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First-trimester choroid-plexus-to-lateral-ventricle disproportion and prediction of subsequent ventriculomegaly

S. PRASAD[1,2], C. DI FABRIZIO[1,2], N. ELTAWEEL[3], E. KALAFAT[4,5] and A. KHALIL[1,2]

[1]*Fetal Medicine Unit, St George's University Hospitals NHS Foundation Trust, University of London, London, UK;* [2]*Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, UK;* [3]*Department of Obstetrics and Gynaecology, University Hospital of Coventry and Warwickshire, Coventry, UK;* [4]*Department of Obstetrics and Gynecology, School of Medicine, Koc University, Istanbul, Turkey;* [5]*Department of Statistics, Faculty of Arts and Sciences, Middle East Technical University, Ankara, Turkey*

KEYWORDS: choroid plexus; first trimester; lateral ventricle; prediction; pregnancy; ultrasound; ventriculomegaly

CONTRIBUTION

What are the novel findings of this work?
Ratios of fetal choroid plexus to lateral ventricle or head at 11 + 0 to 13 + 6 weeks' gestation are significantly lower in fetuses with ventriculomegaly diagnosed later in pregnancy compared with normal fetuses. The ratio of choroid plexus area to lateral ventricular area had an area under the receiver-operating-characteristics curve of 0.90 for prediction of severe ventriculomegaly and 0.84 for prediction of mild ventriculomegaly.

What are the clinical implications of this work?
Ultrasound assessment of ratios of fetal choroid plexus to lateral ventricle or head performed in the standard axial butterfly plane at 11 + 0 to 13 + 6 weeks' gestation can identify fetuses with ventriculomegaly diagnosed later in pregnancy. First-trimester prediction of ventriculomegaly using ratios of fetal choroid plexus to lateral ventricle appears promising.

ABSTRACT

Objective *Ventriculomegaly can be associated with long-term neurodevelopmental impairment. Prenatal diagnosis of ventriculomegaly is most commonly made at the routine second-trimester anomaly scan. The value of first-trimester ultrasound has expanded to early diagnosis and screening of fetal abnormalities. The objective of this study was to assess the predictive accuracy of first-trimester choroid-plexus-to-lateral-ventricle-or-head ratios for development of ventriculomegaly at a later gestational age.*

Methods *This was a case–control study of fetuses with isolated ventriculomegaly diagnosed after 16 weeks' gestation and a control group of normal fetuses (without ventriculomegaly). The exclusion criteria included aneuploidy, genetic syndrome and/or other brain abnormality. Stored two-dimensional first-trimester ultrasound images were analyzed blindly offline and fetal biometry was performed in the axial view of the fetal head. The ratios of choroid plexus area (PA) to lateral ventricular area (VA), choroid plexus length (PL) to lateral ventricular length (VL), choroid plexus diameter (PD) to lateral ventricular diameter (VD) and PA to biparietal diameter (BPD) were measured at 11 + 0 to 13 + 6 weeks' gestation. Intra- and interobserver variability of measurement of these fetal head biometric parameters at 11 + 0 to 13 + 6 weeks' gestation were assessed in 20 normal fetuses using intraclass correlation coefficients with 95% CI. The accuracy of first-trimester biometric measurements for prediction of ventriculomegaly was assessed using the area under the receiver-operating-characteristics curves (AUC).*

Results *The analysis included 683 singleton pregnancies, of which 102 fetuses were diagnosed with ventriculomegaly. Ventriculomegaly was mild in 86 (84.3%) cases and severe in the other 16 (15.7%). All first-trimester fetal choroid-plexus-to-lateral-ventricle/head ratios were significantly lower in cases with ventriculomegaly compared with controls ($P < 0.001$), with good inter- and intraobserver agreement (≥ 0.95) for the majority of the fetal head biometric parameters assessed. On adjusting for crown–rump length, optimism-adjusted AUC values obtained after cross-validation showed that both PL/VL ratio (AUC, 0.87 (95% CI, 0.73–0.98)) and PA/VA ratio (AUC, 0.90 (95% CI, 0.82–0.98)) had good predictive*

Correspondence to: Prof. A. Khalil, Fetal Medicine Unit, Department of Obstetrics and Gynaecology, St George's University Hospitals NHS Foundation Trust, Blackshaw Road, London SW17 0QT, UK (e-mail: akhalil@sgul.ac.uk)

