OBSTETRICS

Diagnostic accuracy of fetal choroid plexus length to head biometry ratio at 11 to 13 weeks for open spina bifida

Erkan Kalafat, MD; Lei Ting, MD; Basky Thilaganathan, MD, PhD; Aris T. Papageorghiou, MD; Asma Khalil, MD

BACKGROUND: Open spina bifida is a major congenital anomaly with an estimated incidence of <1 in 1000. The diagnosis of open spina bifida is usually made during the second trimester, but first-trimester detection rate of spina bifida is increasingly reported. Recently, the mean choroid plexus length to occipitofrontal diameter ratio was reported to be increased in fetuses with open spina bifida. The ratio reflects the so-called dry brain effect caused by cerebrospinal fluid leakage and expansion of the choroid plexus into the lateral ventricles. The mean choroid plexus length to occipitofrontal diameter ratio appears to be a promising tool for early detection of open spina bifida, but its diagnostic accuracy is yet to be determined in a large cohort.

OBJECTIVE: This study aimed to assess the predictive accuracy of mean choroid plexus length to occipitofrontal diameter ratio recorded at 11 to 13 weeks' gestation for the detection of open spina bifida.

STUDY DESIGN: This was a retrospective cohort of patients treated in a tertiary referral center. Fetuses in which open spina bifida was detected at 16 to 24 weeks' gestation and normal fetuses were included in the cohort. Biparietal diameter and occipitofrontal diameter were measured in an axial view. The length of choroid plexus was measured along its longest diameter in the same plane. Ultrasound images were examined offline, and the operator was blinded to the clinical diagnosis. The predictive accuracy was evaluated using the area under the curve and positive and negative predictive values.

RESULTS: We included 3300 pregnant women, of whom 24 (0.73%) had the fetuses affected by open spina bifida. The area under the curve values were 0.921 for mean choroid plexus length to occipitofrontal diameter ratio and 0.933 for its multiple of the median. Mean choroid plexus length to biparietal diameter ratio indicated similar results, with area under the curve values of 0.928 and 0.931 for raw ratio and multiple of the median ratio models, respectively. The optimal cutoffs of the mean choroid plexus to occipitofrontal diameter ratio and multiple of the median ratios were 0.662 and 1.263, respectively. The optimal mean choroid plexus to occipitofrontal diameter ratio and multiple of the median ratio cutoffs provided a positive predictive value of 90.9% and a negative predictive value of 99.6%. The number of affected spinal segments was significantly higher in fetuses with a ratio above 0.662 (P=.022).

CONCLUSION: The mean choroid plexus length to occipitofrontal diameter ratio at 11 to 13 weeks' gestation is a promising tool for the prenatal detection of open spina bifida.

Key words: biparietal diameter, choroid plexus, first trimester, occipitofrontal diameter, prediction, spina bifida

Introduction

Open spina bifida (OSB) is a major congenital anomaly with an estimated incidence of <1 in 1000.[1–3] The diagnosis of OSB is usually made during the second trimester, but first-trimester detection rate of spina bifida is increasingly reported. Syngelaki et al[4] have reported that first-trimester diagnosis was achieved in approximately 60% of OSB cases with the use of first-trimester ultrasound markers.

Intracranial translucency is a promising first-trimester marker associated with high detection rates when employed by fetal medicine experts.[5–7] Other markers such as biparietal diameter and nonvisualization of the choroid plexus (CP) of the fourth ventricle (also known as the crush sign) have been proposed, and varying detection rates have been reported for these markers in the detection of OSB.[8–12]

More recently, Chaoui et al[13] have reported that the mean CP length to occipitofrontal diameter (OFD) ratio is increased in fetuses with OSB. The ratio reflects the so-called dry brain effect caused by cerebrospinal fluid leakage and expansion of the CP into the lateral ventricles. They reported that 88.2% of fetuses with OSB had mean CP length to OFD ratios above 2 standard deviations of expected mean. Moreover, they reported good reproducibility and absence of systemic error for measurements of the ratio. The ease of measurement and utilization of standard scanning windows are proposed advantages of this marker. The mean CP length to OFD ratio appears to be a promising tool for early detection of OSB, but it has not been externally validated, and there is a need for the diagnostic accuracy to be determined in a large cohort.

This study aimed to assess the diagnostic accuracy of mean CP length to fetal head biometry ratio recorded at 11 to 13 weeks' gestation for the detection of OSB. The second aim was to investigate whether other fetal brain biometry measures outperform this ratio.

Methods

This was a retrospective study of fetuses in which OSB was detected by ultrasound scan at 16 to 24 weeks' gestation, following an apparently normal ultrasound at 11 to 13 weeks in the Fetal Medicine Unit at St George's Hospital. Cases were identified by searching the ViewPoint database (ViewPoint 5.6.8.428, ViewPoint Bildverarbeitung

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AJOG at a Glance

Why was the study conducted?

We aimed to detect fetuses with open spina bifida using head biometry measurements obtained between 11 and 13 weeks' gestation.

Key findings

Choroid plexus (CP) to occipitofrontal diameter (OFD) ratio was a simple measure and could detect and rule out open spina bifida cases with high positive and negative predictive values.

What does this add to what is known?

Our study indicates clinically useful cutoffs of CP to OFD ratio, Z-score, and multiple of the median values. A calculator of the risk estimates is also provided. The ratio correlated with the number of affected segments.

GmbH, Weßling, Germany) for scans performed between 2000 and 2018. A control group was selected from the same database and verified by absence of a postnatal diagnosis of OSB. We collected data on maternal characteristics; crown−rump length (CRL), gestational age, and any structural malformations at the first-trimester scan; invasive procedures; karyotype; and second-trimester ultrasound examination findings. The recorded maternal characteristics included maternal age in years, parity, smoking status during pregnancy, and method of conception. Maternal weight and height were measured at the time of first-trimester screening and body mass index (BMI) calculated. Data on pregnancy outcomes were collected from hospital maternity records or the women's general medical practitioners. For pregnancies in which fetuses were affected with OSB, the presence of Arnold−Chiari malformation and number of affected segments were also ascertained from second-trimester scans. All women with fetuses with OSB who continued with their pregnancy had their birth at St George's Hospital, and infants underwent postnatal surgical repair by the pediatric neurosurgical team.

