Hemispheric asymmetry and gender dimorphism of the fetal central sulcus on 7.0-T MRI

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Research Article

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Abstract

Purpose

The hemispheric asymmetry and gender dimorphism of the central sulcus (CS) have been studied since the 19th century. Although there is a clear understanding that hemispheric asymmetry and gender dimorphism exist in adults, the time when the differences begin to occur remains unknown. Therefore, this study aimed to explore whether hemispheric asymmetry and gender dimorphism in the CS of the fetal brain at 13–22 gestational weeks exist, this is of great significance for studies on the early development of CS.

Methods

We used 7.0-T MRI to measure the maximum depth and length of the CS in 58 Chinese fetal specimens from 13 to 22 gestational weeks. The MRI was imported into Amira4.1 to reconstruct three-dimensional brain models, on which the measurements were performed. Then the lateral and gender differences in the CS of the fetal brain at 13–22 gestational weeks were analyzed.

Results

There were significant gender differences in the length of the CS at 13, 14, 16 ($P < 0.01$), and 18 gestational weeks ($P < 0.05$), as well as in the depth of the CS at 18 and 19 gestational weeks ($P < 0.01$). The lengths of the CS at 15 and 19 gestational weeks, and the maximum depth of the CS at 15 gestational weeks showed lateral differences (both $P < 0.05$).

Conclusion

Our findings revealed no stable hemispheric asymmetries or gender dimorphisms of the CS between 13 and 22 gestational weeks.

What does this study adds to the clinical work

-The study, for the first time, investigate whether hemispheric asymmetries and gender dimorphism of the fetal central sulcus (CS) exist in the early development period.

-Our findings suggest that no stable hemispheric asymmetries or gender dimorphisms of the CS were found between 13 and 22 gestational weeks. These data further improve the understanding of the fetal brain in the early development period.

Introduction

It has long been known that the left and right hemispheres of the human brain show different morphology related to their functions in the human body, with this being referred to as asymmetry or hemispheric asymmetry [1]. The earliest evidence of asymmetry comes from the observation of clinical patients with focal cerebral injury. In 1860, Paul Broca found that damage to specific areas (over part of the inferior frontal gyrus) of the left hemisphere could cause aphasia, although this did not happen when similar damage occurred on the right side [2]. Since then, more and more evidence has revealed functional differences between the left and right hemispheres of the human brain [3–6]. The most fundamental reason for the functional differences of the brain is differences in the organization of structures between the left and right hemispheres. To identify the organization and structural basis of the functional asymmetry of the human brain, studies have concentrated on the structural differences in the cerebral hemispheres, and have gradually revealed that multiple structures differ between the left and right hemispheres of the human brain [7–9]. In 2007, Amunts used MRI to measure the depth of the central sulcus (CS) of 103 healthy adults and showed significant differences between the left and right hemispheres of right-handed men, whose left CS was deep in the right side, whereas no obvious differences were found in women [10].

Obvious differences in brain function between men and women have long been found, and include cognitive processing, language, spatial imagination, and logical thinking [11–13]. These differences are also based on differences in the structures of the brain. In 1982, DeLacoste-Utamsing and Holloway published an article in *SCIENCE* magazine that proposed the existence of gender dimorphism in the morphology of the human corpus callosum [14]. Since then, more and more studies have suggested differences in multiple brain structures between men and women [15, 16], including a larger volume of gray matter along the CS in women than in men [17, 18].

However, there are few reports on the study of hemispheric asymmetries and gender dimorphism in the fetal human brain, and we are not aware of any reports of study of hemispheric asymmetries and gender dimorphism in the fetal CS [19].

To ascertain whether hemispheric asymmetries and gender dimorphism of the fetal CS exist in the early development period, this study obtained 7.0-T MRI data of the fetal CS from specimens ranging from 13 to 22 gestational weeks.

Using statistical methods, the condition of the hemispheric asymmetries and gender dimorphism of the fetal CS in the early development period were preliminarily judged, providing data that can further improve the understanding of the fetal brain in the early development period.

Materials and methods

Subjects

Sixty-nine Chinese fetal specimens of between 13 to 22 gestational weeks were available for this study. These samples were collected from dead fetuses in hospitals of Shandong province. The causes of death included premature delivery, abnormal delivery, and maternal diseases. The gestational weeks of the fetuses were calculated on the basis of pregnancy (weeks from the last menstrual period), head circumference, crown–rump length, foot length, and/or pregnancy record [20].

After screening, fifty-eight specimens were included in this study. The screening criteria were as follows: results of an US examination and 3.0-T MRI prescan showing that the fetal CNS was normal in anatomy and development; no history of familial genetic disease; pregnancy records without fetal chromosomal abnormalities, intrauterine pressure, or eclampsia; further imaging examination excluding intracranial diseases or extracranial abnormalities [21]. The demographic distributions of the specimens are listed in Table 1.

Table 1
Information on the selected specimens (n = 58).

Weeks of gestational age(GA)	Sex	Number
13	Male	3
13	Female	2
14	Male	3
14	Female	2
15	Male	3
15	Female	3
16	Male	3
16	Female	3
17	Male	3
17	Female	3
18	Male	3
18	Female	3
19	Male	3
19	Female	3
20	Male	3
20	Female	3
21	Male	3
21	Female	3
22	Male	3
22	Female	3

All specimens were stored in 10% formalin solution immediately after collection and underwent MRI scanning within 1 week. The study was approved by the Human Research Ethics Committees of the Shandong First Medical University. Consent for use of the fetuses in this study was obtained from all parents.

