Revisiting the Implications of a Wide or Narrow Fetal Cavum Septi Pellucidi

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Article includes CME test

Received December 15, 2023, from the Fetal Medicine Unit, Department of Obstetrics and Gynaecology, Mount Sinai Hospital and University of Toronto, Toronto, Ontario, Canada (J.S., T.V.M., S.S.); Woman-Mother-Child Department, Lausanne University Hospital (CHUV), Lausanne, Switzerland (J.S.); Temerty Faculty of Medicine, University of Toronto, Toronto, Ontario, Canada (K.G.-Z.); Ontario Fetal Centre, Toronto, Ontario, Canada (T.V.M., S.S.); Department of Radiology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada (A.T.); Division of Diagnostic Medical Genetics, Department of Pathology and Laboratory Medicine, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada (E.G.); and Prenatal Diagnosis and Medical Genetics, Department of Obstetrics and Gynecology, Mount Sinai Hospital, University of Toronto, Toronto, Ontario, Canada (D.C.). Manuscript accepted for publication April 20, 2024.

The authors declare no conflict of interest.

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Abbreviations

BPSC, Baby Pediatric Symptom Checklist; CNS, central nervous system; CSP, cavum septi pellucidi; ICC, intraclass correlation coefficient; IQR, interquartile range; PPSC, Preschool Pediatric Symptom Checklist; SD, standard deviation; SWYC, Survey of Well-being of Young Children

doi:10.1002/jum.16470

Objectives—To investigate short-term neonatal developmental outcomes in fetuses with an isolated wide or narrow cavum septi pellucidi (CSP) using new reference ranges.

Methods—A cross-sectional study on fetuses at 16 + 0 to 36 + 6 weeks of gestation between December 2020 and January 2022. CSP width reference ranges were constructed from low-risk pregnancies. Wide and narrow CSPs were defined as measurements above the 95th percentile and below the 5th percentile, respectively. For the primary outcome fetuses with normal neurosonograms were included. Neonatal developmental outcomes were assessed using the Survey of Well-being of Young Children (SWYC).

Results—A total of 352 fetuses were included in this study, of whom 138 were healthy and had uncomplicated neonatal outcomes. These fetuses constituted the control group and were used to construct the CSP width reference ranges. Of 185 fetuses in the neurosonography group, 9.7% had wide and 7.6% had narrow CSPs, of whom 33.3% and 22.2%, respectively, scored below the SWYC threshold for expected developmental milestones, a rate similar to that reported in the general population.

Conclusions—The presence of a prenatally isolated wide or narrow CSP does not appear to increase the risk of neonatal neurodevelopmental delay.

Key Words—22q11.2 microdeletion; cavum septi pellucidi; developmental outcomes; reference range

The cavum septi pellucidi (CSP) is a landmark structure in the fetal brain, which should be recognized on ultrasound by 18 weeks of gestation, when the laminae of the septum pellucidum separate to form a small cavity containing cerebrospinal fluid. The CSP disappears at term or in the neonate because the laminae typically fuse around that time, thereby obliterating the cavum.[1]

Nonvisualization of the CSP raises a suspicion of an absent cavum or an absent septum.[2] While an absent CSP or a small CSP is suggestive of complete or partial absence of the corpus callosum, respectively, a wide CSP has also been associated with chromosomal abnormalities including trisomy 21,13, and 18[3,4] and 22q11.2 deletion.[5,6] It has also been linked to the development of schizophrenia spectrum disorders later in life.[7,8]

Previous studies have measured the CSP width and the length-to-width ratio and defined reference ranges across gestation.[5,9–11] Some of these prior reference ranges, however, were derived from a fetal population at high risk of genetic abnormalities and cardiac

anomalies,[5] which may not be a reliable representation of the low-risk population. Additionally, previous studies did not always take into consideration that the standard deviation (SD) was not fixed but was gestational age dependent.[12]

