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Development of the human fetal pons: *in utero* ultrasonographic study

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KEYWORDS: brain mid-sagittal view; cerebellar vermis; fetal pons; ultrasound

ABSTRACT

Objectives *To examine the ultrasonographic feasibility of imaging the fetal pons and to construct a reference chart for its normal development during gestation.*

Methods *A cross-sectional, prospective study on 293 healthy fetuses of low-risk pregnancies between 19 and 34 weeks was performed. The transfontanel approach, via the abdominal or vaginal routes, was used to evaluate the fetal metencephalon (pons and cerebellum). The anteroposterior diameter of the fetal pons was measured in a mid-sagittal plane. The longitudinal diameter of the cerebellar vermis was measured at the same plane and the vermis–pons ratio (VPR) was established.*

Results *One hundred and forty-four fetuses were in vertex position. In 140 (97.2%) satisfactory visualization and measurements of the pons and cerebellar vermis were obtained. One hundred and forty-nine fetuses were breech presentations and measurements were successfully performed in 147 (98.6%). The pons anteroposterior and vermis longitudinal diameters showed a linear correlation with gestational age (GA) ($r = 0.95$ for both measurements; $P < 0.001$). The mean VPR was 1.5 (± 0.1 SD) and did not change in the gestational interval that was considered.*

Conclusion *By using the transfontanel approach, evaluation of the fetal pons is feasible via the mid-sagittal plane. The nomograms developed and the ratio to fetal vermis provides reference data that may be helpful when evaluating anomalies of the brainstem. Copyright © 2004 ISUOG. Published by John Wiley & Sons, Ltd.*

INTRODUCTION

Most fetal brain anomalies are detectable by using the well-known three axial planes of the brain, as was reported by Filly *et al.*[1]. However, congenital brain anomalies involving the median structures are rarely reported during fetal life. This is mainly because the standard views of the fetal brain do not include the mid-sagittal plane, which is essential for the visualization of the metencephalon and brainstem. The brainstem, which is a distinct subdivision of the brain, includes: part of the hypothalamus (diencephalon), the midbrain (mesencephalon), the pons, and the medulla oblongata[2].

The pons, as the main part of the brainstem, can be optimally visualized only by the mid-sagittal view. Although the transfontanel mid-sagittal view is a cornerstone in neonatal brain imaging[3], and quantitative measurements for the brainstem were suggested by magnetic resonance imaging technology[4], there is a lack of *in utero* data regarding the normal development during human gestation.

Basic knowledge of the normal appearance and development of the fetal pons is essential for any prenatal evaluation in cases suspected of brain anomalies, such as Dandy–Walker complex, pontocerebellar atrophy and rhombencephalosynapsis[5–10].

Therefore, this study was designed to evaluate the feasibility of imaging the fetal pons in the mid-sagittal transfontanel approach during routine sonographic examination, and to construct a reference range of pons size during normal human gestation.

METHODS

A cross-sectional prospective study was conducted on low-risk pregnant women whose fetuses had normal

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brains. The fetal brain was scanned in a mid-sagittal plane using the transfontanel approach. All examinations were performed during routine pregnancy follow-up and were in addition to the standard axial views. The Institutional Review Board committee approved the study and all patients gave informed consent for their participation.

Two hundred and ninety-three women with pregnancies between 19 and 34 weeks were selected to form the study group. The study group fulfilled the following criteria: (1) gestational age (GA) based on the beginning of the last menstrual period (LMP) was verified by sonographic measurements of the crown–rump length (CRL) of a singleton gestation in early pregnancy; in cases where the LMP–CRL difference was > 10 days, the pregnancy was dated by the CRL measurements, (2) the estimated fetal weight (EFW) was within the 10^{th} to 90^{th} percentile, (3) absence of maternal disease (e.g. diabetes, pregnancy-induced hypertension (PIH)/pre-eclampsia, intrauterine growth restriction (IUGR), red cell antibodies), (4) clinically-normal fetus at birth, (5) no known maternal or previous sibling with central nervous system defect.