Acquisition of Fetal Brain Images

After the final selection of fetal specimens, the heads of all specimens were scanned with 7.0-T MRI (Bruker company, Germany) within 1 week. The heads were scanned with small animal coils with an inner diameter of 60 mm, slice thickness of 0.5 mm, and interslice spacing of 0.5 mm. The parameters of the

T1-weighted imaging (T1WI) were: repetition time = 384.4 ms, echo time = 15.8 ms, matrix = 512 × 512, excitation number = 1, field of view = 6 × 6 cm, The parameters of the T2-weighted imaging (T2WI) were: TR = 17000.0MS, TE = 50.0MS, matrix = 256×256, excitation times 4, field of view = 6×6cm. SNR ≥ 80%. SNR ≥ 80%. High-resolution T1WI and T2WI 7.0-T MRI were acquired [19, 21].

MRI Processing

In comparison with MRI of lower field strength, 7.0-T MRI can show the boundary between the cerebral cortex and cerebrospinal fluid more clearly, which is very beneficial for image segmentation (Fig. 1). All T2WI images of each fetal brain sample were imported into Amira 4.1 for cerebral cortex image segmentation, and for this purpose, the three-dimensional shape of the fetal brain was reconstructed [19, 21]. The recognition and segmentation of cerebral cortex images were performed by two professionals (an anatomy teacher and an imaging doctor) to ensure the accuracy of image segmentation.

Location of CS

To determine the position of the original CS on the reconstructed fetal brain surface, the midpoint of the upper edge of the cerebral hemisphere and the midpoint of the lateral sulcus were first determined. A straight line was then made between the two points. The depression in the lateral hemisphere along this line was considered to be the original CS (Fig. 2). It was observed that there is a stable primordial CS in the reconstructed fetal brain at 13–22 gestational weeks.

Obtaining the CS Data

Using Amira 4.1, the depth of the CS on both sides of each layer was measured along the full length to obtain the maximum depth of the CS on both sides of the specimen. The maximum length of the CS on both sides of the specimen was also measured. Two professionals (an anatomy teacher and an imaging doctor) carried out image recognition and data measurement, respectively. When there were discontinuities in the depression of the positioned CS area, the maximum length of each depression was measured along the axis, and the accumulated length was used as the maximum length of the CS.

Statistical Analysis

All the data were statistically analyzed using the Statistics Analysis System (SAS 9.2). The maximum lengths of the independent CS measurements by the two professionals were paired for intra-class correlation analysis to determine their consistency. The maximum length and depth of the CS in the 13–22-gestational-week specimens were matched according to gender to detect gender differences between specimens of the same gestational age. In the same way, the maximum length and depth of the CS of the different sides were matched according to gestational week to detect differences between left and right hemispheres across the gestational ages.

Results

Intra-class Correlation Coefficient

The maximum length of the fetal CS and the intra-class correlation coefficient of the left CS measured by the two professionals was 0.989 ($P < 0.001$), with the intra-class correlation coefficient for the right CS measurements by the two professionals being 0.971 ($P < 0.001$). Therefore, we found the measurement data of the two professionals to be highly consistent.

3D-Reconstructed Images of the Fetal Brain

Using the 7.0-T MRI of the fetal brains, 3D images representing the fetal brain shape at each gestational week were reconstructed using Amira 4.1, and the shape of the original CS was identified (Fig. 3).

Measurement of the Fetal CS

The maximum length and depth of the CS from 13–22 gestational weeks were measured and analyzed according to gender and side (Tables 2–5, Fig. 4–7). There were significant gender differences in the length of the CS at 13, 14, 16 ($P < 0.01$), and 18 gestational weeks ($P < 0.05$). There were also significant gender differences in the depth of the CS at 18 and 19 gestational weeks ($P < 0.01$). The lengths of the CS at 15 and 19 gestational weeks, and the maximum depth of the CS at 15 gestational weeks showed lateral differences (both $P < 0.05$).

Table 2
Gender differences in the maximum length of the CS over 13–22 gestational weeks

	Gender		*P*
	Male (cm)	**Female (cm)**	
GA = 13	0.29 ± 0.15	0.56 ± 0.05	0.009
GA = 14	0.85 ± 0.11	1.34 ± 0.12	< 0.001
GA = 15	1.09 ± 0.07	1.14 ± 0.06	0.144
GA = 16	1.24 ± 0.10	1.39 ± 0.05	0.008
GA = 17	2.19 ± 0.37	2.13 ± 0.23	0.775
GA = 18	1.80 ± 0.09	1.45 ± 0.33	0.031
GA = 19	1.53 ± 0.20	1.26 ± 0.37	0.149
GA = 20	1.64 ± 0.23	1.37 ± 0.33	0.124
GA = 21	1.40 ± 0.25	1.44 ± 0.23	0.767
GA = 22	1.16 ± 0.29	1.44 ± 0.38	0.182

Table 3
Left- and right-side differences in the maximum length of the CS over 13–22 gestational weeks

