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DOI:
10.4103/pjog.pjog_13_24

A sonographic evaluation on agreement and time efficiency of fetal central nervous system biometry using semi-automated five-dimensional ultrasound versus standard two-dimensional ultrasound in a Philippine tertiary hospital

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Submitted: 12-Mar-2024
Revised: 30-Mar-2024
Accepted: 08-Apr-2024
Published: 29-Jun-2024

Abstract:

BACKGROUND: Proper assessment and efficient diagnosis of central nervous system anomalies is essential in antenatal surveillance of pregnant patients. These anomalies are usually associated with genetic syndromes or severe malformations requiring timely intervention and antenatal counseling of the expectant couple.

OBJECTIVE: The study aims to evaluate the agreement of cranial biometric measurements and to determine if there is a significant difference in the time needed to complete the evaluation using standard 2D and semi-automated 5D ultrasound.

METHODS: An analytical cross-sectional study was employed on 93 women who underwent pelvic ultrasound scans from August to October 2022 in a tertiary hospital. Basic biometric fetal central nervous system (CNS) measurements were acquired using 2D ultrasound followed by 5D CNS ultrasound. Bland-Altman plots were used to evaluate the agreement of the measurements obtained. The difference in the time to completion was determined using independent t-test.

RESULTS AND CONCLUSION: Our study found that 5D CNS ultrasound measurements showed 96.8% agreement with 2D ultrasound in 90 out of 93 fetuses. The 5D CNS ultrasound takes a shorter time of 90 seconds (s) to completion in comparison to 99 s using the 2D method ($p=0.076$). Upon stratification of the study population per trimester, in the second trimester, it took 76 s with 5D CNS vs 89 s with 2D, resulting to a statistically significant 13-second difference ($p=0.044$). In the third trimester, 5D CNS took 105 s vs 108 s with 2D ($p=0.614$). The time to completion of the scan using this technology is faster when used for second trimester pregnancies but could be affected by fetal-dependent and operator-dependent factors. Therefore, application of this new technology has the potential to improve workflow efficiency after the necessary training on 3D sonography and 5D CNS ultrasound software.

Keywords:

Artificial intelligence, fetal brain, fetal central nervous system, five-dimensional central nervous system, ultrasound

How to cite this article: Caro-Alquiros LR, Gonzaga ZG, Quinio IB. A sonographic evaluation on agreement and time efficiency of fetal central nervous system biometry using semi-automated five-dimensional ultrasound versus standard two-dimensional ultrasound in a Philippine tertiary hospital. Philipp J Obstet Gynecol 2024;48:90-7.

Introduction

Sonographic evaluation of the fetal central nervous system (CNS) is one of the most important antenatal examinations for biometry and the detection of anomalies. CNS anomalies are crucial to be diagnosed since most have a genetic etiology and would lead to a severe prognosis.[1-3] In the Philippines, prenatal diagnosis utilizing two-dimensional (2D) ultrasound abdominally remains the main modality due to its accessibility, low cost, and noninvasiveness.[4] However, it acquires CNS measurements manually and is largely operator dependent.

In this era of advancing technology, ultrasound artificial intelligence omits repetitive manual acquisition of planes and optimizes clinical workflow and quality assurance. It is currently in the early stages of deployment with limited studies on its clinical application.[5,6] In 2015, the five-dimensional (5D) CNS software semiautomated approach (Samsung Electronics Co. Ltd., Suwon, South Korea) has been introduced. 5D CNS ultrasound is a diagnostic tool used to assess the fetal brain during pregnancy. The technology uses real-time ultrasound imaging to create detailed three-dimensional (3D) images of the fetal brain. It offers automatic measurements of axial plane CNS structures and provides instant views of the sagittal and coronal planes. It also permits better visualization allowing the sonographer to manually navigate desired planar displays and measure structures as necessary.[7-9]

The primary objective of the study is to evaluate the agreement of basic cranial biometric measurements using standard 2D and semiautomated 5D ultrasound. The secondary objective is to determine if there is a significant difference in the time needed to complete the evaluation using the two methods.

Methodology

The protocol and patient consent form were peer-reviewed and approved by the institutional review board.

Study population

The study was an analytical cross-sectional study of 93 women who underwent pelvic ultrasound scans from August 2022 to October 2022 in a specialty OBGYN ultrasound referral center of a tertiary hospital. This ultrasound referral center has an average of 450 ultrasound scans per week in 2022. All women included in the study have singleton pregnancies between 18 and 36 weeks age of gestation, aged accurately by their last menstrual period or estimated date of delivery by an early ultrasound scan, with no antenatally detected fetal structural anomalies. Those determined to have factors precluding an adequate sonographic examination were excluded from the study, including unfavorable fetal position and increased abdominal wall thickness.