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*accuracy for severe ventriculomegaly. The PA/BPD ratio (AUC, 0.73 (95% CI, 0.54–0.90)) had modest predictive ability, which was significantly lower compared with that of the PA/VA ratio and PL/VL ratio (*P = *0.003 and* P = *0.001, respectively). The predictive accuracy of PD/VD ratio was low with an AUC of 0.65 (95% CI, 0.47–0.84). Optimism-adjusted AUC values obtained after cross-validation showed that PA/VA ratio offered the highest predictive accuracy for mild ventriculomegaly with an AUC of 0.84 (95% CI, 0.79–0.89), followed by PL/VL ratio (AUC, 0.82 (95% CI, 0.76–0.88)), PA/BPD ratio (AUC, 0.76 (95% CI, 0.69–0.82)) and PD/VD ratio (AUC, 0.75 (95% CI, 0.67–0.81)). Calibration plots showed that both PA/VA and PL/VL ratios had good calibration.*

Conclusion *First-trimester prediction of ventriculomegaly using ratios of fetal choroid plexus to lateral ventricle/head appears promising. Future prospective studies are needed to validate the predictive accuracy of these ultrasound markers as a screening tool for ventriculomegaly.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Ventriculomegaly is a relatively common fetal abnormality with a reported prevalence of 0.3–1.5 per 1000 births, depending on gestational age at the time of the diagnosis[1]. Ventriculomegaly may be an initial presentation of fetal aneuploidy, infection or structural brain malformation and may be associated with variable long-term neurodevelopmental impairment depending on its severity. Currently, there is an emphasis on early detection of fetal anomalies in the first trimester using a standardized anatomical protocol, which includes examination of the fetal cranium. The standard sonographic plane at the level of the choroid plexus (butterfly sign) is examined to diagnose major lethal cranial abnormalities, such as alobar holoprosencephaly and acrania[2–7]. There are two major obstacles to first-trimester diagnosis of ventriculomegaly. First, there are no clear objective criteria for making the diagnosis and, second, most cases of ventriculomegaly manifest after the first trimester, so cannot be visualized at this early stage[8].

Ventriculomegaly in the first trimester has been described variably as dangling of the choroid plexus or a choroid plexus that does not touch the ventricular walls[9]. Manegold-Brauer *et al.*[10] evaluated ratios of choroid plexus area (PA) to lateral ventricular area (VA), choroid plexus length (PL) to lateral ventricular length (VL) and choroid plexus diameter (PD) to lateral ventricular diameter (VD) for objective diagnosis of ventriculomegaly at the first-trimester scan in their cohort of 17 fetuses. They reported that PA/VA, PL/VL and PD/VD ratios were significantly lower in fetuses with ventriculomegaly compared with normal fetuses. Unlike other non-lethal brain anomalies, such as posterior fossa malformations and corpus callosal anomalies, which require an examiner with expertise in multiplanar imaging for diagnosis, usually via the transvaginal route, the assessment for ventriculomegaly can be performed using basic scanning planes and techniques, with which sonographers are familiar.

The objective of this study was to assess the predictive performance of first-trimester ratios of choroid plexus to lateral ventricle or head for development of ventriculomegaly at a later gestational age.

METHODS

This was a retrospective case–control study of singleton pregnancies with isolated fetal ventriculomegaly diagnosed after 16 weeks' gestation at St George's University Hospital NHS Foundation Trust, London, UK, between 1995 and 2021, following an apparently normal first-trimester ultrasound scan. The control group consisted of a randomly selected set of uncomplicated singleton pregnancies resulting in a live birth of a neonate without a diagnosis of ventriculomegaly. We excluded multiple pregnancy, cases with other structural brain anomalies, cases for which first-trimester images were not available, confirmed cases of acquired ventriculomegaly and ventriculomegaly associated with aneuploidy or genetic syndrome.

Data on maternal characteristics, including maternal age, smoking status, parity, body mass index (BMI), crown–rump length (CRL), gestational age at examination and ultrasound findings throughout pregnancy were obtained from the Viewpoint database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH, Weßling, Germany). Gestational age was calculated based on the CRL measurement[11]. Offline analysis of stored two-dimensional ultrasound images in the Viewpoint database (ViewPoint 5.6.8.428; ViewPoint Bildverarbeitung GmbH) was performed by an operator blinded to the clinical diagnosis, and fetal biometry was performed in the axial view of the fetal head. Fetal biparietal diameter (BPD) and occipitofrontal diameter (OFD) were measured using the outer-to-outer method at the level of the choroid plexus. PA/VA, PL/VL and PD/VD ratios were measured at 11 + 0 to 13 + 6 weeks' gestation, as previously described[10] (Figure 1). The PA/BPD ratio was also measured[10]. For the PA/VA ratio, all areas were measured using the tracing method, and an average of two measurements was taken to minimize errors. For PD/VD and PL/VL ratios, measurements were obtained at the widest diameter and longest points, respectively. Ventriculomegaly was defined as atrial width ≥ 10 mm when measured at the level of the glomus of the choroid plexus, perpendicular to the ventricular cavity, with calipers positioned inside the echoes generated by the lateral walls[12]. Ventriculomegaly was classified further into mild when the atrial width was 10–15 mm and severe when it was ≥ 15 mm[1].