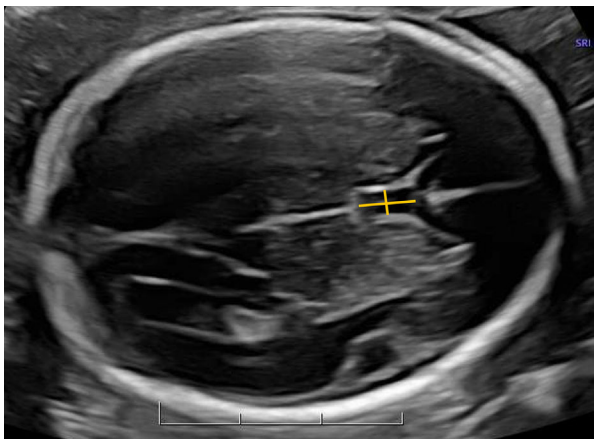
In this study, we therefore aimed to define the normal values for the CSP in a low-risk population (aim 1). Additionally, we wanted to investigate the risk of adverse developmental outcomes in fetuses with a wide or narrow CSP (aim 2).

Materials and Methods

Study Population

We conducted a cross-sectional study on fetuses with a documented CSP between 16 + 0 to 36 + 6 weeks of gestation evaluated in our tertiary center between December 2020 to January 2022. Gestational age was determined by the last menstrual period or first-trimester crown–rump length. The CSP was evaluated in the axial transventricular plane of the fetal head. The anterior portion of the CSP had to be visualized as a well-delineated box-like structure with a hypoechoic center. Measurement of the width of the CSP was performed by placing the calipers on the inner portion of its lateral borders (Figure 1), as previously described.[3,5] CSP length was measured in the same transventricular plane by placing the calipers on the echogenic borders of the callosal sulcus anteriorly and the fornix posteriorly (Figure 1).[13] The CSP ratio was calculated by dividing the CSP length by its width. All measurements were performed by two experienced neurosonographers on previously stored images while utilizing the most optimal image available from either two-dimensional stills or clips. All ultrasound examinations were acquired transabdominally using either Philips iU-22 (Philips Healthcare, PA, USA) or Voluson E10 (GE Healthcare, Zipf, Austria) ultrasound machines and, if feasible, a transvaginal examination was performed as well. The study protocol was approved by our institutional research ethics board.

Figure 1. Transventricular axial plane demonstrating the measurement of the CSP width and ratio in a 21 + 4 week fetus.



For aim 1, CSP width and ratio reference ranges across gestation were constructed based on measurements obtained from routine ultrasound examinations of healthy fetuses of low-risk pregnancies with normal neonatal outcomes. Each fetus was scanned only once. This reference curve was used to establish the cut-off for a wide CSP, defined as a measurement greater than the 95th percentile, and a narrow CSP, defined as a measurement smaller than the 5th percentile.

For aim 2, we reviewed CSP measurements of all fetuses who were evaluated in the fetal neurology clinic and underwent detailed neurosonography for various indications, as per the ISUOG guidelines[14] (defined as the 'neurosonography group'). Although referrals to the clinic include a range of indications—such as a history or suspicion of cerebral anomalies, and not solely conditions related to the CSP—only those with normal neurosonographic assessments were included in the analysis. All ultrasounds were performed by two neurosonographers incorporating the abdominal and, when possible, the transvaginal approaches. Fetuses were excluded if they had a central nervous system (CNS) or extra-CNS anomaly; genetic abnormalities; intra-uterine growth restriction; preterm delivery prior to 37 weeks; and maternal chronic illness impacting the course of the pregnancy. The fetuses with wide or narrow CSP were identified through our standard evaluation process, with those falling outside our low-risk population-derived reference ranges subsequently classified based on these findings.

Short-Term Developmental Outcomes

Developmental short-term outcomes were determined by telephone interviews of parents/caregivers of infants with a prenatally detected wide or narrow CSP, as defined according to our reference ranges.