Sampling method

The sample size was computed based on power and level of confidence set at 95% and was stratified into the equal distribution of second-trimester (18–27 6/7 weeks gestation) and third-trimester (28–36 weeks gestation) pregnancies. After exclusion, the researchers fulfilled the required sample size of 90 participants, consisting of 45 second-trimester fetuses and 45 third-trimester fetuses, and were attained through convenience sampling. The scanner provided the participants with written informed consent before the conduct of the study. All eligible pregnancies were asked to complete the participant information sheet to determine the following: maternal age, age of gestation, and anthropometrics.

Data collection process

All scans were done by the primary investigator who is a senior maternal-fetal medicine (MFM) fellow-in-training with 24 months of hands-on experience in obstetric ultrasound at the start of the study, supervised by either one of the coinvestigators who are MFM subspecialists. All investigators completed a 5-h hands-on workshop in 5D CNS imaging. The scans were performed using a single machine, a 1–8 MHz curved transducer (S-Vue TM_ Transducer CV1-8A) of the Ultrasound System HERA machine (Samsung Medison Co.).

For each study participant, the scanner manually obtained the desired fetal CNS planes and measurements employing the 2D ultrasound method.[2,3] All 2D images were saved and stored in the ultrasound machine. Using the same machine, utilizing the 5D CNS tool, the fetal CNS 3D volume dataset was then acquired in a transventricular view with the fetal head occupying about 75% of the screen as shown in Figure 1a. The scanner manually placed two reference points in the obtained image, corresponding to the middle of the thalami (1st seed) and the midpoint of the cavum septum pellucidum (2nd seed) as shown in Figure 1b.[7] Upon committing the points for reference, the workflow algorithm of the 5D CNS software produced a semiautomated reconstruction of all nine diagnostic CNS planes (3 axial, 4 coronal, and 2 sagittal planes) as shown in Figure 1c and Supplemetary video. This study measured the three axial planes and basic fetal CNS biometric measurements for screening of the fetal brain namely, biparietal diameter (BPD), head circumference (HC), occipitofrontal distance (OFD), transverse cerebellar diameter (TCD), posterior horn of the lateral ventricle (Vp), and cisterna magna (CM) were obtained. The scanner assessed the machine-generated CNS diagnostic planes and biometry. If deemed