In 20 normal fetuses, the measurements were performed twice by the same researcher (S.P.) and by two researchers

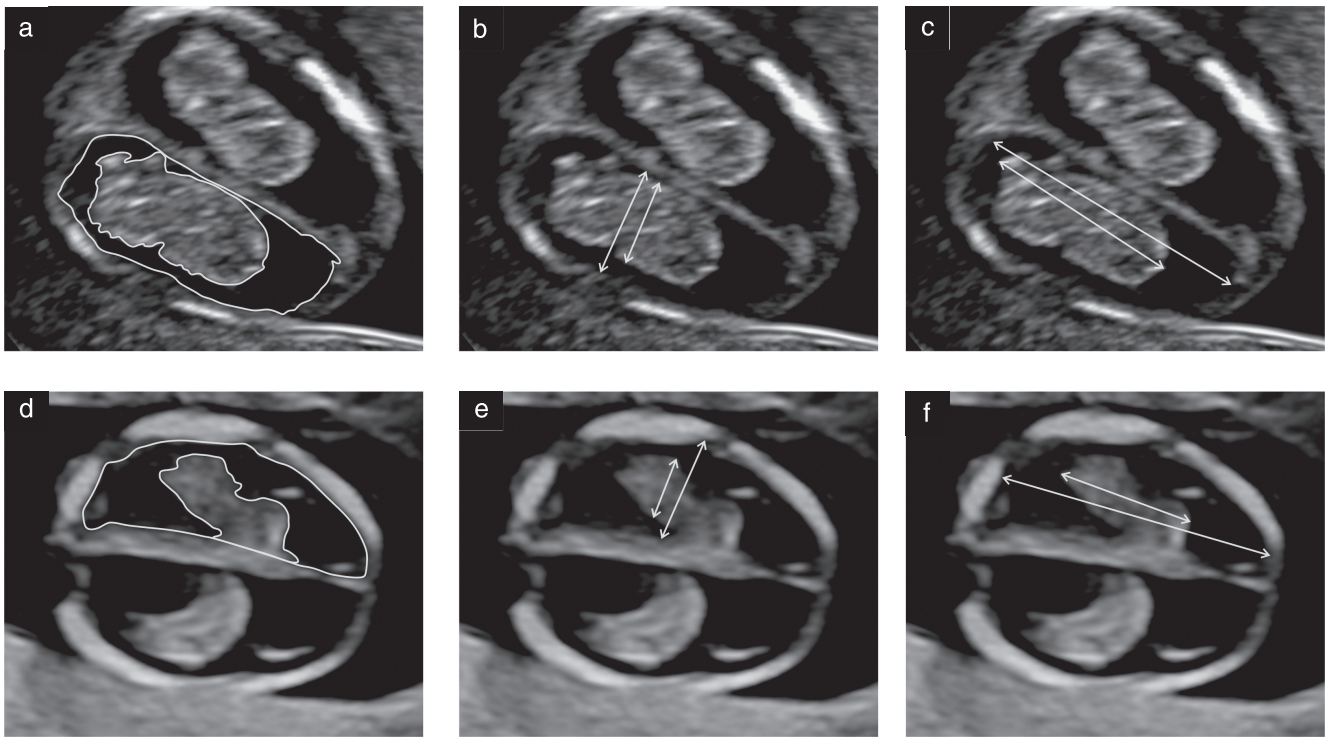

Figure 1 Two-dimensional axial view of brain at 11 + 0 to 13 + 6 weeks' gestation in normal fetus (a–c) and fetus diagnosed with severe ventriculomegaly at 21 weeks' gestation (d–f), demonstrating measurement of choroid plexus and lateral ventricular areas (a,d), choroid plexus and lateral ventricular diameters (b,e) and choroid plexus and lateral ventricular lengths (c,f).

(S.P. and C.D.F.) independently to assess the intra- and interobserver variability. The study involved retrospective review of patient data, so ethical approval was not needed.

Statistical analysis

Continuous variables are presented as median (interquartile range) and categorical variables are presented as *n* (%). Three-group comparisons (mild, severe and controls) were made using non-parametric hypothesis-testing methods with multiplicity correction. The accuracy of first-trimester biometric parameters for prediction of ventriculomegaly was assessed using optimism-adjusted area under the receiver-operating-characteristics curves (AUC). Optimism adjustment was performed with k-fold cross-validation.

We also constructed box-and-whiskers plots and calibration plots for the predictive markers. Intra- and interobserver variability was assessed using intraclass correlation coefficients with 95% CI. Model calibration was assessed visually using calibration curves. Statistical analysis was performed using R for Windows (version 4.1.2; https://www.r-project.org/).