We included in the analysis only those cases with isolated OSB and no associated aneuploidy or other major anomalies. Images were examined offline by 1 of the authors who was blinded to the clinical diagnosis and outcome of pregnancies. Biparietal diameter (BPD) and OFD were measured on an axial view of the fetal head in a plane showing both CPs and the lateral ventricle, and calipers were placed on the outer borders of the skull (outer-outer). The length of the CPs was measured in the anteroposterior direction along their longest diameter with the same technique reported by Chaoui et al[13] (Figure 1); the mean of the 2 diameters was then used. Cases in which spina bifida was detected at the 11 to 13 weeks' scan were excluded because it would have interfered with the blinding, possibly creating bias in BPD, OFD, and CP measurements. The control group consisted of low-risk, uncomplicated singleton pregnancies that resulted in the live birth of a phenotypically normal neonate. In the control group, any pregnancies resulting in fetal demise or in which the fetus had a structural abnormality, aneuploidy, or genetic syndrome were excluded.

This study included retrospective review of available data and was exempt from ethical approval.

Statistical analysis

Continuous variables were presented as median and interquartile ranges or mean and standard deviation, depending on the distribution assumptions. Categorical variables were presented as number and percentage of the total. Group comparisons of continuous and categorical variables were made using the Mann-Whitney U and chi-square tests where appropriate. Permutation test was used for group comparison with small numbers ($n<10$). In such cases, parametric and nonparametric hypothesis testing methods are likely to be underpowered. Multiples of the median (MoMs) were calculated by conditioning the observed value on expected median values derived from linear models. The linear regression models were built using the population of fetuses without spina bifida (Supplemental Figure 1). Z-scores were calculated using prediction equations reported by Chaoui et al[13] for comparison with raw values and MoM ratios. The overall accuracy of each variable was tested using the receiver operating characteristics (ROC) curves, and area under the curve (AUC) values were compared using the De Long test. Variables with the highest AUC values were subject to diagnostic accuracy testing. Binomial regression analyses with logit link functions were used to obtain variable coefficients. Details of the analysis are available online in the supplemental statistical appendix. Statistical analyses were performed using R for Windows (version 3.5.2) statistical computing software.

Results

We included 3300 pregnant women, of whom 24 (0.73%) had the fetuses affected by OSB. There were no significant differences between women regarding maternal characteristics, including maternal age ($P=.685$), BMI ($P=.694$), smoking status ($P=.459$), and conception by means of assisted reproduction ($P=.858$) (Table 1). The scatter plots of OFD, BPD, and mean CP length in relation to the CRL measurements and associated regression equations can be found in Supplemental Figure 1.

Fetuses with OSB had significantly smaller OFD (median, 22.4 vs 23.9 mm; $P=.005$) and BPD (median, 19.7 vs 21.3 mm; $P<.001$) but longer mean CP length measurements (median, 14.4 vs 12.5 mm; $P<.001$) than unaffected fetuses (Table 1). The MoM-corrected values of OFD, BPD, and CP length showed similar results ($P=.001$, $<.001$ and $<.001$, respectively) (Table 1). Fetuses with OSB had a significantly higher mean CP length to OFD and BPD ratio than fetuses without OSB (median, 0.64

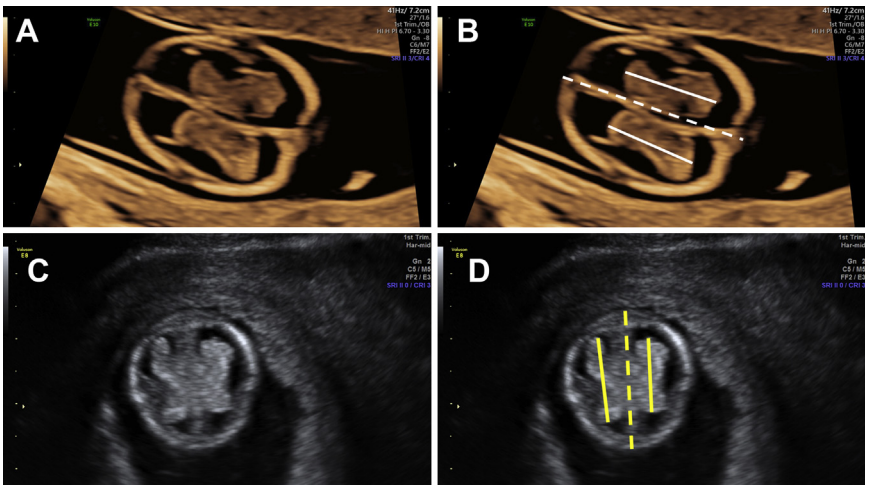
vs 0.52; $P<.001$ and median, 0.74 vs 0.58; $P<.001$ for OFD and BPD ratios, respectively). The MoM ratios of the same variables were also significantly higher in fetuses with OSB than controls (median, 1.22 vs 1.00; $P<.001$ and median, 1.25 vs 1.00; $P<.001$ for mean CP length to OFD and mean CP length to BPD MoM ratios, respectively) (Table 1). The median CP length and OFD ratio Z-scores of fetuses with OSB were also significantly higher than unaffected fetuses (median, 2.54 vs −0.53; $P<.001$).

The AUC values of each variable for predicting OSB and associated ROC curves are presented in Supplemental Table 1 and Supplemental Figure 2. The highest AUC values were provided by mean CP length to OFD ratio and CP length to BPD ratio models, MoM-corrected counterparts, and the mean CP length and OFD ratio Z-score (Supplemental Figure 2 and Supplemental Table 1). The AUC values were 0.921 for mean CP length to OFD ratio and 0.933 for its MoM, with no significant improvement when MoM correction was applied ($P=.101$) (Figure 2). Mean CP length to BPD ratio indicated similar results, with AUC values of 0.928 and 0.931 for raw ratio and MoM ratio models, respectively. Again, there was no significant increase in AUC values with MoM correction ($P=.379$). Finally, the AUC value of mean CP length to OFD ratio Z-score was 0.939 with no significant improvement in prediction compared with raw ratio values ($P=.128$). The ratio values provided consistently higher AUC values compared with its individual components alone (Supplemental Figure 2 and Supplemental Table 2).

