the reliability of these measurements.

4.2. Interpretation of findings

4.2.1. Prenatal ultrasound measurements

We assessed the intra- and interobserver reliability of 27 different prenatal ultrasound measurements. Overall, the reliability was excellent or good; however, APPD, TmT, and TW demonstrated moderate to poor reliability. It is important to consider that the apparent over-representation of excellent to good reliability may be influenced by factors such as publication bias, moderate to high risk of bias in the reliability assessments, and the limited number of studies and sample sizes of the cohorts evaluated. An important consideration in the feasibility of prenatal ultrasound measurements is the GA at the time of assessment and the influence of fetal position or twin pregnancies. Koning et al. showed variable success rates for measuring the CC and

Table 2
Summary of the mean intra- and interobserver reliability of all pre- and postnatal studies.

Prenatal ultrasound measurements										
Intraobserver reliability						Interobserver reliability				
Excellent (>0.90)			Good (0.75–0.90)	Moderate (0.5–0.75)	Poor (<0.50)	Excellent (>0.90)		Good (0.75–0.90)	Moderate (0.5–0.75)	Poor (<0.50)
AHW	CCsw	TOD	ADT		TW	AHW	Hippocampal	ADT	TmT	TW
APPD	Calcarine	VAW	TcT			CC	POF	APPD		
BPNH	FOD	VH	TL			CCF	TLW	BPNH		
CC	Hippocampal	VI	TmT			CCgw	TOD	Calcarine		
CCF	Insula					CCh	VAW	Insula		
CCgw	POF					CCi	VI	Sylvian		
CCh	Sylvian					CCrw		TCD		
CCi	TCD					CCsw		TL		
CCrw	TLW					FOD		TcT		

Postnatal ultrasound									
Intraobserver reliability					Interobserver reliability				
Excellent (>0.90)			Good (0.75–0.90)	Moderate (0.5–0.75)	Poor (<0.50)	Excellent (>0.90)		Good (0.75–0.90)	Moderate (0.5–0.75)	Poor (<0.50)
AHW	FWMH	VAW	AHH	BGIW		BBD	TCDax	AHH	BGIW	CCgw
APPD	HH	VH	APPD	CCh		BFD	TCDcor	AHW	CCh	CCsw
BBD	ICH		CCgw	CMH		BPD	VH	APPD	IHF	CMH
BFD	IHF		CCsw	VW		CC		CCF	TOD	
BPD	SAS		DGMW			FOD		DGMH	VMH	
CC	TBS		FVD			FWMH		FVD	VW	
CCF	TCDax		VI			HH		VAW		
DGMH	TCDcor		VMH			SAS		VI		
FOD	TOD					TBS				

Abbreviations: AHH, anterior horn height; AHW, anterior horn width; APPD, anterior-posterior pons diameter; BBD, bone biparietal diameter; BFD, bifrontal diameter; BGIW, basal ganglia insula width; BPD, biparietal diameter; BPNH, Blake's pouch neck height; CC, corpus callosum length; CCF, corpus callosum–fastigium length; CCgw, corpus callosum genu width; CCi, corpus callosum inner-inner border; CCrw, corpus callosum rostrum width; CCsw, corpus callosum splenium width; CCh, corpus callosum height; CMH, cranial midline height; DGMH, deep gray matter height; DGMW, deep gray matter width; FAPD, frontal anteroposterior diameter; FOD, fronto-occipital diameter; FVD, fourth ventricle diameter; FWMH, frontal white matter height; HH, hemisphere height; ICH, intracranial height; IHF, interhemispheric fissure width; POF, parieto-occipital fissure; SAS, subarachnoid space; TcT, tectal thickness; TCD, transcerebellar diameter; TCDax, transverse cerebellar diameter (axial); TCDcor, transverse cerebellar diameter (coronal); TL, tectal length; TLW, tegmental laterolateral width; TmT, tegmental thickness; TOD, thalamo-occipital distance; TW, thalamus width; TBS, total brain surface; VAW, ventricular atrium width; VH, vermis height; VI, ventricular index; VMH, ventricular midbody height; VW, vermis width.