RESULTS

Baseline characteristics and cranial measurements

We included 683 singleton pregnancies in this study, of which 102 fetuses were diagnosed with ventriculomegaly. Ventriculomegaly was mild in 86 (84.3%) cases and severe in the other 16 (15.7%). The baseline characteristics of the study population are presented in Table 1. There was no significant difference between the study groups with respect to maternal characteristics, including maternal age ($P = 0.314$), ethnicity ($P = 0.564$), BMI ($P = 0.283$) and smoking status ($P = 0.110$). The CRL ($P = 0.491$), BPD ($P = 0.550$) and OFD ($P = 0.765$) were not significantly different in the three groups at the time of first-trimester ultrasound examination. Cases of severe ventriculomegaly are described in Table S1.

When compared with unaffected fetuses in the control group, fetuses with a subsequent diagnosis of ventriculomegaly (mild or severe) had a significantly shorter first-trimester PL ($P < 0.001$), smaller PA ($P < 0.001$), larger VA ($P < 0.001$) and larger VD ($P < 0.001$) (Table 1). Although the VL was slightly greater in fetuses with severe and mild ventriculomegaly ($P = 0.051$) compared with unaffected fetuses, this difference did not reach statistical significance (Table 1). There was no significant difference in the PD between fetuses with ventriculomegaly and unaffected fetuses. All ratios of fetal choroid plexus to lateral ventricle/head were significantly lower in fetuses with severe and those with mild ventriculomegaly later in pregnancy compared with unaffected fetuses, including median PL/VL ratio (0.6 and 0.7 *vs* 0.8; $P < 0.001$), PA/VA ratio (0.5 and 0.5 *vs* 0.7; $P < 0.001$), PD/VD ratio (0.7 and 0.7 *vs* 0.8; $P < 0.001$) and PA/BPD ratio (2.6 and 2.7 *vs* 3.2; $P < 0.001$) (Table 1, Figure 2).

Table 1 Baseline characteristics and ultrasound measurements of cases with ventriculomegaly, according to severity (mild *vs* severe), compared with controls

Variable	*Control* (n = *581*)	*Mild ventriculomegaly* (n = *86*)	*Severe ventriculomegaly* (n = *16*)	P*
Maternal age (years)	32.0 (29.0–35.0)	30.5 (27.2–36.0)	34.0 (31.5–36.0)	0.314
Maternal BMI (kg/m^2)	23.4 (21.3–26.6)	23.0 (20.6–25.8)	24.2 (22.9–26.1)	0.283
Maternal ethnicity†				0.564
White	411/578 (71.1)	51/82 (62.2)	11/14 (78.6)	
Afro-Caribbean	65/578 (11.2)	7/82 (8.5)	1/14 (7.1)	
South Asian	62/578 (10.7)	15/82 (18.3)	2/14 (14.3)	
East Asian	19/578 (3.3)	4/82 (4.9)	0/14 (0)	
Mixed	19/578 (3.3)	5/82 (6.1)	0/14 (0)	
Other	2/578 (0.3)	0/82 (0)	0/14 (0)	
Smoker	20 (3.4)	3 (3.5)	2 (12.5)	0.110
CRL (mm)	62.9 (58.0–68.2)	62.0 (56.0–70.6)	65.8 (59.8–72.4)	0.491
BPD (mm)	21.4 (19.8–23.1)	21.6 (19.7–23.4)	22.3 (20.4–23.9)	0.550
OFD (mm)	24.0 (22.0–26.2)	24.0 (22.0–26.0)	24.1 (23.4–25.9)	0.765
PL (mm)	13.5 (12.4–14.6)	12.4 (10.8–13.6)	11.5 (10.7–12.6)	< 0.001
VL (mm)	17.6 (16.1–19.7)	18.0 (16.6–20.1)	19.4 (18.1–20.4)	0.051
PA (mm^2)	67.0 (57.3–77.3)	60.9 (50.0–67.8)	58.1 (42.0–70.5)	< 0.001
VA (mm^2)	102.3 (88.9–121.4)	113.0 (93.0–137.3)	130.8 (112.7–153.8)	< 0.001
PD (mm)	5.6 (5.1–6.1)	5.5 (4.9–6.0)	5.6 (5.3–6.1)	0.825
VD (mm)	7.3 (6.6–8.0)	8.0 (7.1–9.0)	8.1 (7.3–9.1)	< 0.001
PL/VL ratio	0.77 (0.72–0.81)	0.67 (0.60–0.74)	0.63 (0.57–0.68)	< 0.001
PA/VA ratio	0.66 (0.58–0.74)	0.53 (0.46–0.60)	0.47 (0.41–0.56)	< 0.001
PD/VD ratio	0.77 (0.72–0.82)	0.69 (0.64–0.73)	0.70 (0.66–0.76)	< 0.001
PA/BPD ratio	3.15 (2.81–3.50)	2.73 (2.45–2.97)	2.62 (2.20–2.94)	< 0.001