The mid-sagittal view included the corpus callosum, the cavum septi pellucidi, and the brainstem–vermis plane. At the brainstem–vermis level, attention was paid to include the rostral part of the thalamus, the midbrain, the pons, the medulla oblongata, the fourth ventricle, and the cerebellar vermis. To perform this examination, we viewed the median plane and moved the transducer posteriorly to pass through the posterior fontanel, visualizing the brainstem along a line passing from the posterior fontanel to the chin. This angle enabled us to overcome the artifacts from the surrounding structures (Figure 1).

The pons was measured at its anteroposterior diameter. The contour of its anterior edge could be clarified, when needed, by the course of the basilar artery over the clivus of the occipital and sphenoid bones. The posterior border represented a line across the ventral edge of the fourth ventricle. The cerebellar vermis was measured in a longitudinal diameter from the superior pole of the culmen to the inferior pole of the pyramis (Figure 2). The two measurements and the ratio between them were plotted on a curve.

Each patient was examined once during the study period. Scanning was performed with a multi-frequency ATL 3000 (Bothell, WA, USA) 2–4-MHz abdominal and 4–8-MHz vaginal probes, and with GE Logic 9 (General Electric, Milwaukee, WI, USA) multi-frequency 5–7-MHz abdominal, and 6–8-MHz vaginal probes. All measurements were performed by a single observer (Z.K.). The intraobserver variation of 20 cases was calculated at the beginning of the study. In each case, at least two optimal consecutive measurements were performed, and the mean was established. Freeze frame ultrasound capabilities and electronic on-screen calipers were used for the measurements. Centile ranges were calculated and tabulated for consecutive gestational ages, and regression fitness with GA was determined. The following statistical tests were used in the analysis of the data: Pearson correlations were applied for testing the correlations between weeks and the study parameters (all tests applied were two-tailed), and $P \leq 5\%$ was considered statistically significant. The data were analyzed using the SAS software (SAS Institute, Cary, NC, USA).

RESULTS

One hundred and forty-four fetuses (49%) were in a vertex presentation, and 149 (51%) were in a breech presentation. Among the vertex presentations, 87 (60.4%) were examined vaginally, and 52 (36.1%) abdominally. In five cases (3.5%) a combined approach was used. In the vertex group there were 140 (97.2%) cases with successful mid-sagittal views of the pons–vermis plane, in which measurements of both structures could be