The diagnostic accuracy of mean CP length and OFD ratio, MoM ratio, and ratio Z-score variables were assessed with regression modeling. The optimal cutoffs of the raw ratio, MoM ratio, and ratio Z-score were 0.662, 1.263, and 3.03, respectively (Table 2). The optimal raw ratio and MoM ratio cutoffs provided a positive predictive value of 90.9% (95% confidence interval, 57.1%−98.7%) and a negative predictive value of 99.6% (99.4%−99.7%) for diagnosing OSB along with significant accuracy gains compared with no information rate ($P=.033$). Further adjusting positive and negative predictive values according to the expected population prevalence resulted in a decrease of positive predictive value down to 64.0% (Table 2). The likelihood ratios were 234.0, 341.2, 682.5, and 1365.0 for the cutoffs of 0.636, 0.644, 0.656, and 0.662, respectively. No model showed adequate goodness-of-fit according to the Hosmer-Lemeshow test ($P<.001$ for all) because of extremely low event probability. A calculator for estimating the risk of individual patients has been provided (Appendix). The clinicians can calculate the risk of OSB and check the corresponding accuracy measures from Supplemental Table 3.

We also compared the ultrasound features observed during the second-trimester scan in fetuses with OSB above and below the proposed optimal cutoffs. Arnold-Chiari malformation later developed in all cases (10/10) with a ratio above the cutoffs, whereas the incidence was 85.7% (12/14) in fetuses with a ratio below these cutoffs (Supplemental Table 4). Furthermore, the number of affected spinal segments was significantly higher in fetuses with a ratio above 0.662 than fetuses with a ratio below 0.662 (median, 5 segments; interquartile range, 5−5 segments vs median, 3 segments; interquartile range, 3−5 segments, respectively; $P=.022$, approximate general independence test) (Figure 3). The number of fetuses with talipes was higher in the abnormal ratio group than fetuses with a normal ratio (40.0% vs 14.3%, $P=.151$) but the difference did not reach statistical significance level. The number of fetuses with ventriculomegaly was similar between the 2 groups (60.0% vs 57.1%, $P=.887$).

FIGURE 1
Axial views of the fetal head at 11−13 weeks' gestation and the measurement technique



A, B, Axial views of the fetal head at 11−13 weeks' gestation in an unaffected fetus and (C, D) a fetus with open spina bifida. Measurements were performed at level of transventricular plane, with both CPs visualized. OFD and longest diameters of left and right CPs were measured (B, D). The fetus with open spina bifida has long CPs in comparison with the OFD when compared with the unaffected fetus.

CP, choroid plexus; *OFD*, occipitofrontal diameter.

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Comment

Principal findings

Fetuses with OSB had a significantly smaller OFD and BPD, longer mean CP length, and higher mean CP length to OFD or BPD ratios than fetuses without OSB. The optimal mean CP length to OFD ratio had a positive predictive value of 90.9%, negative predictive value of 99.6%, and positive likelihood ratio of

TABLE 1
Maternal characteristics and first-trimester ultrasound findings in pregnancies with and without open spina bifida

Maternal characteristics	Without open spina bifida (n=3276)	With open spina bifida (n=24)	*P* value
Maternal age, y	32.0 (28.0–35.0)	32.5 (26.0–35.2)	.685
Body mass index, kg/m^2	24.4 (21.8–28.0)	23.9 (22.0–26.3)	.694
Assisted reproduction conception	88 (0.3)	0 (0.0)	.858
Smoker during pregnancy	182 (0.6)	0 (0.0)	.459
Ultrasound findings			
Crown–rump length, mm	62.7 (57.1–69.0)	59.6 (55.5–66.5)	.252
Occipitofrontal diameter, mm	23.9 (21.8–26.2)	22.4 (20.0–23.8)	.005
Occipitofrontal diameter, MoM	1.00 (0.95–1.05)	0.95 (0.90–0.99)	.001
Biparietal diameter, mm	21.3 (19.7–23.0)	19.7 (18.8–20.2)	<.001
Biparietal diameter, MoM	1.0 (0.96–1.03)	0.95 (0.91–0.98)	<.001
Mean choroid plexus length, mm	12.5 (11.3–13.6)	14.4 (13.4–15.0)	<.001
Mean choroid plexus length, MoM	1.00 (0.93–1.07)	1.17 (1.10–1.22)	<.001
Mean choroid plexus length to occipitofrontal diameter ratio	0.52 (0.49–0.55)	0.64 (0.58–0.70)	<.001
Mean choroid plexus length to occipitofrontal diameter MoM ratio	1.00 (0.95–1.06)	1.22 (1.12–1.30)	<.001
Mean choroid plexus length to occipitofrontal diameter Z-score[a]	−0.53 (−1.37 to 0.19)	2.54 (1.06–3.68)	<.001
Mean choroid plexus length to biparietal diameter ratio	0.58 (0.55–0.62)	0.74 (0.66–0.76)	<.001
Mean choroid plexus length to biparietal diameter MoM ratio	1.00 (0.93–1.07)	1.25 (1.11–1.28)	<.001

Continuous variables are presented as median and interquartile ranges. Categorical variables are presented as number and percentage of total.

MoM, multiple of the median.

[a] Calculated from Chaoui et al,[13] 2019.

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1365.0 in our study cohort. Correcting measures for fetal CRL, such as the MoM ratio or ratio Z-scores, did not substantially (Supplemental Table 2) improve the diagnostic accuracy. Fetuses with OSB with ratios above the proposed threshold also had a significantly higher level of spinal defect than those with ratios below the threshold, suggesting more severe disease.