Data are given as median (interquartile range), *n*/*N* (%) or *n* (%). *Three-group comparison with multiplicity correction. †Maternal ethnicity data available for 674 participants. BMI, body mass index; BPD, biparietal diameter; CRL, crown–rump length; OFD, occipito-frontal diameter; PA, choroid plexus area; PD, choroid plexus diameter; PL, choroid plexus length; VA, lateral ventricular area; VD, lateral ventricular diameter; VL, lateral ventricular length.

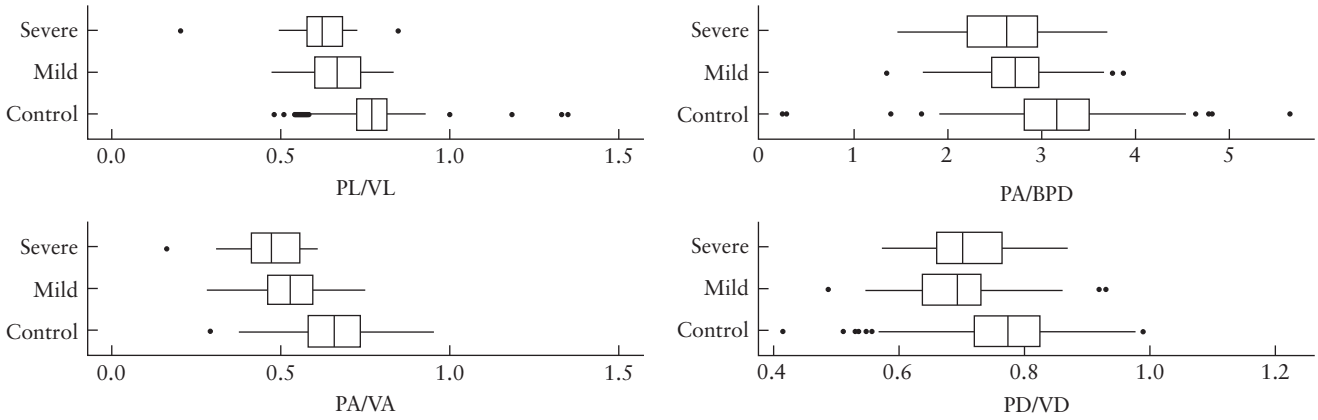

Figure 2 Box-and-whiskers plots of ratios of choroid plexus to lateral ventricle or head of fetuses subsequently diagnosed with severe or mild ventriculomegaly compared with controls. BPD, biparietal diameter; PA, choroid plexus area; PD, choroid plexus diameter; PL, choroid plexus length; VA, lateral ventricular area; VD, lateral ventricular diameter; VL, lateral ventricular length.

Inter- and intraobserver agreement was ≥ 0.95 for the majority of the fetal head biometric parameters assessed (Table 2).

Prediction models

Four ratios were tested (PL/VL, PA/VA, PD/VD, PA/BPD) for their predictive accuracy in the first trimester for subsequent development of severe ventriculomegaly. The CRL measurements were added to all models to account for gestational age at the time of measurement. Optimism-adjusted AUC values obtained after cross-validation showed that the PA/VA ratio offered the highest predictive accuracy with an AUC of 0.90 (95% CI, 0.82–0.98), followed by PL/VL ratio (AUC, 0.87 (95% CI, 0.73–0.98)), PA/BPD ratio (AUC, 0.73 (95% CI, 0.54–0.90)) and PD/VD ratio (AUC, 0.65 (95% CI, 0.47–0.84)) (Figure 3). The predictive ability

Table 2 Intraclass correlation coefficients (ICC) with 95% CI for cranial measurements on first-trimester ultrasound scan in 20 normal fetuses

	ICC (95% CI)	
Fetal biometric parameter	*Intraobserver*	*Interobserver*
Choroid plexus length	0.98 (0.95–0.99)	0.95 (0.87–0.98)
Lateral ventricular length	0.97 (0.94–0.99)	0.98 (0.94–0.99)
Choroid plexus area	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Lateral ventricular area	0.99 (0.99–1.00)	0.99 (0.99–1.00)
Choroid plexus diameter	0.96 (0.89–0.98)	0.77 (0.52–0.90)
Lateral ventricular diameter	0.99 (0.97–0.99)	0.94 (0.85–0.97)