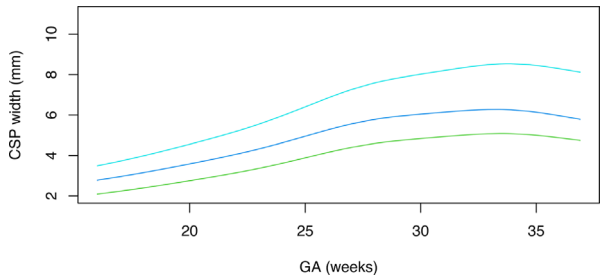
Parents of children with normal CSP measurements could not be contacted given limitations of our study's ethical approval. All parents completed the Survey of Well-being of Young Children (SWYC). This survey is a validated screening instrument for children under the age of 5, and it is recommended by the American Academy of Pediatrics for developmental screening in primary healthcare.[15] Each SWYC form includes: 1) SWYC Milestones; 2) Baby Pediatric Symptom Checklist (BPSC) or Preschool Pediatric Symptom Checklist (PPSC) (depending on age).[16] The SWYC Milestones questionnaire includes 10 age-specific questions to assess the child's cognitive, motor, and language development. Each item is scored on a 3-point scale, indicating the proficiency with which a child performs: "not yet" (0 points), "somewhat" (1 point), or "very much" (2 points). The total sum of question scores is cross-referenced with a fixed table of norms by age; a score below the relevant cut-off indicates a positive screen for possible developmental issues.[16]

The BPSC and PPSC assess behavioral and emotional symptoms for children under 18 months and from 18 to 66 months, respectively. Children were identified as having suspected behavior abnormalities if they generated a score of ≥3 across any criteria of the BPSC (eg, inflexibility, irritability or difficulty with routines) or if they scored ≥9 on the PPSC.[16]

Statistical Analysis

Continuous variables are presented as mean ± SD or median (interquartile range [IQR]), as appropriate. Categorical variables are expressed as n (%). The Shapiro–Wilk test was used to determine the normality of distribution of CSP width measurements. As the CSP width measurement did not have a normal distribution across all gestational ages, we chose to construct the CSP width percentile curve by using the LMS method.[17] Briefly, this method uses a Box–Cox power transformation to remove the skewness and normalize data for each age.[17] The same approach was used to create the reference values for the CSP ratio. Interobserver reliability for CSP measurements was assessed by calculating the intraclass correlation coefficients (ICCs). All analyses were performed using STATA software (version 14IC; Stata Corporation, College Station, TX, USA) and R software (version 4.1.2; http://www.r-project.org).

Figure 2. Reference ranges for the CSP from a low-risk fetal population between 16 + 0 and 36 + 6 weeks of gestation.



Results

Overall, 352 fetuses were included in this study, of whom 138 were healthy and had uncomplicated neonatal outcomes and were used to construct the CSP width and ratio reference ranges. A total of 185 fetuses (who had 273 neurosonography scans) were included in the neurosonography group and 29 fetuses were included in the 22q11.2 microdeletion group. Median gestational age at examination was 20 weeks (IQR 19.4–27.7) for the low-risk group, 24.9 weeks (IQR 21.9–28.4) for the neurosonography group, and 23.0 weeks (IQR 20.9–25.7) for the 22q11.2 microdeletion group.

The CSP width reference curves are illustrated in Figure 2. Table 1 displays the median (M), generalized coefficient of variation (S), and power in the Box–Cox transformation (L) parameters for each gestational week.[17] Using these findings, Table 1 provides the CSP width measurements corresponding to the 5th, 50th, and 95th percentiles for each gestational week, where 6 (4.3%) fetuses had a CSP measurement above the 95th percentile, and 7 (5.0%) had measurements below the 5th percentile, thereby providing a robust basis for the reference curves. Reliability analysis of CSP width measurements between the two sonographers showed excellent interobserver reliability (ICC = 0.94, 95% confidence interval 0.61–0.99). When plotting CSP width of the neurosonography group on the reference curves, 18 (9.7%) fetuses had an isolated wide CSP above the 95th centile and 14 (7.6%) a narrow CSP, below the 5th centile (Figure 3).