	Side		*P*
	Left (cm)	**Right (cm)**	
GA = 13	0.38 ± 0.24	0.42 ± 0.11	0.744
GA = 14	0.99 ± 0.33	1.10 ± 0.22	0.569
GA = 15	1.16 ± 0.05	1.07 ± 0.05	0.010
GA = 16	1.33 ± 0.12	1.30 ± 0.109	0.642
GA = 17	2.22 ± 0.27	2.10 ± 0.33	0.533
GA = 18	1.48 ± 0.36	1.78 ± 0.09	0.082
GA = 19	1.61 ± 0.18	1.18 ± 0.28	0.011
GA = 20	1.41 ± 0.39	1.60 ± 0.18	0.291
GA = 21	1.35 ± 0.28	1.49 ± 0.15	0.327
GA = 22	1.44 ± 0.23	1.15 ± 0.41	0.171

Table 4
Gender differences in the maximum depth of the CS over 13–22 gestational weeks

	Gender		*P*
	Male (cm)	**Female (cm)**	
GA = 13	0.02 ± 0.02	0.03 ± 0.03	0.549
GA = 14	0.07 ± 0.03	0.05 ± 0.01	0.156
GA = 15	0.19 ± 0.05	0.24 ± 0.08	0.227
GA = 16	0.22 ± 0.03	0.24 ± 0.04	0.425
GA = 17	0.18 ± 0.03	0.20 ± 0.04	0.411
GA = 18	0.57 ± 0.13	0.25 ± 0.08	< 0.001
GA = 19	0.20 ± 0.05	0.37 ± 0.05	< 0.001
GA = 20	0.24 ± 0.07	0.22 ± 0.04	0.714
GA = 21	0.23 ± 0.07	0.28 ± 0.04	0.209
GA = 22	0.32 ± 0.13	0.29 ± 0.04	0.612

Table 5
Left- and right-side differences in the maximum depth of the CS over 13–22 gestational weeks

	Side		*P*
	Left (cm)	**Right (cm)**	
GA = 13	0.02 ± 0.02	0.03 ± 0.03	0.653
GA = 14	0.05 ± 0.01	0.05 ± 0.03	1.000
GA = 15	0.17 ± 0.04	0.26 ± 0.07	0.021
GA = 16	0.24 ± 0.04	0.21 ± 0.02	0.114
GA = 17	0.19 ± 0.04	0.18 ± 0.03	0.504
GA = 18	0.46 ± 0.24	0.36 ± 0.14	0.381
GA = 19	0.29 ± 0.08	0.27 ± 0.12	0.734
GA = 20	0.20 ± 0.04	0.26 ± 0.05	0.080
GA = 21	0.24 ± 0.06	0.27 ± 0.05	0.251
GA = 22	0.28 ± 0.08	0.33 ± 0.10	0.317

Discussion

Debate on the Asymmetry and Gender Differences in the Human Cerebral Cortex

Since studies found differences in the functions of the human left and right cerebral hemispheres, and in cognitive, logical thinking, and other functions between men and women, research into exploring the structural basis behind these asymmetries and gender differences, that is, the anatomical basis of human brain structure, has been continually ongoing [22–24]. Many researchers have studied the morphology of the cerebral cortex, and although most research has shown obvious lateral and gender differences in the morphology of the cerebral cortex, some studies have found no obvious inter-hemispheric asymmetries or gender dimorphism [25–27].

Such conflicting results illustrate the value of this study. The reasons for the differing research conclusions may be based on the different research participants or specimens selected (age-stage, value orientation, living or specimen), different research methods (direct examination of brain specimens, medical images of brain tissue, different quality medical images), or different technical routes (observation of brain structure, simple weighing, computerized automatic measurement). However, the gestational time at when differences begin to occur generally remains unknown.

There have been related studies on the early growth of fetal brain [28–30], and research on the reconstruction of the fetal cerebral cortex [19]; however, little work has been done on early CS development using modern technology and statistical methods to produce consistent objective data [21].

This study is based on 7.0-T MRI of fetal brains scanned within 1 week of death, which allowed the natural state of the fetal brain to be imaged. The high resolution MRI ensured the accuracy of the imaging and measurement data.

Asymmetry and Gender Differences of the Fetal CS

Studies on asymmetry and gender differences of the CS began in the last century [31]. Currently, there is evidence that asymmetries exist in the adult CS [32], but the time at which these differences begin to occur remains unknown.

In 2013, Zhonghe et al. studied the development of the fetal cerebral cortex at 12–22 gestational weeks with 7.0-T MRI, and analyzed the sequential development of the different fissures and sulci. Their measurements of fetal brains showed that each sulcus of the brain had different growth rates, which linearly increased with gestational week, but they found no sexual dimorphisms or cerebral asymmetries [19].

Previous work has not revealed lateral and gender differences in the CS of the fetal brain at 13–22 gestational weeks. Differences occurring over a few gestational weeks may be temporarily affected by cortical development and cell migration [19].

We assume that fetal brain asymmetry and gender differences may develop during the third trimester, an assumption that is consistent with the results of Zhuoran Li[33].

Significance of Asymmetry and Gender Differences in Fetal CS

The development and maturation of the fetal brain involves many parallel processes, the most obvious of which include migration of nerve cells, sulcus formation, and myelination [1–11]. The formation of brain sulci is a sign of fetal cortical maturity, and some main brain sulci can be used as a sign of different brain development stages, and can therefore be used to judge whether fetal brain development is consistent with gestational age [13]. The CS is one of the earliest sulci in the fetal cerebral cortex and is easy to identify. Its developmental process and morphological characteristics are of great significance for prenatal examination. In the cases of fetal malformations, the proportion of central nervous system abnormalities is as high as 50% [34]. Because of the importance of the structure and functions of the cerebral cortex, it is included as one of the studied items in almost all research on the fetal cerebral cortex, and is considered a key to revealing cortical sensory and motor function localization areas [14, 15].