Strengths and limitations

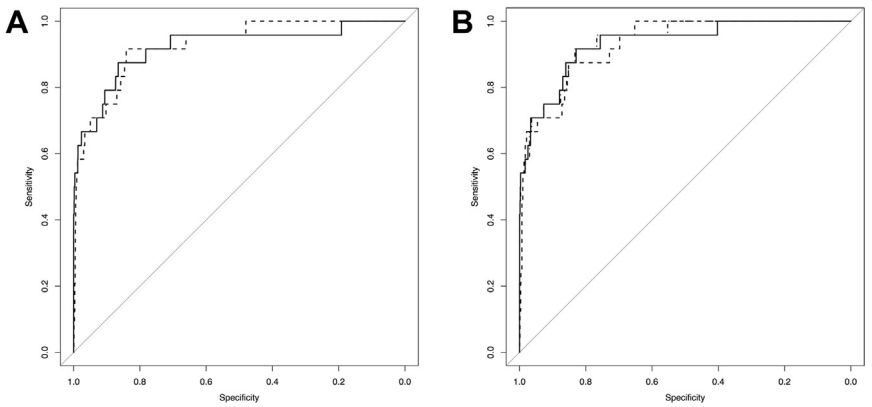
We validated the prognostic utility of the mean CP length to OFD ratio in a large group of pregnancies. The strengths of our study include the blinded assessment of offline images, comparison of raw ratios, CRL-corrected measures, and ratio's derivatives. Furthermore, using robust statistical tools, we reported specific cutoffs. Finally, we included only isolated OSB cases without chromosomal abnormalities because other studies have reported them to be a possible confounder for assessing the ratio.[13]

Some limitations also apply for the interpretation of our findings. First, our cohort does not reflect the real-life incidence of spina bifida. We have a higher incidence of most fetal abnormalities because of the nature of being a tertiary referral center. However, we reported positive and negative predictive values adjusted for the expected prevalence of OSB. Second, we did not assess the intrarater variability of the ratio measurements. We do not believe this point would have affected our results because of the simplicity of these measurements performed on ultrasound images of standard first-trimester scanning planes. Moreover, Chaoui et al[13] reported good reproducibility using the same technique. Third, although we performed blinded measurements of offline ultrasound images, true blinding may not be possible because of the distinctive appearance of dry brain effect. Finally, we did not assess the mean CP area to fetal head area ratio reported by Chaoui et al.[13] However, the results of the original study did not show any indication of a superior performance based on Z-score differences, and simple length measurement is preferred.

Results in context

After the original observation that the mean CP length to OFD ratio is

FIGURE 2
Receiver operating characteristics curves of mean CP length to fetal head biometry measurement ratios



A, Receiver operating characteristics curves depict mean CP length to OFD ratio (*straight line*) and mean CP length to BPD ratio (*dashed line*). **B,** Receiver operating characteristics curves of the crown–rump length–corrected variables. Straight, dot-dash, and dashed line depict mean CP length to OFD MoM ratio, Z-score, and mean CP length to BPD MoM ratio, respectively.

BPD, biparietal diameter; *CP*, choroid plexus; *MoM*, multiple of the median; *OFD*, occipitofrontal diameter.

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significantly different between OSB cases and controls, we observed good predictive accuracy.[13] Our findings expand on the original study and confirm that the ratio has potential for clinical utility. The ratio also provided higher AUC values than its derivatives on their own, such as OFD MoM or mean CP length MoM. CRL-corrected BPD measurements were reported to be significantly associated with OSB.[11,14,15] We did not see any appreciable predictive accuracy difference between the mean CP length to OFD and BPD ratios. However, the AUC values suggest that the performance of the ratio is likely to be superior to the CRL-corrected BPD measurements alone. The superior performance is probably because of the mean CP length component of the ratio. Loureiro et al[16] reported that the amount of cerebrospinal fluid in the ventricles is reduced in the cases of spina bifida during the first trimester. However, the predictive accuracy was also not formally assessed in their study. We did not see a significant improvement in the predictive accuracy when we corrected the ratio for CRL measurement.

Chaoui et al[13] reported the ratio Z-scores and we tested the proposed Z-scores, which did not provide superior performance over the simple ratio. When Z-score correction was applied to our cohort, unaffected fetuses had a median ratio Z-score of −0.53, indicating poor external validity. The difference can be explained by 2 factors. First, the number of unaffected fetuses in their cohort was relatively small (n=160). Second, and more importantly, the CRL measurements did not explain a large portion of variability in the ratio measurements according to the R-squared value reported in their study (r^2=0.1451). Both mean CP length and OFD measurements are positively correlated with CRL, and regression models suggest that the amount of

TABLE 2
Diagnostic accuracy characteristics of the mean choroid plexus length to occipitofrontal diameter ratio, ratio Z-score, and MoM ratio models at their optimal cutoffs

	Optimal cutoffs		
Characteristic	Mean CP/OFD ratio >0.662	Mean CP/OFD MoM ratio >1.263	Mean CP/OFD ratio Z-score >3.03
Sensitivity	41.7 (22.1–63.4)	41.7 (22.1–63.4)	41.7 (22.1–63.4)
Specificity	100.0 (99.8–100.0)	100.0 (99.8–100.0)	99.9 (99.8–100.0)
PPV	90.9 (57.1–98.7)	90.9 (57.1–98.7)	83.3 (53.6–95.6)
NPV	99.6 (99.4–99.7)	99.6 (99.4–99.7)	99.6 (99.4-99.7)
+LR	1365.0 (181.8–10,249.4)	1365.0 (181.8–10,249.4)	682.5 (157.9–2951.0)
−LR	0.58 (0.42–0.82)	0.58 (0.42–0.82)	0.58 (0.42–0.82)
Adjusted PPV[a]	64.0 (19.1–93.0)	64.0 (19.1–93.0)	47.1 (17.0–79.3)
Adjusted NPV[a]	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–100.0)

Data are presented as number (percentage) or LR.

CP/OFD, choroid plexus to occipitofrontal diameter; *LR*, likelihood ratio; *NPV*, negative predictive value; *PPV*, positive predictive value.

[a] Adjusted according to the expected population prevalence.