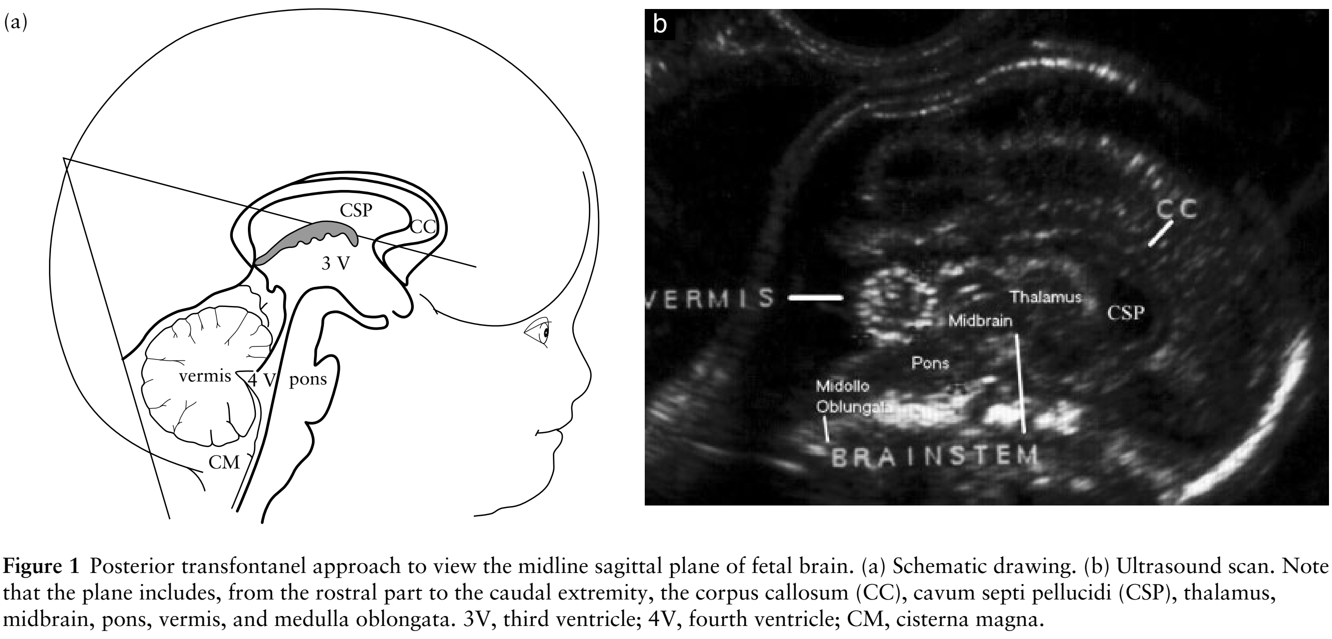

Figure 1 Posterior transfontanel approach to view the midline sagittal plane of fetal brain. (a) Schematic drawing. (b) Ultrasound scan. Note that the plane includes, from the rostral part to the caudal extremity, the corpus callosum (CC), cavum septi pellucidi (CSP), thalamus, midbrain, pons, vermis, and medulla oblongata. 3V, third ventricle; 4V, fourth ventricle; CM, cisterna magna.

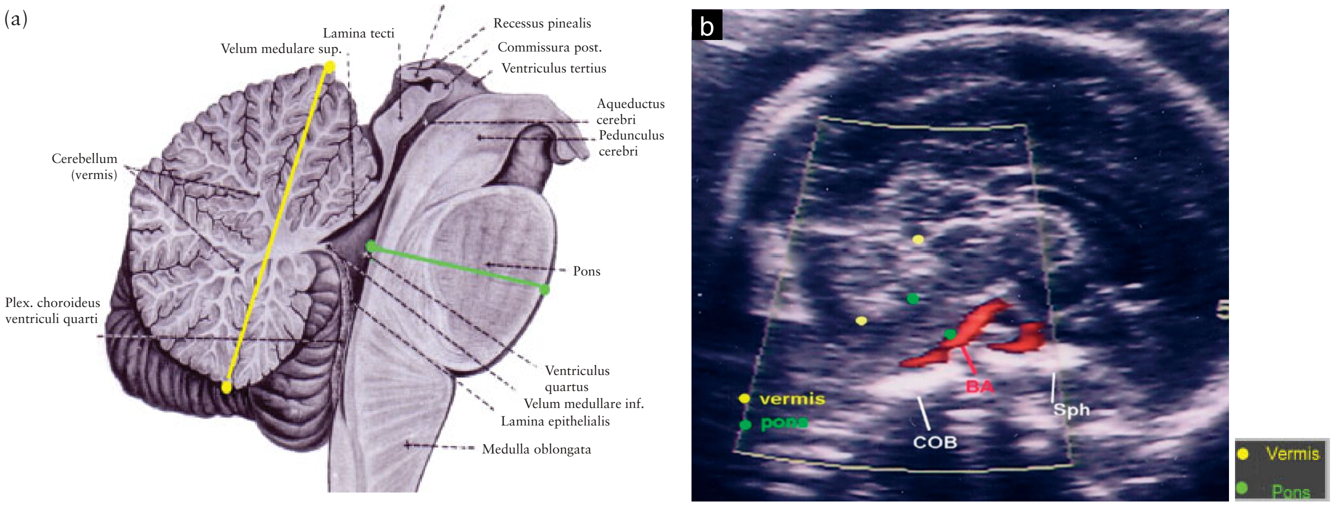

Figure 2 Measurements of the pons anteroposterior diameter and the cerebellar vermis longitudinal diameter. (a) Schematic drawing of anatomical landmarks. (b) Sonographic scan. Note the course of the basilar artery (BA), along the clivus of the occipital bone (COB) and the sphenoid bone (Sph).