For the developmental assessment, 10 parents/primary caregivers could not be reached for questioning and one declined participation (34.3% in total of missing outcomes), leaving 12 (66.6%) and 9 (64.0%) parents/primary caregivers, from the wide and narrow CSP groups for developmental assessment, respectively. The median age of the infants at the time of the assessment was 11.8 months (IQR 8.8–14.4). Overall health was normal for all infants in both the wide and narrow CSP groups. Of note, one infant in the narrow CSP group had an isolated atrial septal defect detected postnatally. In the wide CSP group, 4 (33.3%) infants scored below the SWYC threshold for expected developmental milestones. In the narrow CSP group, two (22.2%) infants scored below the expected developmental threshold. Four (33.3%) infants from the wide CSP group and 2 (22.2%) infants from the narrow CSP group were found to be at risk of behavioral symptoms. Only 2 infants from the wide CSP group (16.7%) and none from the narrow CSP group had concerning scores on both the SWYC milestones and behavioral symptom checklist. Overall, 31.2% of infants with a wide or narrow CSP were at risk of developmental and/or behavioral concerns. However, parents expressed developmental concern for only 1 (8.3%) infant in

Figure 3. Percentile curves for CSP width, based on LMS method. Lines represent the 5th, 50th, and 95th percentiles of the low-risk population. Hollow circles represent fetuses from the neurosonography group. Black circles represent neonates with abnormal SWYC questionnaire results.

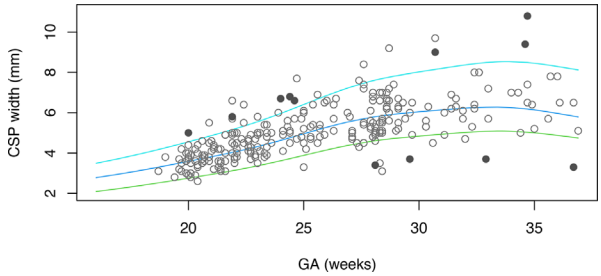


Table 1. Reference Chart for CSP Width According to Gestational Age (in Weeks)

				Percentiles (CSP Length in mm)		
GA (weeks)	***L***	***M***	***S***	**5th**	**50th**	**95th**
16	0.855	2.778	0.153	2.1	2.8	3.5
17	0.746	2.957	0.153	2.2	3.0	3.7
18	0.633	3.153	0.153	2.4	3.2	4.0
19	0.517	3.365	0.153	2.6	3.4	4.3
20	0.398	3.587	0.153	2.8	3.6	4.6
21	0.276	3.815	0.153	2.9	3.8	4.9
22	0.152	4.057	0.152	3.1	4.1	5.2
23	0.024	4.327	0.152	3.4	4.3	5.6
24	−0.107	4.628	0.152	3.6	4.6	6.0
25	−0.240	4.952	0.152	3.9	5.0	6.4
26	−0.376	5.275	0.152	4.2	5.3	6.9
27	−0.514	5.563	0.151	4.4	5.6	7.3
28	−0.655	5.785	0.151	4.6	5.8	7.6
29	−0.799	5.938	0.151	4.7	5.9	7.8
30	−0.945	6.046	0.151	4.8	6.0	8.0
31	−1.094	6.142	0.151	4.9	6.1	8.2
32	−1.245	6.227	0.150	5.0	6.2	8.4
33	−1.399	6.277	0.150	5.1	6.3	8.5
34	−1.554	6.254	0.150	5.1	6.3	8.5
35	−1.712	6.142	0.150	5.0	6.1	8.5
36	−1.873	5.966	0.149	4.9	6.0	8.3

For each week of gestation, the median (*M*), the generalized coefficient of variation (*S*), and the power in the Box–Cox transformation (*L*) are provided. To calculate the value (*Y*) of a CSP width measurement at a specific percentile, the following equation is utilized: $Y = M(1 + [L \times S \times Z])^{1/L}$, where *L*, *M*, and *S* are the values at the corresponding gestational age (GA), and *Z* is the *Z*-score that corresponds to the intended percentile.[17]

the wide CSP group and 1 (11.1%) in the narrow CSP group.