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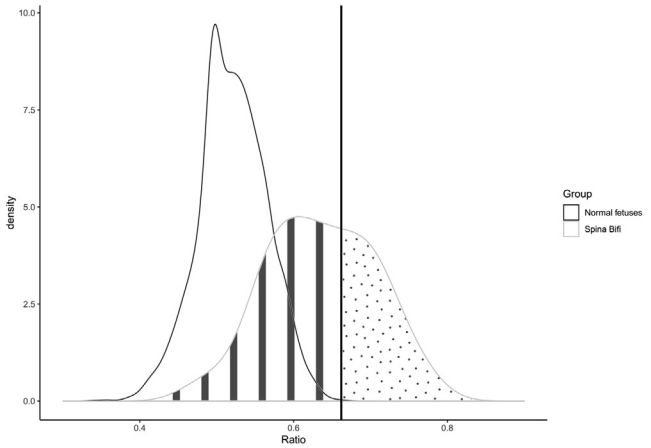
FIGURE 3
The density plot of mean CP length to OFD ratio in normal and abnormal fetuses



Mean choroid plexus length to occipitofrontal diameter ratio of fetuses not affected by spina bifida (*gray density line*) and fetuses with open spina bifida (*light gray density line*). Straight vertical line depicts the 0.662 cutoff. Fetuses above the cutoff (*dotted pattern*) have a higher median number of affected segments compared with fetuses below the cutoff (*stripe pattern*). Fetuses with an abnormal ratio had a median of 5 segments affected (interquartile range, 5—5 segments) compared with fetuses with a ratio below the cutoff who had a median of 3 segments affected (interquartile range, 3—5 segments). The difference was statistically significant according to permutation test (P=.022, approximate general independence test).

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variability explained by CRL is similar for both measurements (Supplemental material). Conditioning one variable to another would neutralize the effect of CRL variability, which explains the similar performance of the raw ratio to CRL-corrected ratios.

We did not compare our findings to other first-trimester OSB markers such as the ratio of brain stem (BS) to its distance of occipital bone (brain stem—occipital bone [BSOB]). Wertaschnigg et al[9] have recently reported almost perfect discrimination using the BS to BSOB ratio. However, the AUC value for BPD alone were also very high in their cohort (0.93) compared with previous studies, suggesting that they may have had a selected cohort of OSB cases. Moreover, the likelihood ratios we have obtained in our study are higher than those of the BS to BSOB ratio, according to the metaanalysis of Sirico et al.[17] Even though there are multiple markers for early detection of spina bifida, most require expertise or special scanning planes (Supplemental Table 5). We believe the uptake of this simple ratio to clinical practice could be better than other, more technically challenging ultrasound markers and measurements.

Clinical and research implications

Mean CP length is an easily measured marker by utilizing the standard scanning planes in the first trimester. We have developed a risk assessment calculator to enable its use in clinical practice. Whether the diagnostic performance of mean CP length and OFD ratio is superior to posterior fossa assessment and intracranial translucency measurements is yet to be determined, although it is reasonable to expect the ratio to be easier to assess than the intracranial translucency and related measures, which has an approximately 3% measurement failure. However, it may be best to consider them as complimentary tools, and an abnormal ratio should prompt an investigation of the posterior fossa and the fetal spine. Regardless, accuracy of each method on their own or in combination should be assessed in future studies. Finally, external validation studies should be performed for the cutoffs proposed in our study.

Conclusion

In this study, we reported the diagnostic accuracy of mean CP length to fetal head ratio and its individual compartments. The mean CP length to fetal head biometry measurement ratios at 11 to 13 weeks' gestation appears to be a promising tool for the prenatal detection of OSB. We observed high positive and negative predictive values with a mean CP length to OFD ratio >0.662. We also developed an online calculator for risk assessment. External validation studies are needed to confirm our findings. ■

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Author and article information

From the Fetal Medicine Unit, St George's Hospital, St George's University of London, London, United Kingdom (Drs Kalafat, Ting, Thilaganathan, Papageorghiou, and Khalil); Department of Statistics, Faculty of Arts and Sciences, Middle East Technical University, Ankara, Turkey (Dr Kalafat); Department of Obstetrics and Gynecology, Faculty of Medicine, Ankara University, Ankara, Turkey (Dr Kalafat); Vascular Biology Research Centre, Molecular and Clinical Sciences Research Institute, St George's University of London, London, United Kingdom (Drs Thilaganathan and Khalil).

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Corresponding author: Asma Khalil, XX. akhalil@sgul.ac.uk