In this study, we found that there were no stable lateral or gender differences in the CS during weeks 13–22 of pregnancy, the result is consistent with the findings of Zhang et al [19] and Li et al [33].

Conclusions

Our finding revealed that no stable hemispheric asymmetries or gender dimorphisms of the CS were found between 13 and 22 gestational weeks.

Declarations

Data availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Contributions

Conceptualization: HZ and MZ; Methodology: AD and SL; Formal analysis and investigation: AD, SL, ZZ, LJ, SWL; Writing—original draft preparation: AD and SL; Writing—review and editing: HZ and MZ; Resources: ZZ, LJ, SWL; Supervision: AD, SL, MZ, HZ. All authors read and approved the final manuscript.

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Ethics declarations

Conflict of interest

The authors have no relevant financial or non-financial interests to disclose.

Ethical approval

The study was approved by the Human Research Ethics Committees of the Shandong First Medical University. Consent for use of the fetuses in this study was obtained from all parents.

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Figures

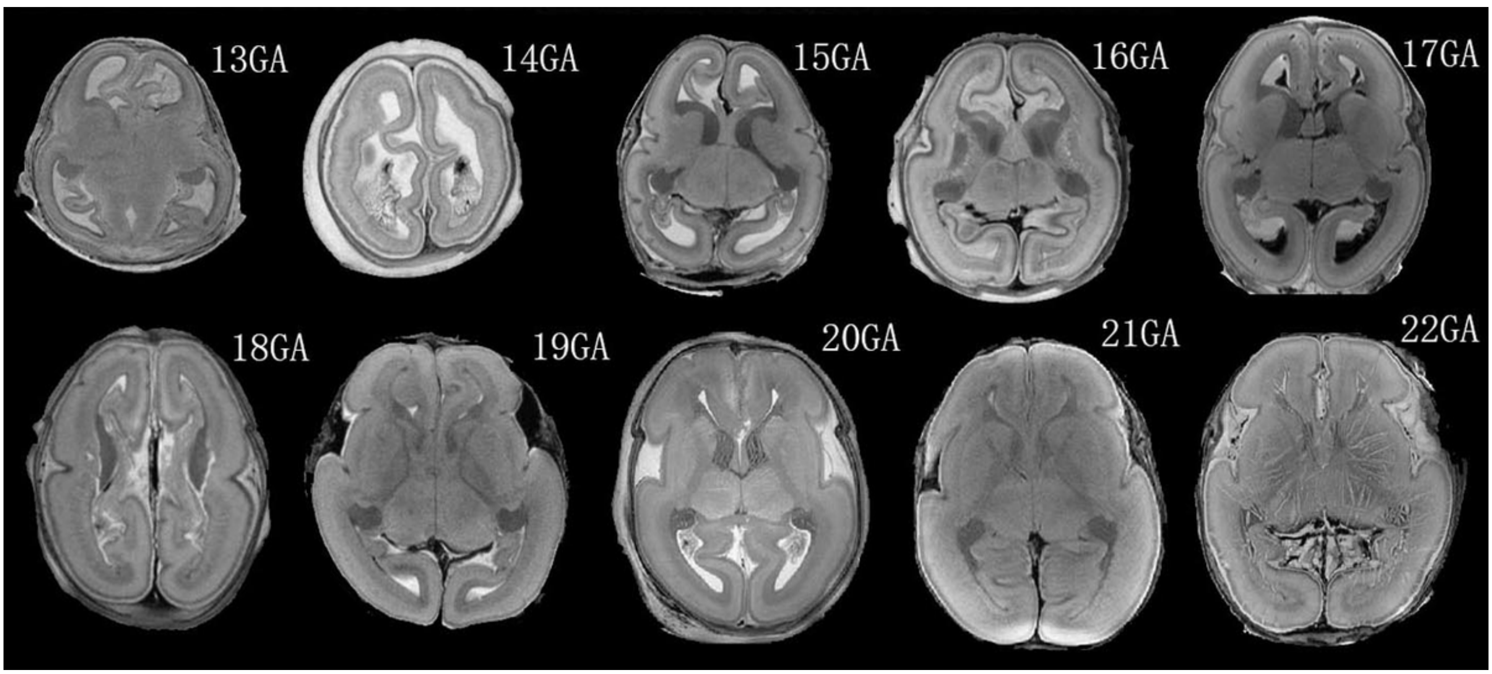

Figure 1

7.0-T MRI of the fetal brain at 13–22 gestational weeks

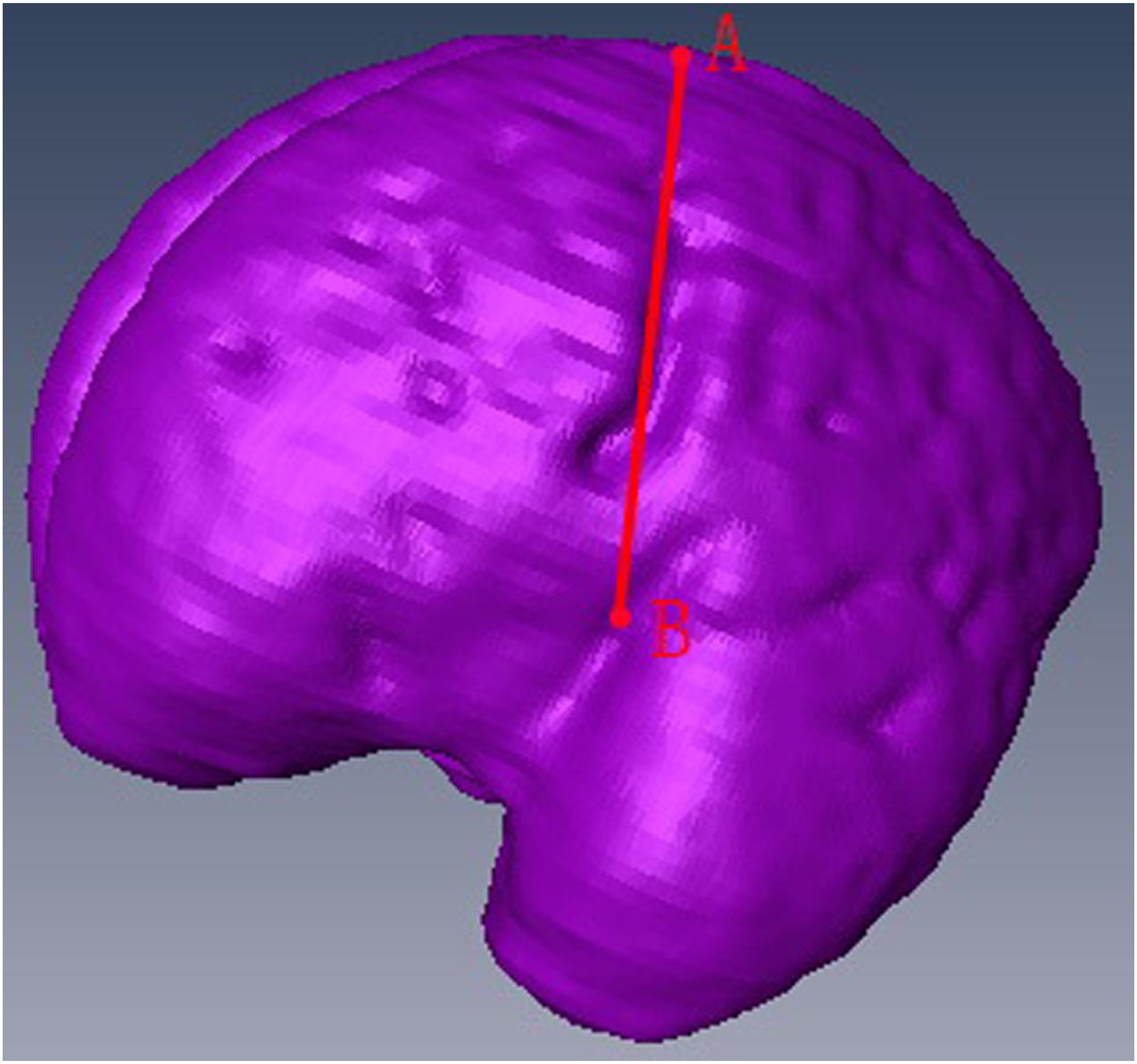

Figure 2

Location of the CS. (A) Midpoint of the sagittal line (B) Midpoint of the lateral sulcus

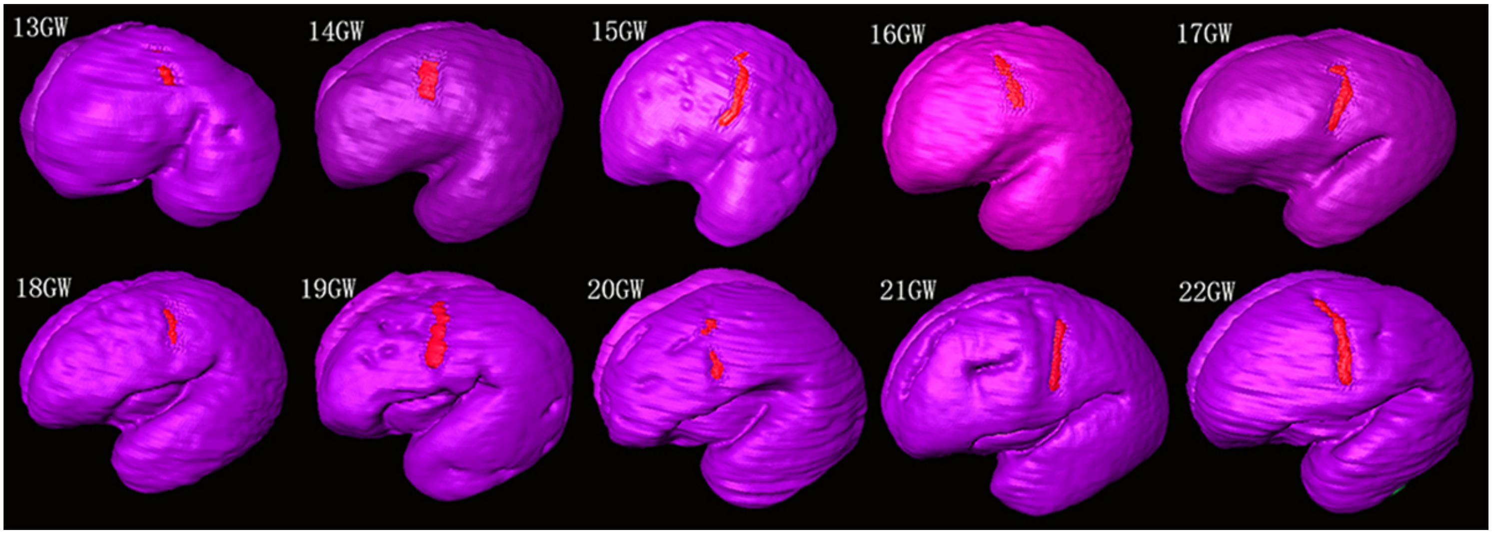

Figure 3

3D reconstructed images of the fetal brain and CS from 13 to 22 gestational weeks