CCF lengths during the prenatal period, ranging from 59 % to 75 % [2]. Another study demonstrated a high success rate of 80 % for measuring CC length at 13 weeks of gestation [24]. Measurements of other structures showed similar high success rates: AHW (92 %), VI, (92 %), TOD (66 %), and VAW (100 %) between 18 and 34 weeks of gestation; APPD (97 %) and vermis height (VH 97 %) between 21 and 36 weeks; TCD, 88 % and FOD, 95 % at 22 weeks of gestation [20,22,25].

4.2.2. Postnatal ultrasound measurements

We assessed the intra- and interobserver reliability of 32 different postnatal ultrasound measurements. Overall, reliability was excellent or good, particularly for overall brain size, ventricular measurements, and specific structures, such as CC length, CCF length, TCD, and VH. However, smaller structures or those with less distinct anatomical landmarks showed moderate to poor reliability, including measurements such as CCgw, CCsw, CCh, CMH, VMH, and BGIW. Arena et al. proposed a reproducible set of ultrasound measurements for the postnatal period, representing different brain areas, as the so-called Brain Growth Evaluation Assessed with Transfontanellar ultrasound (B-GREAT) method [1]. This set includes CC length, CCF length, anterior horn width, frontal white matter, deep gray matter height, hemisphere height, total brain surface, transverse cerebellum diameter, and interhemispheric fissure. This method also incorporates CC and CCF, as suggested by Koning et al., to bridge the gap between the pre- and postnatal period [2]. However, hemisphere height, deep gray matter height, and frontal white matter height are particularly challenging to measure in the prenatal period, making the B-GREAT method not fully generalizable for both pre- and postnatal applications. Furthermore, IHF showed moderate reliability in some studies, suggesting that it may not be the most suitable measurement to include in standard recommended sets [15,17]. Boswinkel and Groene et al. used an extensive set of measurements, most of which are suitable for the prenatal period; however, this set also includes less reliable measurements such as VW, IHF, and BGIW [15,17]. The sets of Vo and Cuzilla et al. contained a substantial number of measurements with moderate or poor reliability, such as CCh, CCgw, CCsw, and VMH. These studies highlight that the ideal set based on the reliability of measurements for sequential assessment of brain growth postnatally remains controversial. The intra- and interobserver reliability for some postnatal ultrasound measurements (e.g. CCh, CCgw, CCsw, CMH, BGIW, and VMH) were probably moderate because their borders were often not clearly visible, making these structures difficult to distinguish from their surroundings or very small in diameter and therefore error-prone. Using a higher-frequency probe, and thus higher near-field resolution, could potentially contribute to more precise measurements of superficial structures. Vo van et al. showed that postnatal ultrasound is a reliable tool for assessing selected 2D measurements in the developing brain and showed good to excellent correlation with MRI measurements of BPD, CC length, TCD, VAW and IHF and SAS [8]. A low correlation was seen between ultrasound and MRI for APPD, VH, CCw, BFD, FVD [8].

4.2.3. Pre- and postnatal ultrasound measurements

Only one study evaluated both pre- and postnatal ultrasound measurements, and showed that CC and CCF length are reliable markers of brain growth from 22 weeks of gestation into the postnatal period [2]. This underscores the substantial gap in the literature between the pre-

and postnatal period for integrated ultrasound measurements for assessing brain growth. The main challenge prenatally for measuring the CC and CCF lies in obtaining an accurate midsagittal plane, which is affected by factors such as acoustic shadowing and fetal position [31]. In contrast, postnatal measurement of the CC and CCF is generally not difficult for experienced practitioners [1,8,9,15,17,19,28,29]. Frequently assessed ultrasound measurements in pre- and postnatal studies with a good or excellent intra- and interobserver reliability, include the CC, CCF, AHW, VI, VH, TOD, FOD and TCD.