Appendix

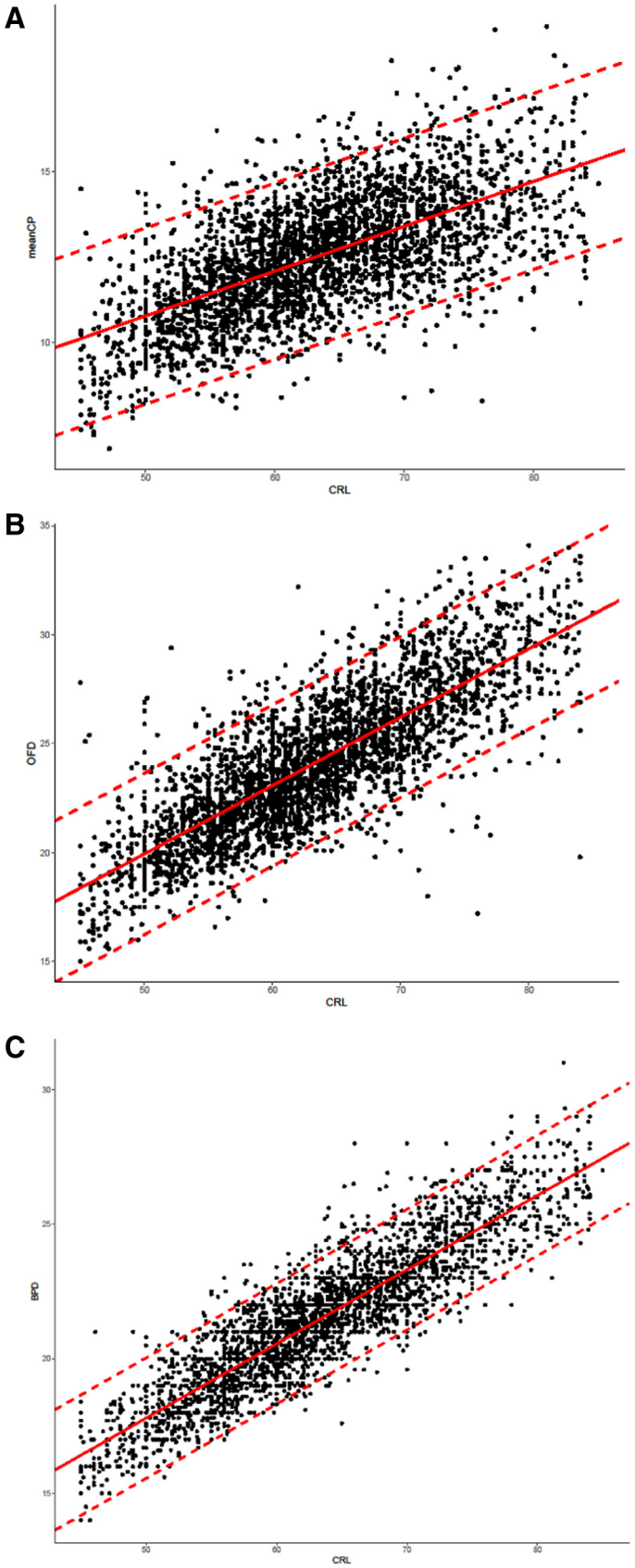
Supplemental statistical appendix

Undersampling was used to obtain stable, unbiased coefficients because of the extremely low event probability of the sample. The dataset was resampled with 1:4 event to control ratio for regression analyses, and the mean value of Monte Carlo simulated regression coefficients (100,000 iterations) was used for each variable. The predicted probability of open spina bifida (OSB) was then calculated using the whole cohort, and confusion matrix analysis was used to obtain diagnostic accuracy parameters. Positive and negative predictive values were further adjusted according to the expected population prevalence of OSB. If possible, cutoffs offering significantly higher accuracy over no information rate were identified as optimal cutoffs. Hosmer-Lemeshow test was used for testing the model's goodness-of-fit.

How to use the online calculator (step by step)

1. Obtain the mean choroid plexus length and occipitofrontal diameter (OFD) ratio as follows:
   a. Obtain the axial plane of the fetal head and measure the length of each choroid plexus to calculate the mean value. Then measure the OFD to calculate the ratio (Supplemental Figure 3, A).
   b. Obtain the crown–rump length in the sagittal plane (Supplemental Figure 3, B) if you want to calculate the multiples of the median (MoMs) (not essential).
2. Enter the required values in the calculator shown in the red rectangle in Supplemental Figure 3, C. After entering the values, you will obtain the predicted probability shown in the red ellipse in Supplemental Figure 3, C. You can do the same if you want to use the MoM values (blue rectangle and blue ellipse in Supplemental Figure 3, C).
3. A predicted probability below 80% has a 99.9% negative predictive value for OSB. Supplemental Table 3 shows the PPVs for probabilities above 80%.
4. Instead of the calculator, a simple cutoff of 0.662 also could be used for clinical practice.

SUPPLEMENTAL FIGURE 1
Scatter plots with fitted regression lines for mean CP length, OFD, and BPD



Scatter plots of CRL vs (A) mean CP length, (B) OFD, and (C) BPD with associated regression lines. Straight red lines depict the predicted mean, whereas the dashed lines represent the prediction intervals. (Regression equations for expected mean: $Y_{CP}=4.2141+0.1313\times CRL_{mm}$, $r^2=0.405$, $Y_{OFD}=4.2551+0.3138\times CRL_{mm}$, $r^2=0.654$, $Y_{BPD}=4.0063+0.2758\times CRL_{mm}$, $r^2=0.799$)

BPD, biparietal diameter; *CP*, choroid plexus; *CRL*, crown–rump length; *OFD*, occipitofrontal diameter.

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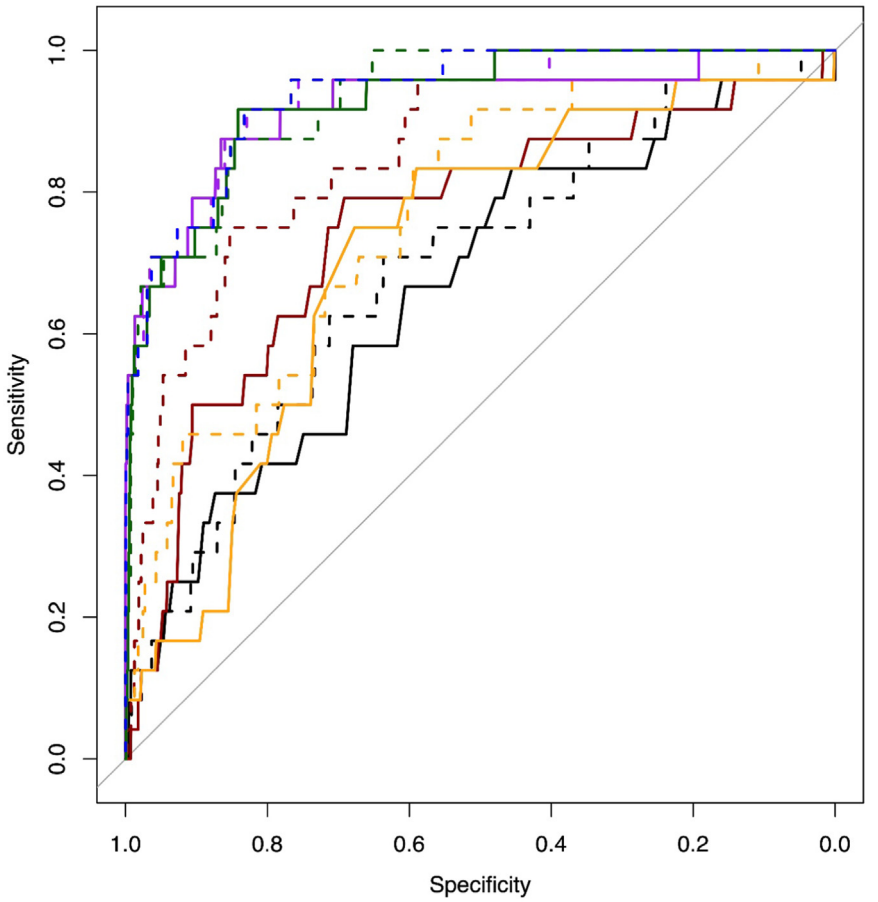
SUPPLEMENTAL FIGURE 2

The receiver operating characteristics curves of fetal head biometry variables



ROC curves of the occipitofrontal diameter (black), biparietal diameter (orange), mean choroid plexus length (red), mean choroid plexus length to occipitofrontal diameter ratio (purple), mean choroid plexus length to biparietal diameter ratio (green), and mean choroid plexus length to occipitofrontal diameter ratio Z-score (blue). Straight lines depict raw values models and dashed lines depict multiple of the median—corrected counterpart.