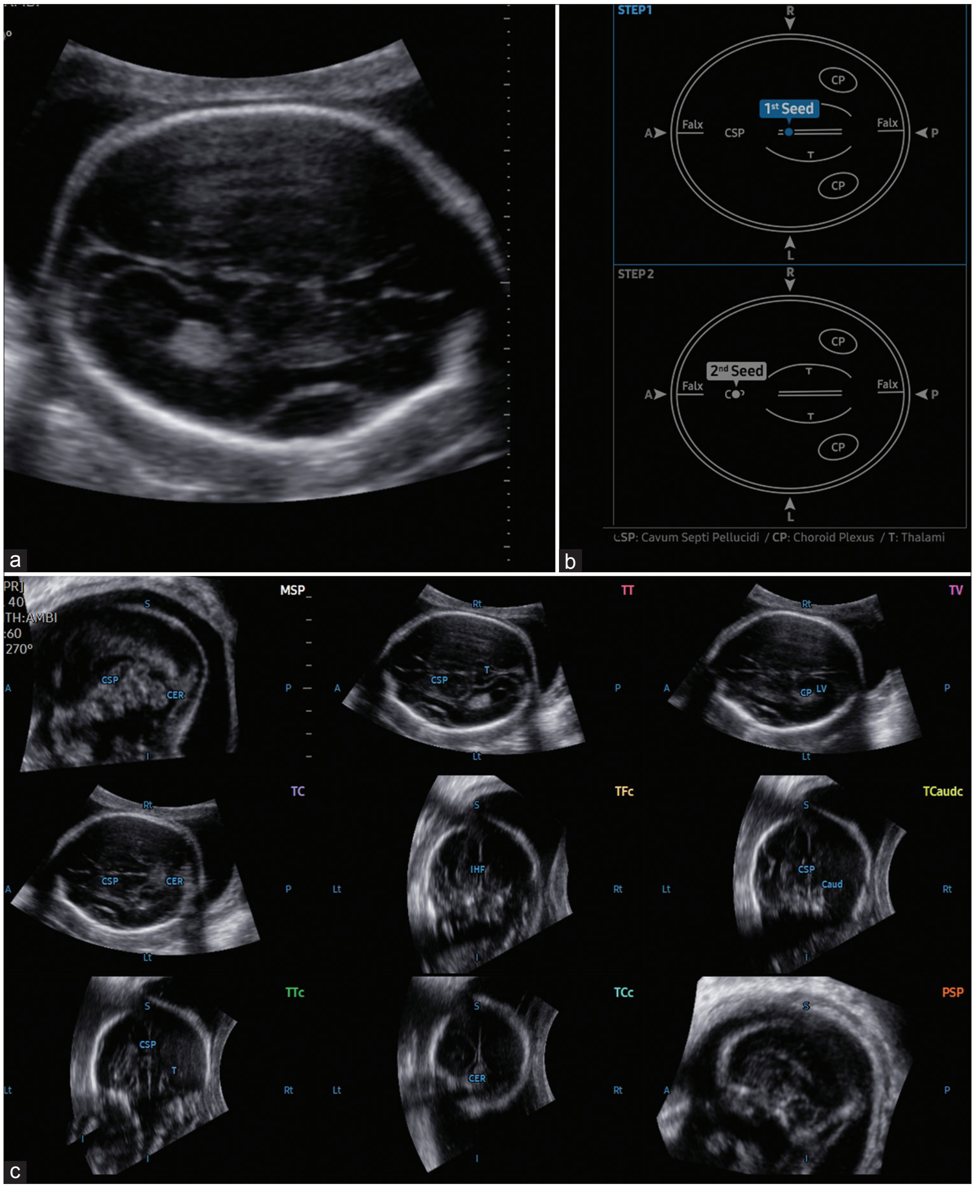

Figure 1: (a) Image of the fetal cranium in the axial plane, transventricular view. (b) After the three-dimensional volume was acquired, the five-dimensional (5D) central nervous system (CNS) software tool was utilized, and two reference points were manually placed corresponding to the middle of the thalami (1st seed) and the midpoint of the cavum septum pellucidum (2nd seed). (c) Upon committing the points for reference, the workflow algorithm of the 5D CNS software produced a semiautomated reconstruction of all nine diagnostic CNS planes (3 axial, 4 coronal, and 2 sagittal planes). A refers to anterior, Caud: Caudate, CER: Cerebellum, CP: Choroid plexus, CSP: Cavum septum pellucidi, IHF: Interhemispheric fissure, LV: Lateral ventricle, MSP: Midsagittal plane, P: Posterior, PSP: Parasagittal plane, TC: Transcerebellar plane, TCaudc: Coronal transcaudate plane, TCc: Coronal transcerebellar plane, TFc: Coronal transfrontal plane, TT: Transthalamic plane, TTc: Coronal transthalamic plane, and TV: Transventricular plane

satisfactory, the measurements are recorded. Otherwise, manual adjustments on planes and/or measurements were done as necessary. All 3D volume data and 5D CNS measurements obtained were saved in the ultrasound machine. During the whole scanning, a timekeeper was tasked to record the required time to complete each technique. The timekeeper noted the start and end of 2D scanning, and the start of 5D CNS scanning as the scanner started 3D volume acquisition and ended as the scanner committed her final fetal cranial measurement. The results released to the patient only included the 2D imaging measurements and the 5D CNS measurements obtained were used only for this research.

Analysis

The independent sample and paired samples *t*-test were used to compare the mean difference and standard deviation of each cranial measurement using each technique. $P < 0.05$ was considered statistically significant. To evaluate the agreement of measurements, a Bland–Altman plot was used to graphically describe the mean difference between scanning methods for each cranial measurement plotted against the mean cranial measurement obtained by 2D ultrasound. Each plot indicated 95% limits of agreement. The differences in time required to complete the analysis using each scanning method were analyzed using an independent *t*-test. SPSS version 22.0 statistical software, (International Business Machines Corporation (IBM), United States, modified April 2020) was used for data analyses.

Results

The general characteristics of the study population are indicated in Table 1, showing a mean gestational age of 27 weeks with a range of 18–36 weeks. The 5D CNS software was able to successfully analyze the acquired 3D volumes in 90 out of 93 (96.8%) participants. The remaining three cases where analysis was not possible were third-trimester pregnancies with an unfavorable fetal head position in the occiput anterior or posterior position. In these cases, the 5D CNS software was unable to process volumes with poor-quality images of the intracranial structures which were necessary to be identified by the machine before the placement of reference points.