Discussion

In this study, we found that the width of the CSP increases gradually between 20 and 30 weeks of gestation, at which time it slowly plateaus and then starts to decrease in size at around 34 weeks. Infants with a prenatal diagnosis of an isolated wide or narrow CSP, who are otherwise healthy at birth, exhibited positive screening results for developmental delay and behavioral abnormalities in 31.2%.

When comparing our study population's developmental outcomes to those in the primary care settings, we found a similar risk of suspected delays in developmental milestones or behavioral symptoms in infants with a wider or narrower CSP in comparison to the reported baseline risk in the general population. Indeed, previous studies suggests that 21.8% to 33.8% of children in the general population exhibit a positive score on the milestones assessment,[18,19] while 28% exhibit a positive score on the behavioral assessment.[20] Studies investigating the association between the fetal CSP size and development are sparce. Recently it has been demonstrated by Cooper et al, that a wide or narrow CSP on prenatal MR is not associated with abnormal development.[21] Although our findings are similar with respect to lack of association, our methodology differs from Cooper et al, because in our study all neurosonograms were normal aside from the CSP width measurement, whereas Cooper et al included fetuses with an abnormal anterior complex on ultrasound (ie, absent septum or absent cavum). Additionally, whereas Copper et al employed previously published ultrasound reference ranges for their MR measurements, we generated our own ultrasound curves, thereby ensuring validity and reproducibility. Lastly, we used a screening questionnaire, as it was done over the phone, while Cooper et al utilized a diagnostic questionnaire.

Our paper is noteworthy due to the methodology used to devise the CSP age-specific reference ranges. We utilized a cross-sectional study design, where each fetus is depicted only once, and the measurements were obtained independently by two sonographers. In contrast to previous studies where dependency of the SD on gestational ages was not recognized,[3,5] in our non-normal CSP width distribution, we constructed centiles that smoothly change with gestational age and provided a good fit to the data. The LMS method is very versatile and is able to generate centile curves even when the data appear to be complex in shape. Moreover, this method can handle time-varying skewness, which cannot be accounted for by using traditional log-transformation techniques.[12,22] Additionally, all patients in the study group underwent a detailed neurosonographic assessment to ensure that no CNS anomalies were present. Lastly, the SWYC screening questionnaire we chose to use is relatively short and easy for parents/caregivers to understand, especially when done over the phone. Its primary purpose, to gather a large amount of reliable information from parents through self-report,[18] aligns well with aim 2 of the study.

Several limitations need to be acknowledged. First, our CSP width reference ranges were constructed retrospectively on a cohort of low-risk pregnancies with normal neonatal outcomes. As a result, these fetuses did not necessarily undergo genetic testing. Second, among the fetuses with a prenatal isolated diagnosis of a wide or narrow CSP no postnatal brain imaging was done, nor did they all undergo genetic testing pre- or postnatally to ascertain the isolated nature of this finding. Third, despite numerous attempts by telephone and email we were able to reach only approximately two thirds of the parental cohort with a narrow and wide CSP and thus a potential sampling bias may exist. Still, this response rate is considered reasonable.[23] Fourth, we did not contact the parents of neonates with a prenatally normal CSP. We presume that given the low-risk nature of these pregnancies, the SWYC milestone assessment in this population would be comparable to the available literature. Lastly, our developmental and behavioral assessment were conducted at a mean age of approximately 1 year, limiting their longer term prognostic value. Nonetheless, the questions presented to the parents/caregivers were age appropriate.

Conclusion

We conclude that the finding of an isolated wide or narrow CSP, as defined by our reference ranges, does not increase the risk for suspected delayed developmental or

behavioral milestones. Approximately, one third of our cohort scored positively on the screening test, a proportion that is similar to that observed in the general population.

Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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