ROC, receiver operating characteristic.

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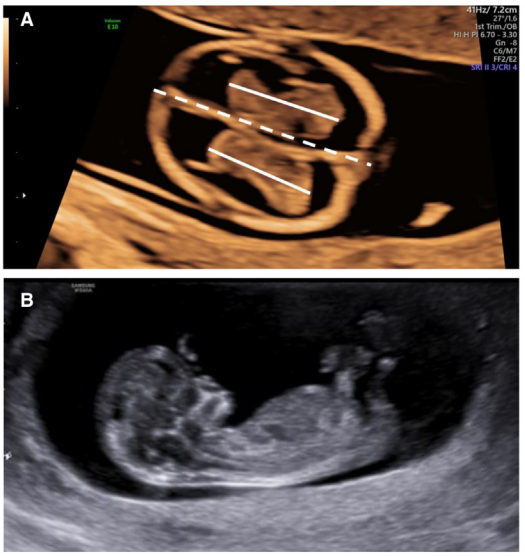
SUPPLEMENTAL FIGURE 3
Measurement technique and calculator use for risk prediction



C Risk of open spina bifida using the mean choroid plexus length to occipitofrontal diameter ratio at 11-13 weeks

Probability calculator raw ratio	Choroid plexus 1 in mm	Choroid plexus 2 in mm	OFD in mm	Predicted probability % (Raw ratio)
	14.3	13.7	25.6	9.21

Probability calculator MoM ratio	Choroid plexus 1 in mm	Choroid plexus 2 in mm	OFD in mm	CRL in mm	Predicted probability % (MoM ratio)
	14.3	13.7	25.6	61.4	8.12

A, Axial plane. **B,** sagittal plane. **C,** Risk of open spina bifida using the mean choroid plexus length to OFD ratio at 11 to 13 weeks.
CRL, crown-rump length; *MoM*, multiple of the median; *OFD*, occipitofrontal diameter.
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SUPPLEMENTAL TABLE 1
Results of the ROC curve analysis for the predictive accuracy of the CP to OFD ratio for open spina bifida

Models	Raw value AUC (95% CI)	MoM AUC (95% CI)	*P* value[a]
OFD	0.666 (0.550–0.781)	0.691 (0.581–0.800)	.271
BPD	0.716 (0.617–0.815)	0.768 (0.675–0.860)	.177
Mean CP length	0.752 (0.641–0.861)	0.846 (0.757–0.935)	.001
Mean CP length to OFD ratio	0.921 (0.852–0.991)	0.933 (0.881–0.986)	.101
Mean CP length to BPD ratio	0.928 (0.989–0.978)	0.931 (0.889–0.973)	.379

AUC, area under the curve; *BPD*, biparietal diameter; *CI*, confidence interval; *CP*, choroid plexus; *MoM*, multiple of the median; *OFD*, occipitofrontal diameter.
[a] De Long test comparing raw value variables with MoM-corrected variables for improvement in AUC values.
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SUPPLEMENTAL TABLE 2

Comparison of area under the curve values between predictive models with De Long test

	OFD	OFD MoM	BPD	BPD MoM	Mean CP length to OFD ratio	Mean CP length to OFD ratio MoM	Mean CP length to OFD ratio Z-score	Mean CP length to BPD ratio	Mean CP length to BPD ratio MoM
OFD	NA	0.271	0.025	0.069	<0.001	<0.001	<0.001	<0.001	<0.001
OFD MoM	—	NA	0.306	0.072	<0.001	<0.001	<0.001	<0.001	<0.001
BPD	—	—	NA	0.177	<0.001	<0.001	<0.001	<0.001	<0.001
BPD MoM	—	—	—	NA	<0.001	<0.001	<0.001	<0.001	<0.001
CP length/OFD ratio	—	—	—	—	NA	0.101	0.128	0.339	0.101
CP length to OFD ratio MoM	—	—	—	—	—	NA	0.187	0.702	0.559
CP length to OFD ratio Z-score	—	—	—	—	—	—	NA	0.857	0.720
CP length to BPD ratio	—	—	—	—	—	—	—	NA	0.379
CP length to BPD ratio MoM	—	—	—	—	—	—	—	—	NA

BPD, biparietal diameter; *CP*, choroid plexus; *MoM*, multiple of the median; *NA*, not applicable; *OFD*, occipitofrontal diameter.

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SUPPLEMENTAL TABLE 3

Diagnostic accuracy characteristics of the mean choroid plexus length/occipitofrontal diameter ratio, ratio Z-score, and MoM ratio models