Figure 2 shows the Bland–Altman plots for the mean difference and the 95% limits of agreement between 2D and 5D CNS measurements for the whole study population (n = 90). The percentage of the study population that was able to show agreement per cranial measurement are as follows: 86 out of 90 (95.5%) for BPD and HC, 84 out of 90 (93.3%) for OFD and TCD, and 85 out of 90 (94.4%) for Vp and CM.

Table 1: General characteristics of the study population

Variable	mean±SD	median (range)
Maternal age (years)	33.4±5.34	34 (20–46)
Maternal BMI (kg/m^2)	23.8±4.48	23 (16–44)
AOG	27.3±5.14	27 (18–36)

SD: Standard deviation, BMI: Body mass index, AOG: Age of gestation

Figure 3 graphically presents the agreement of biometry of fetal CNS using each technique stratified into second and third trimester (n = 45). The study population in the second trimester revealed agreement of measurements: 41 out 45 (91.1%) for BPD, 43 out of 45 (95.6%) for HC, OFD, TCD and CM, and 42 out of 45 (93.3%) for Vp. The Bland–Altman plots for the third trimester showed the following percentage of agreement of measurements: for BPD, 42 out of 45 (93.3%) had agreeable measurements, 43 out of 45 (95.6%) for HC, Vp, and CM, 100% for OFD, and 44 out of 45 (97.8%) for TCD.

Table 2 shows the average time required for cranial biometric measurements using 2D and 5D CNS across the trimesters. It takes a shorter time of 90 s to complete a fetal CNS ultrasound evaluation using 5D CNS in comparison to an average time of 99 s using the 2D method. However, this 9-s difference was not found to be statistically significant (P = 0.076). In the second trimester [Table 3], the cranial biometric measurement took 76 s with 5D CNS versus 89 s when 2D was used. This 13-s difference was found to be statistically