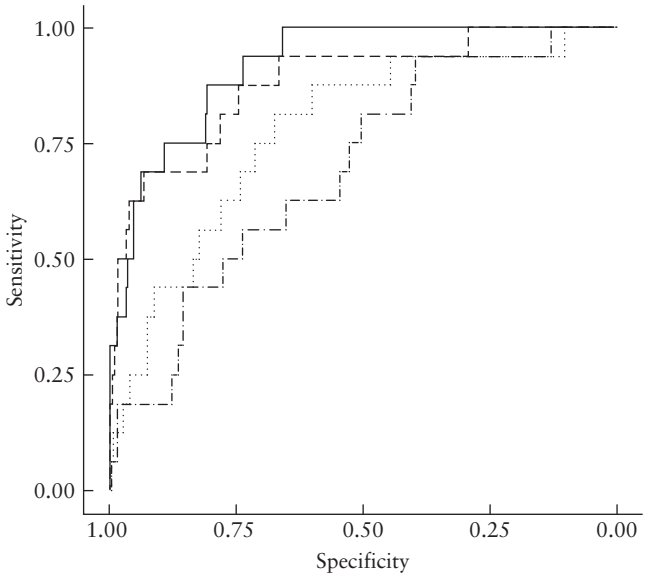

Figure 3 Receiver-operating-characteristics (ROC) curves for prediction of severe ventriculomegaly using ratios of choroid plexus length to lateral ventricular length (optimism-adjusted area under ROC curve (AUC), 0.866 (95% CI, 0.734–0.977)) (– – -), choroid plexus area to lateral ventricular area (AUC, 0.903 (95% CI, 0.819–0.983)) (——), choroid plexus area to biparietal diameter (AUC, 0.728 (95% CI, 0.536–0.900)) (·····) and choroid plexus diameter to lateral ventricular diameter (AUC, 0.650 (95% CI, 0.465–0.838)) (·–·–).

of the PA/BPD ratio was significantly lower compared with that of the PA/VA ratio and PL/VL ratio ($P = 0.003$ and $P = 0.001$, respectively).

The predictive performance of the models for severe ventriculomegaly was tested at their Youden index cut-off values. PA/VA ratio and PL/VL ratio had positive likelihood ratios of 6.45 and 5.96 and positive predictive values of 11.1% and 8.6%, respectively (Table 3). The negative predictive value of all ratios was high (≥ 99%), owing to the rarity of the outcome (Table 3). According to these performance metrics, the number needed to perform an additional scan to identify a case of severe ventriculomegaly is eight for PA/VA ratio and 12 for PL/VL ratio, and the modalities would detect 80.7% and 74.5% of all cases, respectively. The optimal cut-offs for PA/VA ratio and PL/VL ratio were 0.58 and 0.70, respectively. Calibration plots also showed that

Table 3 Predictive accuracy of first-trimester ultrasound parameters for subsequent development of ventriculomegaly at their Youden index cut-offs

	Mild ventriculomegaly	*Severe ventriculomegaly*
PA/BPD ratio		
Sensitivity	0.76 (0.73–0.80)	0.67 (0.63–0.71)
Specificity	0.73 (0.62–0.82)	0.81 (0.54–0.96)
NPV	0.95 (0.92–0.96)	0.99 (0.98–1.00)
PPV	0.31 (0.25–0.38)	0.06 (0.03–0.11)
LR+	2.87 (2.02–4.09)	3.60 (1.29–9.99)
LR−	0.31 (0.25–0.38)	0.40 (0.31–0.52)
PA/VA ratio		
Sensitivity	0.80 (0.77–0.83)	0.81 (0.77–0.84)
Specificity	0.68 (0.57–0.78)	0.87 (0.62–0.98)
NPV	0.94 (0.92–0.96)	0.99 (0.98–1.00)
PPV	0.34 (0.27–0.42)	0.11 (0.06–0.18)
LR+	2.57 (1.87–3.52)	6.45 (1.76–23.62)
LR−	0.28 (0.22–0.35)	0.22 (0.17–0.28)
PL/VL ratio		
Sensitivity	0.76 (0.72–0.79)	0.75 (0.71–0.78)
Specificity	0.77 (0.67–0.86)	0.87 (0.62–0.98)
NPV	0.95 (0.93–0.97)	1.00 (0.98–1.00)
PPV	0.32 (0.26–0.39)	0.09 (0.05–0.14)
LR+	3.44 (2.30–5.13)	5.96 (1.63–21.80)
LR−	0.30 (0.25–0.36)	0.29 (0.23–0.38)
PD/VD ratio		
Sensitivity	0.76 (0.73–0.80)	0.40 (0.36–0.44)
Specificity	0.73 (0.62–0.82)	0.87 (0.62–0.98)
NPV	0.95 (0.92–0.96)	0.99 (0.97–1.00)
PPV	0.31 (0.25–0.38)	0.04 (0.02–0.06)
LR+	2.87 (2.02–4.09)	3.19 (0.87–11.69)
LR−	0.31 (0.25–0.38)	0.69 (0.56–0.84)

Values in parentheses are 95% CI. BPD, biparietal diameter; LR−, negative likelihood ratio; LR+, positive likelihood ratio; NPV, negative predictive value; PA, choroid plexus area; PD, choroid plexus diameter; PL, choroid plexus length; PPV, positive predictive value; VA, lateral ventricular area; VD, lateral ventricular diameter; VL, lateral ventricular length.

both models (PA/VA ratio and PL/VL ratio) had good calibration (Figure S1).