Characteristic	Mean choroid plexus length/occipitofrontal diameter ratio model			
	Predicted risk >80% or ratio >0.636	Predicted risk >85% or ratio >0.644	Predicted risk >90% or ratio >0.656	Predicted risk >95% or ratio >0.674
Sensitivity	50.0 (29.1–70.9)	41.7 (22.1–63.4)	41.7 (22.1–63.4)	29.2 (12.6–51.1)
Specificity	99.8 (99.6–99.9)	99.9 (99.7–100.0)	99.9 (99.8–100.0)	100.0 (99.9–100.0)
PPV	63.2 (42.5–79.9)	71.4 (45.7–88.1)	83.3 (53.6–95.6)	100.0 (NA)
NPV	99.6 (99.5–99.7)	99.6 (99.4–99.7)	99.6 (99.4–99.7)	99.5 (99.2–99.7)
+LR	234.0 (100.9–542.7)	341.2 (115.0–1012.7)	682.5 (157.9–2951.0)	NA
−LR	0.50 (0.34–0.75)	0.58 (0.42–0.82)	0.58 (0.42–0.82)	0.71 (0.55–0.92)
Adjusted PPV[a]	23.3 (11.6–41.4)	30.8 (13.0-56.9)	47.1 (17.0–79.3)	100.0 (NA)
Adjusted NPV[a]	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.7–100.0)
	Mean choroid plexus length to occipitofrontal diameter MoM ratio model			
	Predicted risk >80% or MoM ratio >1.211	Predicted risk >85% or MoM ratio >1.226	Predicted risk >90% or MoM ratio >1.246	Predicted risk >95% or MoM ratio >1.278
Sensitivity	54.2 (32.8–74.5)	50.0 (29.1–70.9)	41.7 (22.1–63.4)	33.3 (15.6–55.3)
Specificity	99.6 (99.3–99.8)	99.7 (99.5–99.9)	99.9 (99.6–100.0)	100.0 (99.8–100.0)
PPV	50.0 (34.2–65.8)	57.1 (38.3–74.1)	66.7 (42.5–84.4)	88.9 (51.0–98.4)
NPV	99.7 (99.5–99.8)	99.6 (99.5–99.8)	99.6 (99.4–99.7)	99.5 (99.4–99.6)
+LR	136.5 (70.9–262.9)	182.0 (84.7–391.3)	273.0 (100.9–738.8)	1092.0 (142.0–8396.0)
−LR	0.46 (0.30–0.71)	0.50 (0.34–0.75)	0.58 (0.42–0.82)	0.67 (0.50-0.88)
Adjusted PPV[a]	15.1 (8.5–25.5)	19.2 (9.9–33.7)	26.2 (11.6–49.0)	58.7 (15.6–91.6)
Adjusted NPV[a]	100.0 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–99.9)
	Mean choroid plexus length/occipitofrontal diameter ratio Z-score model[b]			
	Predicted risk >80% or ratio Z-score >2.32	Predicted risk >85% or ratio Z-score >2.52	Predicted risk >90% or ratio Z-score >2.80	Predicted risk >95% or ratio Z-score >3.23
Sensitivity	54.2 (32.8–74.5)	50.0 (19.1–70.9)	45.8 (25.6–67.2)	33.3 (15.6–55.3)
Specificity	99.5 (99.3–99.7)	99.7 (99.4–99.8)	99.8 (99.6–99.9)	99.9 (99.8–100.0)
PPV	46.4 (31.7–61.8)	52.2 (34.9–69.0)	64.7 (42.5–82.0)	80.0 (47.3–94.7)
NPV	99.7 (99.5–99.8)	99.6 (99.4–99.8)	99.6 (99.4–99.7)	99.5 (99.4–99.6)
+LR	118.3 (63.3–221.0)	148.9 (73.0–303.7)	250.3 (100.7–621.8)	546.0 (122.3–2438.7)
−LR	0.46 (0.30–0.71)	0.50 (0.34–0.75)	0.54 (0.38–0.78)	0.67 (0.50–0.89)
Adjusted PPV[a]	13.3 (7.6–22.3)	16.2 (8.7–28.3)	24.6 (11.6–44.7)	41.6 (13.7–76.0)
Adjusted NPV[a]	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–100.0)	99.9 (99.9–99.9)

The table depicts the corresponding sensitivity, specificity, positive predictive values, negative predictive values, and other accuracy variables given predicted risk or cutoff points. The predicted risk of individual patients can be calculated with the supplemental calculator, available online. Data are presented as number (percentage) or as LR.

LR, likelihood ratio; *MoM*, multiple of the median; *NA*, not applicable; *NPV*, negative predictive value; *PPV*, positive predictive value.

[a] Adjusted according to the expected population prevalence; [b] Calculated from Chaoui et al,[13] 2019.

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SUPPLEMENTAL TABLE 4
The number of fetuses in the normal and abnormal CP to OFD groups

Anomaly	Mean CP length to OFD ratio >0.662 (n=10)	Mean CP length to OFD ratio ≤0.662 (n=14)	*P* value
Talipes	4 (40.0)	2 (14.3)	.151
Ventriculomegaly	6 (60.0)	8 (57.1)	.887
Arnold–Chiari malformation	10 (100.0)	12 (85.7)	.617

CP, choroid plexus; *OFD*, occipitofrontal diameter.

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SUPPLEMENTAL TABLE 5
Literature review for diagnostic markers of open spina bifida during the first-trimester scan

Author, y	OSB cases/ sample size	OSB prevalence (per 1000)	Marker	Expected change in OSB cases	Suggested cutoff	Reported diagnostic accuracy measure
Kalafat et al, 2020 (current study)			Mean choroid plexus length and occipitofrontal diameter ratio	Increase	>0.662	PPV: 90.9% (57.1%–98.7%)
Wertaschnigg et al,[9] 2020	27/1030	2.6	Brainstem to brainstem–occipital bone distance ratio	Increase	>95th percentile	DR: 95.4% (85.7%–100.0%) for 1% FPR
Chaoui et al,[13] 2020	34/194	175.2	Mean choroid plexus length to occipitofrontal diameter ratio	Increase	Not reported	Not reported
Ushakov et al,[12] 2020	53/53	Case series	Crush sign	Not quantifiable	Not reported	Not reported
Ramkrishna et al,[18] 2019	14/114	122.8	Maxillo–occipital line	Not reported	Not reported	Not reported
Chen et al,[6] 2017	11/16164	0.68	Intracranial translucency	Decrease	<1st percentile	DR: 45%
Khalil et al,[11] 2013	27/7802	3.5	Biparietal diameter	Increase	>0.95 MoM	DR: 55.6% for 11.6% FPR
Iuculano et al,[19] 2014	17/17	Case series	Four-line view	Decrease	Number of lines <4	Sensitivity: 88.0% (65.0%–96.0%)
Mangione et al,[20] 2013	52/260	200.0	Cisterna magna	Decrease	Nonvisualization	DR: 50.0%–73.1% for 11.1%– 15.4% FPR
Finn et al,[21] 2011	9/466	19.3	Aqueduct of Sylvius to occiput distance	Decrease	<2.5th percentile	Not reported
Lachmann et al,[22] 2010	20/120	166.6	Frontomaxillary facial angle	Decrease	<5th percentile	DR: 90.0% for 4.0% FPR

DR, detection rate; *FPR*, false-positive rate; *MoM*, multiple of the median; *PPV*, positive predictive value.

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