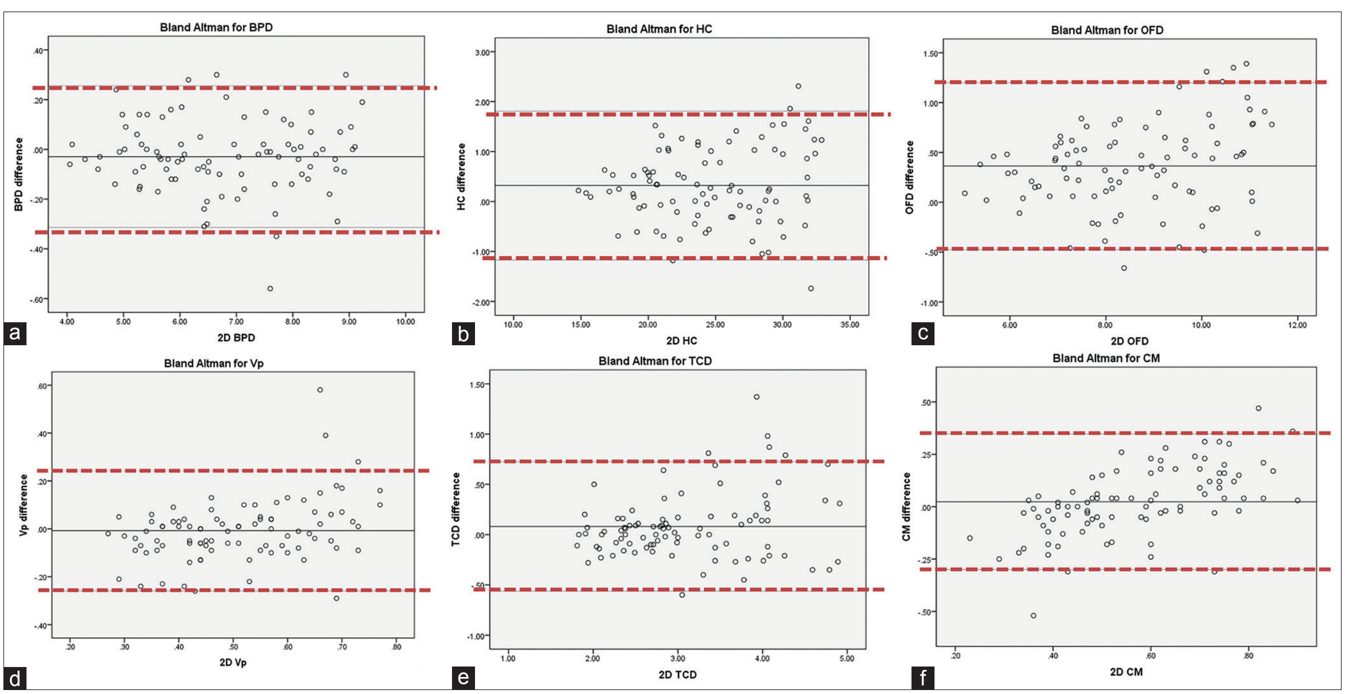

Figure 2: Bland–Altman plots for the mean difference and the 95% limits of agreement (indicated by red dotted lines) between two-dimensional (2D) and five-dimensional (5D) central nervous system (CNS) measurements for both second- and third-trimester fetuses. The percentage of the study population that was able to show agreement per cranial measurement are as follows: (a) 86 out of 90 (95.5%) for biparietal diameter, (b) 86 out of 90 (95.5%) head circumference, (c) 84 out of 90 (93.3%) for occipitofrontal distance, (d) 85 out of 90 (94.4%) for posterior horn of the lateral ventricle, (e) 84 out of 90 (93.3%) for transverse cerebellar diameter, and (f) 85 out of 90 (94.4%) for cisterna magna. Y-axis: difference (mean) =2D measurement − 5D CNS measurement; X-axis: 2D − mean 2D measurement. 2D: Two-dimensional, BPD: Biparietal diameter, HC: Head circumference, OFD: Occipitofrontal distance, Vp: Posterior horn of the lateral ventricle, TCD: Transverse cerebellar diameter, and CM: Cisterna magna