4.3. Clinical relevance of pre- and postnatal ultrasound measurements of brain growth

Vo et al. recently reported that MRI and cUS demonstrated good to excellent correlation when measuring BPD, CC length, TCD, and lateral ventricle diameters [8]. This suggests that MRI and cUS measurements align well for several parameters. Previous research identified a strong correlation between postnatally measured BPD and TCD, and total brain and cortical gray matter volumes on MRI [32,33]. BPD/ventricle ratio was associated with lower mental developmental index and psychomotor developmental index at two years of age, using the Bayley Scales of Infant Development, second edition [34]. Also, enlarged ventricles postnatally have been linked to white matter loss and are correlated with lower cognitive and motor scores at two years of age after exclusion of brain pathology [35–37]. The cerebellar diameter at term-equivalent age appears to be independently associated with cognitive and motor outcomes [37,38]. This association is further supported by the correlation observed between abnormal cerebellar dimensions and long-term neurodevelopmental outcome [39,40]. Additionally, smaller dimensions of the TCD during prenatal ultrasound are associated with impaired neurodevelopmental outcome in childhood [41,42]. In preterm infants, a shorter CC length is associated with an increased risk of mental developmental index <70 and higher risk of cerebral palsy at two years of corrected age [5,43,44]. CCF length is indicative of the development of the thalamus, which is critical for cognitive functioning. Disruptions in thalamic development have been linked to impaired neurodevelopmental outcome [45]. Furthermore, reduced growth of the CC length and cerebellar vermis size in preterm infants was associated with cerebral palsy or mental retardation at five years of age [44]. However, Vo Van et al. reported a poor correlation for vermis dimensions, limiting the generalizability of these findings to cUS. Brain size, ventricular, cerebellar and corpus callosum measurements may provide valuable information for identification of infants at risk of long-term neurodevelopmental impairment. While some ultrasound measurements were associated with long-term neurodevelopmental outcome, our review focused solely on measurement reliability, we did not assess prognostic accuracy, and thus reliability should not be conflated with clinical validity.

Although 2D ultrasound remains the standard for the evaluation of pre- and postnatal brain growth due to the accessibility and ease of use, it provides limited information about volumetric brain growth and development [46,47]. Several fetal studies have showed strong associations between 3D volumetric measurements on both ultrasound and MRI and long-term neurodevelopmental outcome [48–52]. Neonatal MRI studies in preterm and IUGR infants confirm the clinical relevance of volumetric brain assessments in relation to neurodevelopmental outcome [53,54]. However, in the postnatal period, the routine use of 3D cranial ultrasound measurements remains limited due to technical constraints such as restricted acoustic windows and the lack of 3D-compatible probes for neonatal use. Recent advancements in 3D ultrasound measurements showed the potential for research purposes and use in clinical practice [55–57].

4.4. Recommended ultrasound measurements

In clinical practice, brain growth measurements should be simple, reproducible, and based on standard imaging planes from routine care. In light of the findings of this systematic review, the association of structural brain measurements with neurodevelopmental outcomes, intra- and interobserver reliability, successful measurement rates and clinical experience, we propose the following ultrasound measurements to monitor brain growth during the pre- and postnatal period: overall brain size (FOD, BPD), ventricular (AHW, VI, VAW), cerebellar (TCD, VH), and corpus callosum (CC, CCF) measurements. In the prenatal period, BPD, TCD and VAW should be measured in the transverse plane; CC length, CCF length, FOD, and VH should be measured in the midsagittal plane; and AHW, and VI in the coronal plane (Fig. 4). In the postnatal period, AHW, BPD, TCD, VAW and VI should be measured in the coronal plane, whereas, CC length, CCF length, FOD and VH should be assessed in the midsagittal plane. This standardized set of ultrasound measurements enables consistent assessment of brain growth and could be implemented in a longitudinal cohort from 20 weeks to postnatal.