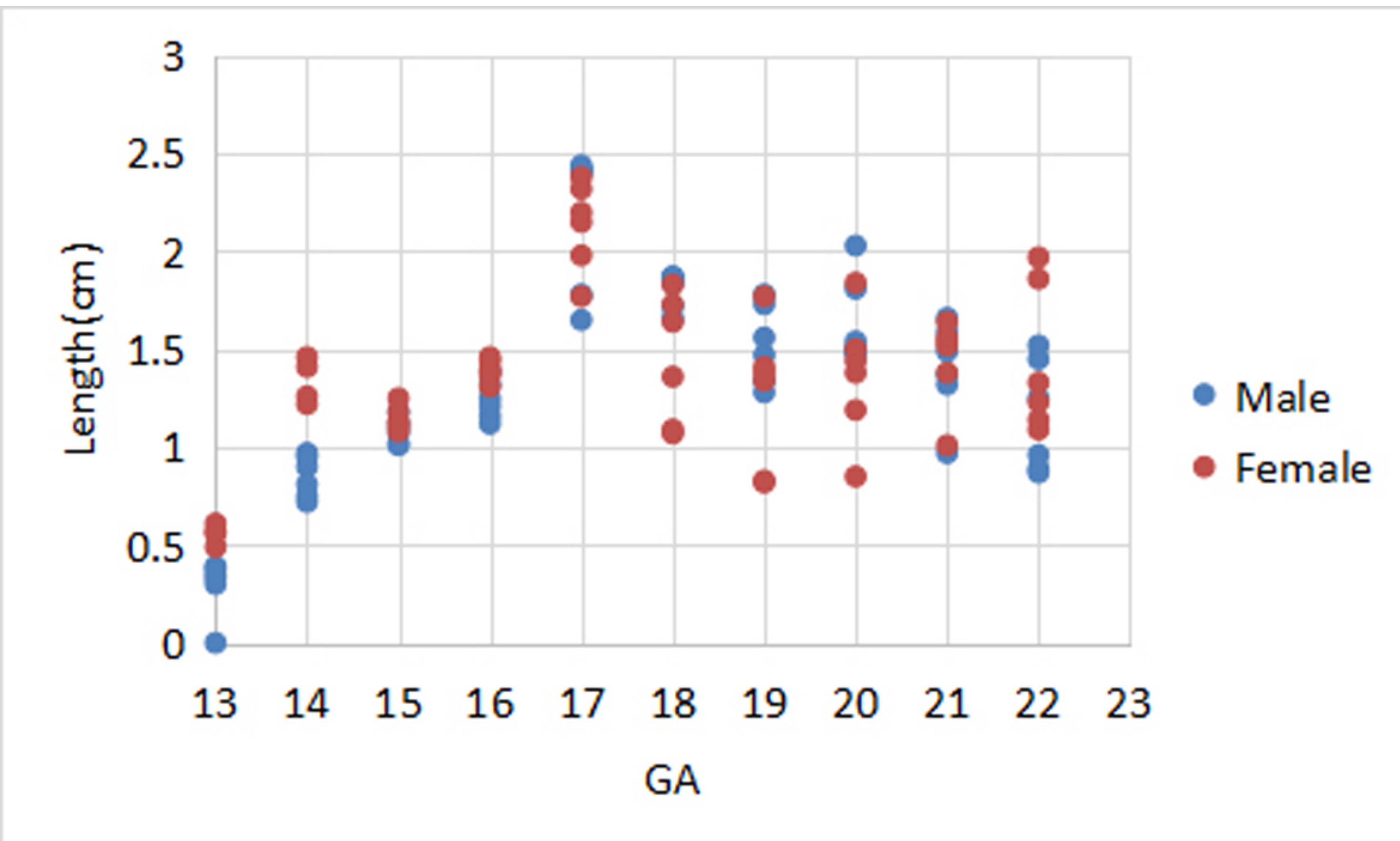

Figure 4

Data distribution of the maximum length of the fetal CS according to gender from 13 to 22 gestational weeks