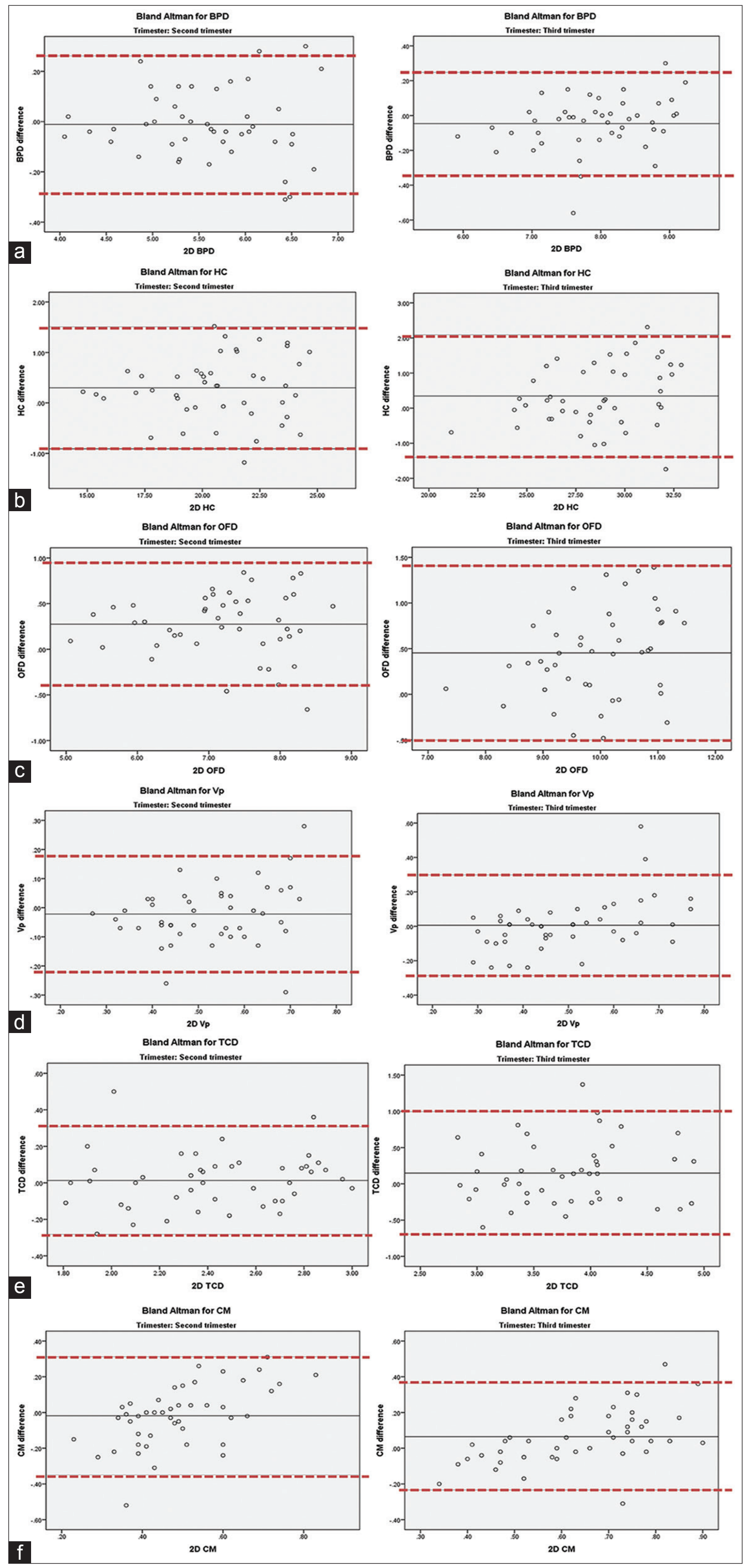

Figure 3: Bland–Altman plots showing agreement of measurements (95% limit of agreement indicated by red dotted lines) for the second-trimester (1st column) versus Bland–Altman plots for the third-trimester (2nd column). (a) biparietal diameter 41 out of 45 (91.1%) for second trimester versus 42 out of 45 (93.3%) for third trimester, (b) head circumference 43 out of 45 (95.6%) for second trimester versus 43 out of 45 (95.6%) for third trimester, (c) occipitofrontal distance 43 out of 45 (95.6%) for second trimester versus 45 out of 45 (100%) for third trimester, (d) posterior horn of the lateral ventricle 42 out of 45 (93.3%) for second trimester versus 43 out of 45 (95.6%) for third trimester, (e) transverse cerebellar diameter 43 out of 45 (95.6%) for second trimester versus 44 out of 45 (97.8%) for third trimester, and (f) cisterna magna 43 out of 45 (95.6%) for second trimester versus 43 out of 45 (95.6%) for third trimester. 2D: Two-dimensional, BPD: Biparietal diameter, HC: Head circumference, OFD: Occipitofrontal distance, Vp: Posterior horn of the lateral ventricle, TCD: Transverse cerebellar diameter, and CM: Cisterna magna

Table 2: Time required to analyze the fetal brain using two-dimensional versus five-dimensional central nervous system (*n*=90)

Variable	Mean±SD	Median (range)	*P* (95% CI)
2D time	98.6±36.9	88 (51–227)	
5D time	90.2±47.0	80.5 (18–220)	
2D–5D time	8.4±44.2		0.076 (−0.88–17.6)

SD: Standard deviation, CI: Confidence interval, 2D: Two dimensional, 5D: Five dimensional

Table 3: Time required to analyze the fetal brain using two-dimensional versus five-dimensional central nervous system in the second trimester (*n*=45)

Variable	Mean±SD	*P* (95%CI)
2D time	89.1±24.4	
5D time	75.8±39.0	0.044 (0.365–26.3)
2D–5D time	13.3±43.2	

2D: Two dimensional, 5D: Five dimensional, SD: Standard deviation, CI: Confidence interval

Table 4: Time required to analyze fetal brain using two-dimensional versus five-dimensional central nervous system in the third trimester (*n*=45)

Variable	Mean±SD	*P* (95% CI)
2D time	108.0±44.4	
5D time	104.6±50.3	0.614 (−10.15–17.00)
2D–5D time	3.4±45.2	

2D: Two dimensional, 5D: Five dimensional, SD: Standard deviation, CI: Confidence interval

significant ($P = 0.044$). In the third trimester [Table 4], completion of the 5D CNS method took 105 s versus 108 s when 2D was used. The 3-s difference was not statistically significant ($P = 0.614$).