The same four ratios were tested (PL/VL, PA/VA, PD/VD, PA/BPD) for their predictive accuracy in the first trimester for subsequent development of mild ventriculomegaly. Optimism-adjusted AUC values obtained after cross-validation showed that PA/VA ratio offered the highest predictive accuracy with an AUC of 0.84 (95% CI, 0.79–0.89), followed by PL/VL ratio (AUC, 0.82 (95% CI, 0.76–0.88)), PA/BPD ratio (AUC, 0.76 (95% CI, 0.69–0.82)) and PD/VD ratio (AUC, 0.75 (95% CI, 0.67–0.81)) (Figure 4). Calibration plots showed that both PA/VA and PL/VL ratios had good calibration (Figure S2).

The predictive performance of models for mild ventriculomegaly was also tested at their Youden index cut-off values. PA/VA ratio and PL/VL ratio had positive likelihood ratios of 2.57 and 3.44, respectively, and positive predictive values of 34.0% and 32.0%, respectively (Table 3). The negative predictive value of all ratios was very high (94–95%), owing to the low incidence of the outcome in this cohort (Table 3).

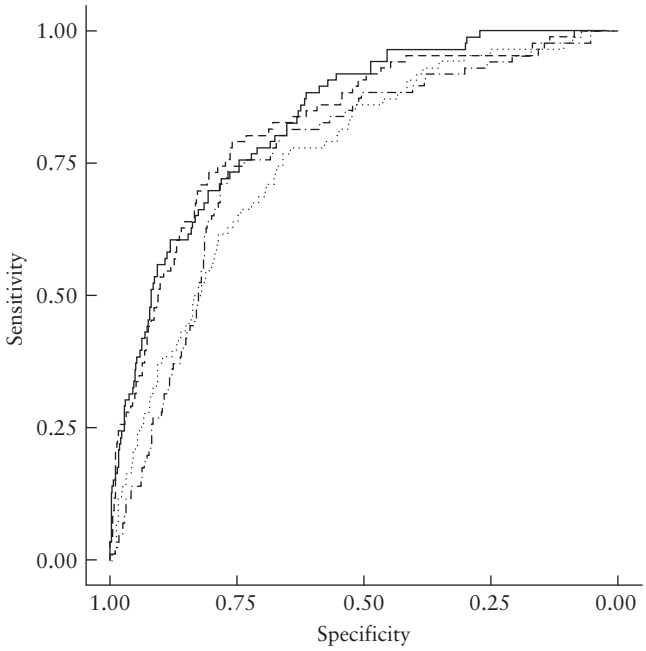

Figure 4 Receiver-operating-characteristics (ROC) curves for prediction of mild ventriculomegaly using ratios of choroid plexus length to lateral ventricular length (optimism-adjusted area under ROC curve (AUC), 0.823 (95% CI, 0.761–0.881)) (– – -), choroid plexus area to lateral ventricular area (AUC, 0.837 (95% CI, 0.787–0.887)) (——), choroid plexus area to biparietal diameter (AUC, 0.756 (95% CI, 0.687–0.815)) (·····) and choroid plexus diameter to lateral ventricular diameter (AUC, 0.746 (95% CI, 0.672–0.808)) (–·–).

DISCUSSION

Summary of key findings

Fetuses with a subsequent diagnosis of ventriculomegaly had significantly lower PL and PA, greater VD and VA, and lower PL/VL, PA/VA, PD/VD and PA/BPD ratios, compared with unaffected fetuses. Of these, PA/VA and PL/VL ratios were good predictors of severe ventriculomegaly with AUCs of 0.90 and 0.87, respectively. For mild ventriculomegaly, AUC values for PA/VA and PL/VL ratios were 0.84 and 0.82, respectively.