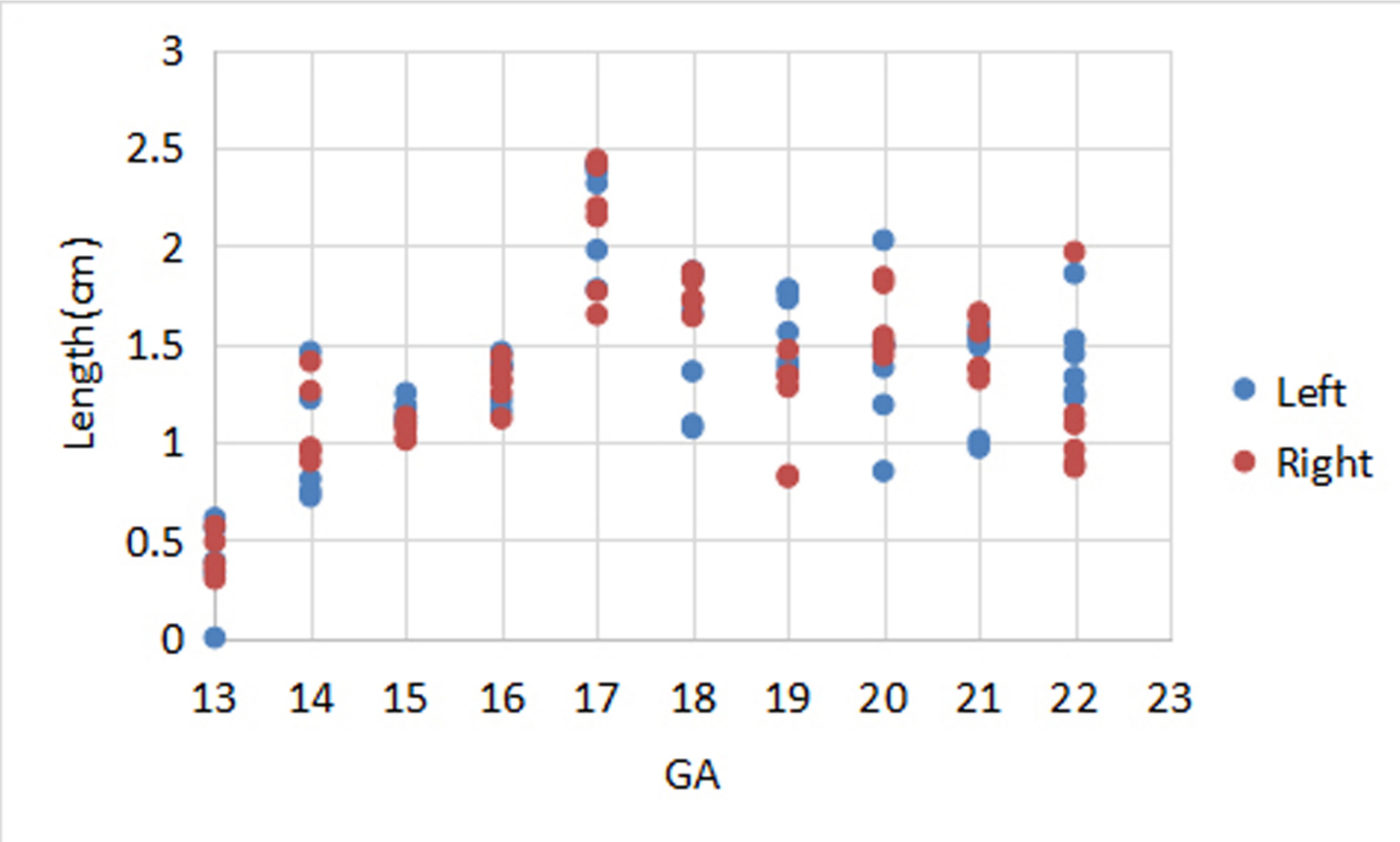

Figure 5

Data distribution of the maximum length of the fetal CS according to side from 13 to 22 gestational weeks