Discussion

Since the evolution of the 5D CNS software, there have been few attempts to establish its utility in the clinical setting. A prospective study by Rizzo involved 183 normal singleton pregnancies who underwent routine 2D sonographic examination at 18–24 weeks' gestation. The 5D CNS software was applied and showed 98.4% success in the reconstruction of all the fetal brain diagnostic planes. A Cohen coefficient for axial planes alone demonstrated a 0.96 agreement rate between two independent observers. The agreement or concurrence of fetal CNS measurements between 2D and 5D CNS measurements was high with intraclass correlation coefficients of >0.920 with a limit of agreement set at 95%.[7,10,11]

Another prospective study by Rizzo *et al*., which involved 120 low-risk singleton second-trimester pregnancies showed that the fetal brain measurements during routine scan obtained by 5D CNS correlated with those acquired by standard 2D imaging in 118 out of 120 (98.3%) pregnancies. Moreover, the authors in this study evidenced that 5D CNS software had a quicker analysis average time of 54 s compared to 115 s of standard 2D imaging. However, these prior studies were limited by having the scans performed only by expert fetal CNS sonographers which may play a factor in obtaining a high success rate of volume acquisition and reconstruction of the diagnostic planes.[11]

According to recent data published by Welp *et al*., the authors tested the validity of 5D CNS for the detailed assessment of the fetal brain in a bigger study population size of 1110 volume data sets of uncomplicated singleton second- and third-trimester pregnancies. After the exclusion of cases with anomalies, the data again showed proper reconstruction of the fetal brain diagnostic planes in 958/1019 (94%) of the volume data sets included in the study. Similar to other studies, the examinations were also evaluated by fetal CNS expert sonographers.[12]

With this established information on the utility of 5D CNS, the researchers of this study aimed to evaluate the clinical utility of 5D CNS software in our local clinical setting with some differences in the methodology and data analysis of prior studies. Majority of the previous studies were participated in pregnancies in the second trimester. The researchers recognize the challenge of scanning a developing fetal brain throughout the trimesters of pregnancy. Hence, our study will include a stratified analysis of both second- and third-trimester pregnancies to determine if there will be any difference in the results when data analysis will be stratified per trimester.

Another difference of this research is the performance of the scans by a senior MFM fellow-in-training supervised by either one of the coinvestigators who are MFM subspecialists with more than 10 years of experience in fetal anatomy scan. In this process of data collection, the investigators will determine the utility of the 5D CNS in the usual day-to-day setting in a training tertiary hospital.

The 5D CNS semiautomated software is proposed to increase productivity and consistency, omitting repetitive tasks such as manually acquiring standard planes and tedious placement of calipers.[6] Consequently, this will allow more time for quality patient care that adds value such as communicating results and counseling patients. Moreover, the software is envisioned to facilitate the efficient sharing of readily available 5D CNS 3D volume data sets for cases requiring ultrasound referrals to neurosonography experts. It will omit unnecessary repetitive patient scanning and will still allow sonographic evaluation if the patient is unable to travel to the specialty ultrasound referral center.

Our study results support the findings of earlier studies abroad by Rizzo *et al*. in 2016 and Welp *et al*. in 2020 that showed an agreement of fetal CNS measurements and proper reconstruction of the fetal CNS diagnostic planes for both second- and third-trimester pregnancies.[11,12] However, we found that the 5D CNS software was affected by advanced gestational age and fetal head position at the time of the scan, suggesting that the 5D CNS tool may be more useful during the second trimester of pregnancy.

As presented in Table 2, there was a wide range of time to completion using 5D CNS, ranging from 18 to 220 s. One possible explanation for this wide duration range is the skill or expertise of the sonologist doing the 5D CNS scan. During data collection of this research, a shorter time to completion was observed during the latter part of the data collection which may represent the familiarity and ease of the scanner as the study progressed. Another study by Rizzo *et al*. in 2016 showed a faster time to completion taking 54 s when 5D CNS measurements were acquired by an expert versus an average time of 90 s obtained by an average sonographer. Because the technique is semiautomated, there remains an operator-dependent factor that may limit the duration of the examination.[13] Hence, care should be taken in generalizing our findings on time efficiency since our scans were performed solely by a supervised MFM fellow.

The 5D CNS significantly reduced the examination time only for second-trimester pregnancies. This is likely because of the more ossified calvarium in the third trimester precluding adequate imaging of the intracranial structures necessary to acquire 3D volume scans. Multiple attempts in acquiring 3D volume and manual adjustment of planes and measurements prolong examination time in more advanced stages of the pregnancy. Moreover, the persistent unfavorable position of the fetal head in the occiput anterior or posterior during this trimester caused a time delay.

Conclusion

Our study found the clinical utility of 5D CNS ultrasound in fetal cranial biometry by showing agreement in the biometric measurements with standard 2D scan. In terms of time for completion of the 5D CNS sonographic study, there are fetal-dependent and operator-dependent factors affecting the duration of the ultrasound evaluation.