achieved. In the breech group, 147/149 (98.6%) fetuses showed appropriate view for adequate measurements. The total feasibility rate was (287/293) 97.9%. The intraobserver variability was 10.0% and 9.7% for the measurements of the pons and vermis, respectively. The pons anteroposterior and vermis longitudinal diameters showed a linear increase during pregnancy, $r = 0.945$ and 0.947, respectively (Figures 3 and 4). The relative centile charts are presented in Tables 1 and 2.

The mean vermis–pons ratio (VPR) during pregnancy was 1.5 ($\pm$0.1 SD). This ratio showed a slight fluctuation from 1.44 at 19–20 weeks of gestation to 1.67 at

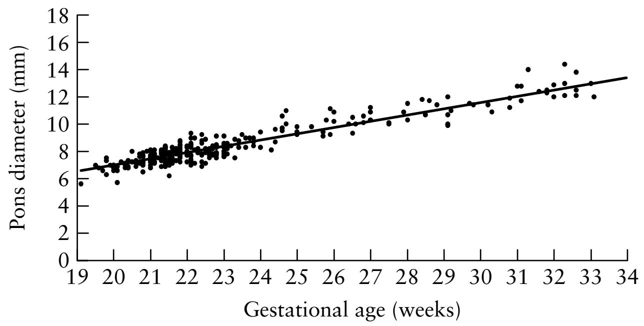

Figure 3 Correlation between the anteroposterior diameter of the pons and gestational age ($r = 0.945$).

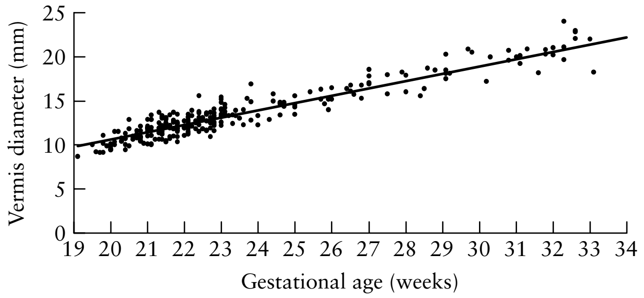

Figure 4 Correlation between vermis superoinferior diameter and gestational age ($r = 0.947$).

Table 1 Percentile measurements of the pons (anteroposterior diameter) according to gestational age

GA (weeks)	n	*Anteroposterior diameter (mm)* 5th	25th	50th	75th	95th
19–20	18	4.2	6.3	6.8	7.0	7.5
21–22	114	6.8	7.2	7.5	8.0	8.3
23–24	82	7.2	7.7	8.2	8.5	9.1
25–26	20	8.4	9.3	9.6	10.2	11.0
27–28	15	9.3	10.0	10.3	10.9	11.5
29–30	11	9.9	10.7	11.4	11.7	12.0
31–32	13	10.9	11.7	12.3	12.8	14.0
33–34	14	12.0	12.4	12.8	13.5	15.7

GA, gestational age.

Table 2 Percentile measurements of cerebellar vermis (superoinferior diameter) according to gestational age

GA (weeks)	n	*Superoinferior diameter (mm)* 5th	25th	50th	75th	95th
19–20	18	6.5	9.1	9.5	10.0	11.1
21–22	114	10.1	10.9	11.7	12.1	13.2
23–24	82	11.4	12.3	13.0	13.6	15.2
25–26	20	13.1	14.3	14.8	15.4	16.4
27–28	15	15.3	16.0	16.8	17.9	18.6
29–30	11	15.6	17.5	18.5	20.3	20.9
31–32	13	17.2	19.6	20.1	20.7	21.0
33–34	14	18.3	20.6	21.5	22.8	24.0

GA, gestational age.