Interpretation of study findings and comparison with existing literature

This study provides objective evidence that first-trimester choroid-plexus-to-lateral-ventricle/head ratios are significantly lower in fetuses subsequently diagnosed with ventriculomegaly, and can be used to identify fetuses at risk. These pregnancies may benefit from a follow-up ultrasound scan at 16 weeks' gestation to facilitate earlier diagnosis. These ratios were initially described by Manegold-Brauer *et al.*[10] in their cohort of 17 fetuses with ventriculomegaly in the first trimester, in which lower PA/VA, PL/VL and PD/VD ratios were identified in affected fetuses. In their cohort, PA/VA (5th percentile, 0.36–0.48), PL/VL (5th percentile, 0.56–0.66) and PD/VD (5th percentile, 0.54–0.60) ratios were indicative of ventriculomegaly in the first trimester with a sensitivity of 94.1%, 94.1% and 82.4%, respectively. Most of those pregnancies were terminated in the first trimester due to aneuploidy and associated brain malformation; therefore, the predictive capability of these ratios for later development of ventriculomegaly could not be assessed. In this study, we excluded fetuses with aneuploidy and/or associated brain malformation, as they are potential confounders for fetal cranial biometry. Loureiro *et al.*[13] have reported previously that, in fetuses with trisomy 13 or 18, the PA/VA ratio is lower than in euploid fetuses. However, they did not observe any significant difference in the PA/VA ratio between trisomy-21 and euploid fetuses. In the study of Manegold-Brauer *et al.*[10], 31% (4/13) of karyotyped fetuses had aneuploidy. Similarly, measurement of ratios of choroid plexus to lateral ventricle/head can be misleading in cases with malformations such as open spina bifida and alobar holoprosencephaly[14–16], which were excluded from this study.

The incidence of neurodevelopmental impairment can be as high as 50% in cases of severe ventriculomegaly, while up to 10% of mild ventriculomegaly cases have variable degrees of neurodevelopmental impairment[17,18]. In this study, we demonstrate good predictive accuracy of PA/VA and PL/VL ratios for development of both mild and severe ventriculomegaly at a later gestational age.

We demonstrate good inter- and intraobserver measurement agreement (≥ 0.94) for all parameters, with the exception of PD (interobserver intraclass correlation coefficient, 0.77 (0.52–0.90)). This may be attributed to the clinical finding that, out of the three measurements (length, area and diameter), the lateral measurements (such as PD and VD) are affected least in the early evolution of ventriculomegaly. Manegold-Brauer *et al.*[10] also noted lower interobserver agreement for the PD/VD ratio (0.63 (95% CI, 0.34–0.81)).

Clinical and research implications

Ultrasound assessment of ratios of fetal choroid plexus to lateral ventricle/head can be performed in the standard axial butterfly plane and does not require specialist skills or a high-resolution ultrasound machine. We propose that objective measurements such as PA/VA and PL/VL ratios should be obtained at the first-trimester scan and, if abnormal (above a predefined threshold), women should be offered an early anatomical scan (around 16 weeks' gestation), rather than the usual midtrimester scan at 20–22 weeks' gestation. An ultrasound scan at 16 weeks' gestation would provide an opportunity to make an early diagnosis of ventriculomegaly and identify any associated brain malformations, as well as extracranial abnormalities, allowing early discussion of further management options. Moreover, in cases with abnormal PA/VA and PL/VL ratios, a more detailed assessment of cranial anatomy may be offered in the first trimester via the transvaginal route and employing three-dimensional multiplanar imaging techniques[5].

These ratios may also be used to provide reassurance to women with a previous pregnancy affected by ventriculomegaly, with the caveat that some cases manifest only at a later gestational age. Normal first-trimester ratios of choroid plexus to lateral ventricle/head may be reassuring to these patients.

Strengths and limitations

In this study, we have established the predictive accuracy of first-trimester choroid-plexus-to-lateral-ventricle/head ratios for the development of ventriculomegaly at a later gestational age. We report the findings according to severity of ventriculomegaly. We included cases with isolated ventriculomegaly only and excluded cases with acquired/genetic or associated brain malformations to avoid potential confounding. We employed blinded offline image analysis and confirmed minimal inter- and intraobserver variation.

The study limitations include the small number of severe ventriculomegaly cases, its retrospective nature with its inherent risk of bias and its case–control design with a relatively high prevalence of fetuses with ventriculomegaly.

Conclusions

First-trimester choroid-plexus-to-lateral-ventricle/head ratios, specifically PA/VA and PL/VL ratios, are promising tools for prediction of ventriculomegaly. External validation of these findings and prospective studies are warranted.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Figures S1 and S2 Calibration plots for first-trimester prediction models for subsequent diagnosis of severe (Figure S1) and mild (Figure S2) ventriculomegaly. BPD, biparietal diameter; PA, choroid plexus area; PD, choroid plexus diameter; PL, choroid plexus length; VA, lateral ventricular area; VD, lateral ventricular diameter; VL, lateral ventricular length.

Table S1 Description of cases of severe ventriculomegaly