4.5. Strengths and limitations of this systematic review

To our knowledge, this is the first systematic review assessing the reliability of pre- and postnatal ultrasound measurements of brain growth. It was conducted according to standardized PRISMA methodology and utilizing the validated QAREL scale to assess risk of bias in the included studies. Due to its structured approach and the relatively large number of studies included, it provides valuable information for obstetricians and neonatologists regarding currently used measurements for assessing brain growth. Furthermore, we provide a set of ultrasound measurements that can be used for both pre- and postnatal brain growth monitoring, based on the reliability, association with neurodevelopmental outcome, and our own clinical experience. However, our results should be interpreted with some caution due to limitations identified in the current literature: (1) a moderate to high risk of bias was observed using the QAREL scale in the assessment of reliability across most studies; (2) the reliability of some ultrasound measurements has only been evaluated in a single study at a single timepoint; (3) recommended ultrasound measurements still need to be evaluated and validated in a pilot study; (4) no adjustments were made for observer experience, the use of more advanced equipment, transabdominal or transvaginal ultrasound, (5) most included studies did not examine the relation between brain growth and long-term outcomes, had limited follow-up information, and lacked adjustment for key confounders, limiting causal interpretation, and (6) alternative reliability measures, such as Bland-Altman plots, coefficients of variation, and limits of agreement, were not included, which may have introduced potential selection bias.

4.6. Implications for clinical practice and research

Collaboration between obstetricians, neonatologists, radiologists and researchers, is crucial for bridging the gap in monitoring brain growth using pre- and postnatal ultrasound measurements. In this systematic review, we have defined a reliable and reproducible set of ultrasound measurements that could serve as the foundation for future studies to assess brain development during both the prenatal and postnatal period. The implementation of these measurements in observational studies involving both healthy controls and specific patient populations would facilitate the development of integrated growth charts for both the prenatal and postnatal period. These charts could assist clinicians in identifying fetuses and neonates at risk of abnormal brain development and potential long-term neurodevelopmental impairment. Future research should explore the relationship between the proposed ultrasound measurements and long-term neurodevelopmental outcome. Large, longitudinal studies with extended follow-up (including at ages 5–8 years) and control for key confounding factors such as socioeconomic status, maternal behavior, and genetic predispositions to ensure more accurate causal interpretations. This