The 5D CNS software has the potential to optimize workflow efficiency in our local clinical setting. To maximize this potential, an additional hands-on training on 3D sonography and the use of the 5D CNS software is necessary. Moreover, evaluation of the fetal head position before employing the 5D CNS technique is suggested.

Limitation

This study was limited to the sonographic evaluation of the basic fetal CNS measurements of the axial planes alone. Future studies on the comparison of the fetal cranial evaluations obtained in more diagnostic planes including coronal and sagittal planes are suggested.

Acknowledgment

This endeavor would not have been possible without the support of the Clinical and Translational Research Institute (CTRI). We are grateful for their provision of a research grant funding to support the completion and possible publication of this study.

Authorship contributions

Lizzette R. Caro-Alquiros, MD - Involved in the conceptualization, methodology, formal analysis, provision of resources, data curation, writing-original draft, review and editing, visualization, supervision and funding acquisition.

Zarinah G. Gonzaga, MD - Involved in the conceptualization, methodology, data curation, writing-review and editing and funding acquisition.

Irene B. Quinio, MD - Involved in the conceptualization, methodology, data curation, writing-review and editing and funding acquisition.

Financial support and sponsorship

This research study received funding from the Clinical and Translational Research Institute (CTRI) of The Medical City, Ortigas.

Conflicts of interest

There are no conflicts of interest.

References

1. Chitty LS, Pilu G. The challenge of imaging the fetal central nervous system: An aid to prenatal diagnosis, management and prognosis. Prenat Diagn 2009;29:301-2.
2. Malinger G, Paladini D, Haratz KK, Monteagudo A, Pilu GL, Timor-Tritsch IE. ISUOG practice guidelines (updated): Sonographic examination of the fetal central nervous system. Part 1: Performance of screening examination and indications for targeted neurosonography. Ultrasound Obstet Gynecol 2020;56:476-84.
3. Salomon LJ, Alfirevic Z, Da Silva Costa F, Deter RL, Figueras F, Ghi T, *et al.* ISUOG practice guidelines: Ultrasound assessment of fetal biometry and growth. Ultrasound Obstet Gynecol 2019;53:715-23.
4. He F, Wang Y, Xiu Y, Zhang Y, Chen L. Artificial intelligence in prenatal ultrasound diagnosis. Front Med (Lausanne) 2021;8:729978.
5. Weichert J, Welp A, Scharf JL, Dracopoulos C, Becker WH, Gembicki M. The use of artificial intelligence in automation in the fields of gynaecology and obstetrics – An assessment of the state of play. Geburtshilfe Frauenheilkd 2021;81:1203-16.
6. Leung KY. Applications of advanced ultrasound technology in

obstetrics. Diagnostics (Basel) 2021;11:1217.

7. Rizzo G. From 2D to 5D the Evolution of Fetal Neurosonography. Samsung Business; 2015. Available from: https://www.samsung.com/global/business/healthcare. [Last accessed on 2022 Feb 01].
8. Yang F, Leung KY, Lee YP, Chan HY, Tang MH. Fetal biometry by an inexperienced operator using two- and three-dimensional ultrasound. Ultrasound Obstet Gynecol 2010;35:566-71.
9. Benacerraf BR, Shipp TD, Bromley B. Three-dimensional US of the fetus: Volume imaging. Radiology 2006;238:988-96.
10. Rizzo G, Pietrolucci ME, Capece G, Cimmino E, Colosi E, Ferrentino S, *et al.* Satisfactory rate of post-processing visualization of fetal cerebral axial, sagittal, and coronal planes from three-dimensional volumes acquired in routine second trimester ultrasound practice by sonographers of peripheral centers. J Matern Fetal Neonatal Med 2011;24:1071-6.
11. Rizzo G, Capponi A, Persico N, Ghi T, Nazzaro G, Boito S, *et al.* 5D CNS+software for automatically imaging axial, sagittal, and coronal planes of normal and abnormal second-trimester fetal brains. J Ultrasound Med 2016;35:2263-72.
12. Welp A, Gembicki M, Rody A, Weichert J. Validation of a semiautomated volumetric approach for fetal neurosonography using 5DCNS+in clinical data from >1100 consecutive pregnancies. Childs Nerv Syst 2020;36:2989-95.
13. Rizzo G, Aiello E, Pietrolucci ME, Arduini D. The feasibility of using 5D CNS software in obtaining standard fetal head measurements from volumes acquired by three-dimensional ultrasonography: Comparison with two-dimensional ultrasound. J Matern Fetal Neonatal Med 2016;29:2217-22.