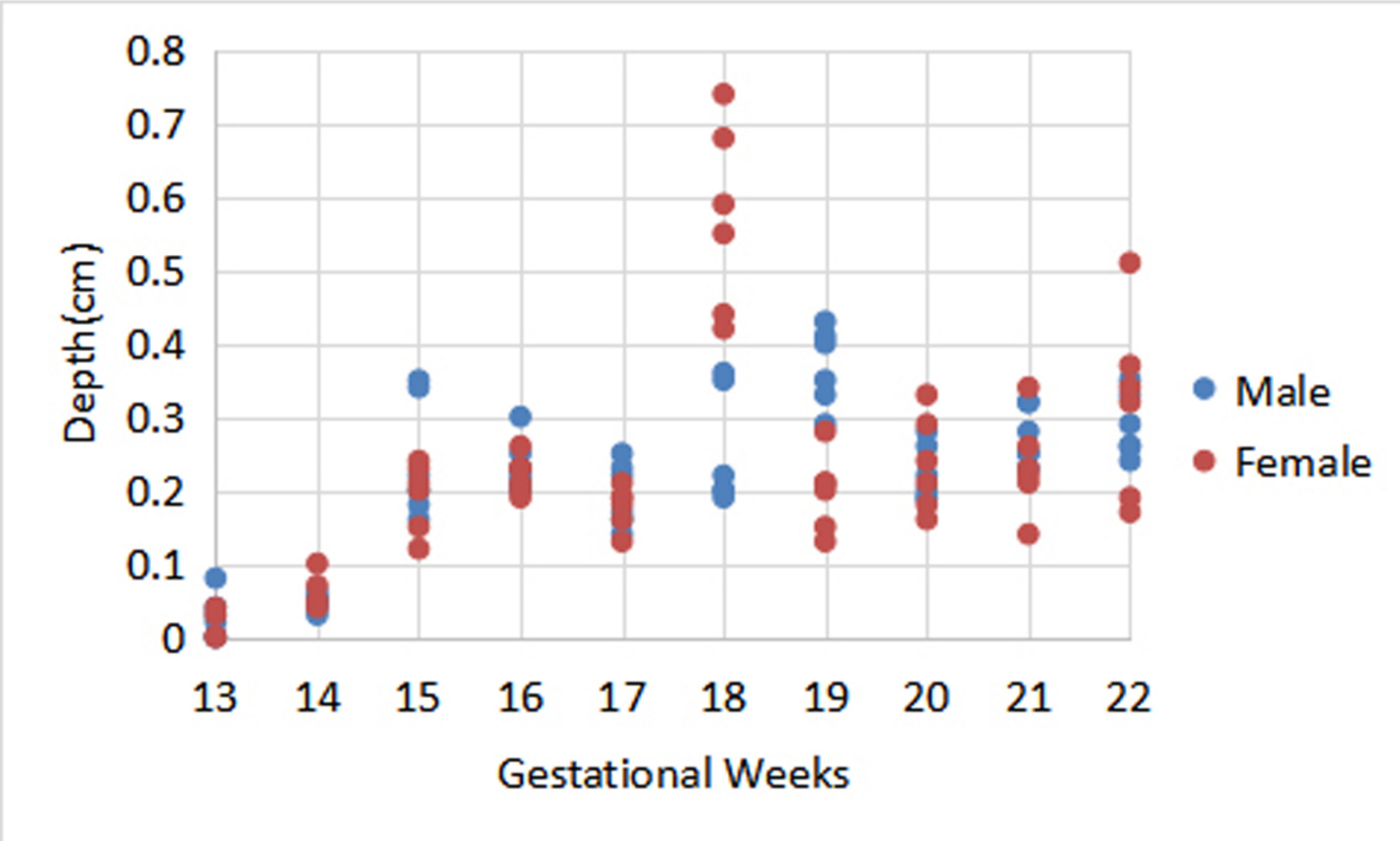

Figure 6

Data distribution of the maximum depth of the fetal CS according to gender from 13 to 22 gestational weeks

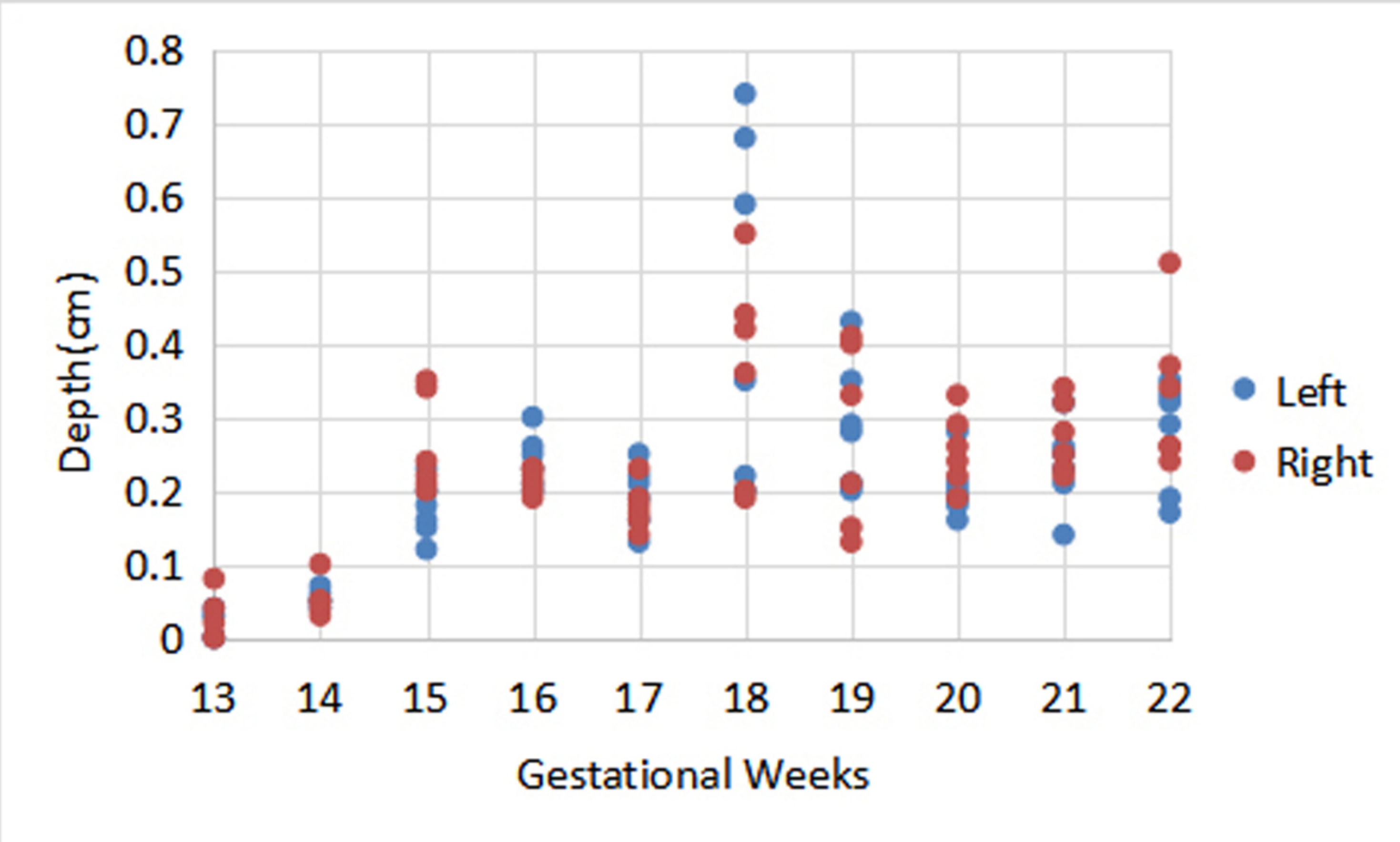

Figure 7

Data distribution of the maximum depth of the fetal CS according to side from 13 to 22 gestational weeks