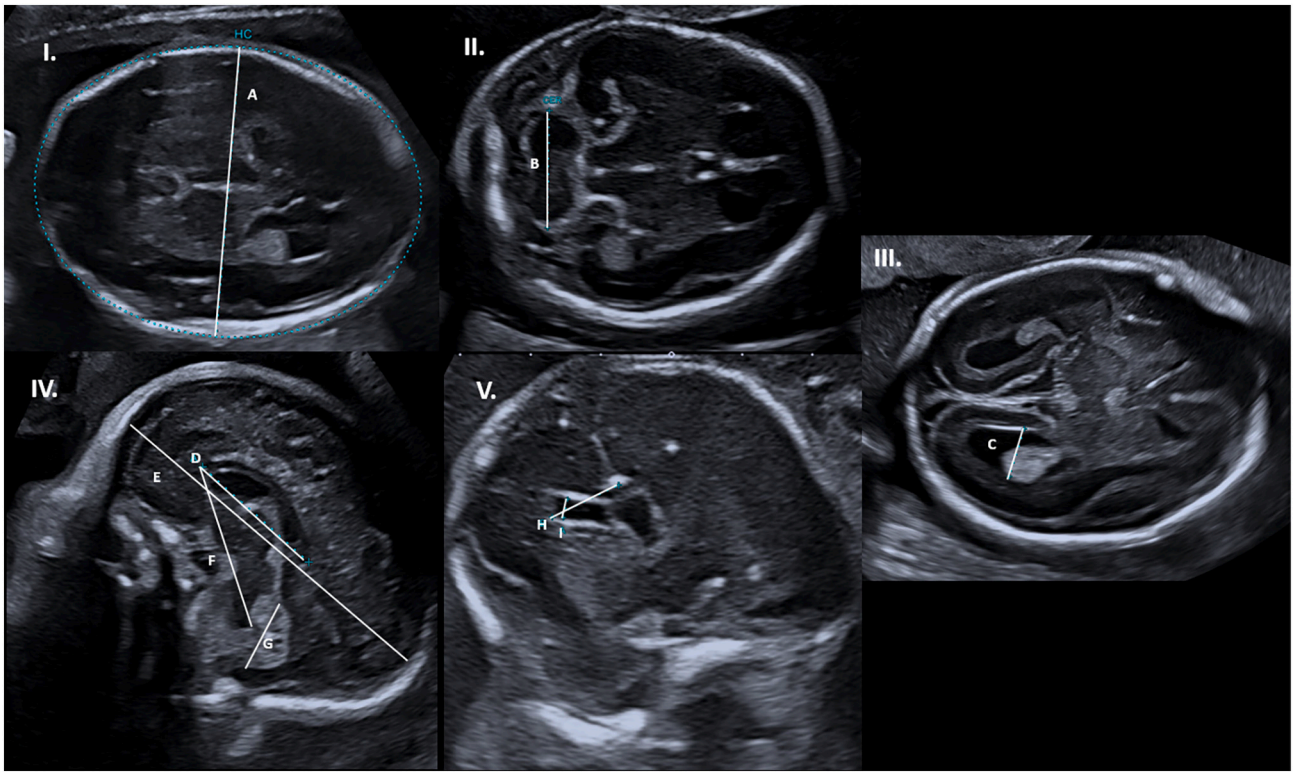

Fig. 4. Recommended prenatal ultrasound measurements.
BPD (A), TCD (B), VAW (C), CC (D), FOD (E), CCF (F), VH (G), VI (H), AHW (I). I, II and III are obtained in the transverse plane, IV in the (mid) sagittal plane and V in the coronal plane.

approach could ultimately offer a comprehensive, reliable, and practical set of ultrasound measurements for monitoring brain growth in clinical settings, thereby facilitating the early identification of patients at risk. The development of software that automatically identifies 2D-measurements both online and offline could further enhance the accuracy and efficiency of these measurements in clinical practice. Furthermore, the feasibility and clinical relevance of integrating 3D ultrasound into postnatal imaging and the longitudinal application of 3D ultrasound measurements across the pre- and postnatal period, to monitor brain growth in both healthy and infants at high-risk for neurodevelopmental impairment should be evaluated. Strong collaboration between obstetric sonographers, radiologists and neonatologists is essential to establish reliable and reproducible ultrasound measurements for sequential assessment of brain growth from the prenatal through the neonatal period, which could help to identify infants at risk of abnormal brain growth and potential neurodevelopmental impairment.

5. Conclusion

The reliability of current ultrasound measurements showed predominantly excellent or good intra- and interobserver reliability in the pre- and postnatal period. However, most studies exhibit a moderate to high risk of bias and lack standardization in the reliability assessment. This review also identified a substantial gap in studies evaluating brain growth by ultrasound across both the prenatal and postnatal period, highlighting the need for collaboration between obstetricians, radiologists, neonatologists to establish reliable and integrated methods for longitudinal brain growth assessment. This could ultimately help identify infants at risk of abnormal brain growth and potential neurodevelopmental impairment.

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CRediT authorship contribution statement

Mathies Rondagh: Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Bregje O. van Oldenmark:** Writing – review & editing, Validation, Methodology, Investigation, Formal analysis, Data curation. **Phebe J. Adama van Scheltema:** Writing – review & editing, Writing – original draft, Visualization, Supervision, Methodology, Investigation, Formal analysis, Conceptualization. **Enrico Lopriore:** Writing – review & editing, Validation, Supervision. **Jeanine M.M. van Klink:** Writing – review & editing, Methodology, Investigation, Conceptualization. **E.J.T. (Joanne) Verweij:** Writing – review & editing, Visualization, Validation, Methodology, Conceptualization. **Linda S. de Vries:** Writing – review & editing, Visualization, Supervision, Methodology, Investigation, Conceptualization. **Sophie G. Groene:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition, Conceptualization. **Sylke J. Steggerda:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Resources, Project administration, Methodology, Investigation, Funding acquisition, Formal analysis, Conceptualization.

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Declaration of competing interest

The other authors have no conflicts of interest to disclose.

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