29–30 weeks, and to 1.65 at 33–34 weeks that was not statistically significant ($r = 0.33$; $P = 0.121$) (Figure 5).

DISCUSSION

To the best of our knowledge, this is the first prospective, cross-sectional study aimed at investigating the feasibility

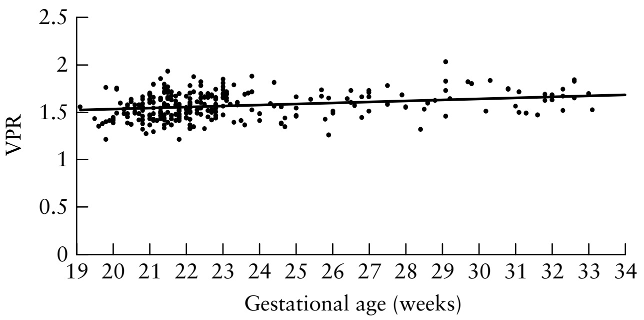

Figure 5 Correlation between the vermis–pons ratio (VPR) and gestational age ($r = 0.333$).

Table 3 Syndromes associated with maldevelopment of the brainstem: dysplasia, hypoplasia and atrophy (OMIM™ clinical synopsis)

Syndrome	*OMIM*
Marden–Walker	248 700
Joubert	213 300
Achondroplasia	100 800
De Sanctis–Cacchione	278 800
Canavan Van Bogaert Bertrand	171 900
Behcet	109 650
Wolfram	222 300
Carbohydrate deficient glycoprotein type 1	212 065
Progressive encephalopathy with hypsarrhythmia and optic atrophy	260 565
Cerebral ataxia and hypogonadotropic hypogonadism	212 840
Cardiofaciocutaneous (CFC)	115 150

of using the transfontanel approach in evaluating the fetal pons.

The pons is the major part of the brainstem. It serves mainly as a relay center between the spinal cord, cerebellar and cerebral cortices, and also contains ten of the cranial nerve nuclei, and important centers that control respiration, heart beat, reflex movements, auditory and visual functions[2,11].

Brainstem maldevelopment are associated with diverse significant pontocerebellar malformations[12–14]. It can also be associated with cerebral anomalies, such as lissencephaly[15], and the various syndromes listed in Table 3.

As *in utero* sonographic data of normal fetal brainstem development are lacking, and pontocerebellar anomalies originate from the same embryonic organ, the metencephalon, we decided to investigate both the pons and cerebellum.

We used the transfontanel approach to view the mid-sagittal plane of the fetal brain as previously described by Timor-Tritsch *et al.*[16,17]. However, this method failed to gain routine clinical application. Our group has gathered experience with the use of this approach in analyzing the fetal corpus callosum[18,19]. Therefore, we felt confident in further expanding this approach, and studying the fetal pons. Our results have shown that the mid-sagittal view is achievable during routine examination in almost 98% of cases. Nomograms of vermis development through gestation have been described[20,21], however, the anteroposterior diameter of the pons and mean vermis–pons ratio (VPR) have not been evaluated as yet. We have established three nomograms: the superoinferior length of the cerebellar vermis, the anteroposterior diameter of the pons, and the ratio between them. The idea of measuring both structures was based on the assumption that fetuses with anomalies involving the metencephalon, can affect either the pons or the cerebellar vermis, and consequently change the ratio between them. In cases in which both structures are abnormal the ratio will not change, and in such circumstances, referral to the proposed nomograms will indicate the severity of the hypoplasia and its deviation from the mean.

The size of the pons and vermis may also serve as a reference guide in cases evaluated for fetal posterior fossa and diffuse cerebral anomalies, fetuses at high risk for pontocerebellar dysgenesis, and during routine follow-up examinations.

The mean VPR, which is relatively stable through gestation, may serve as a simple and valuable screening tool during sonographic examination of the brainstem and the cerebellum. Further examination of the possible applicability of this ratio in the prenatal classification and prognostic evaluation of various anomalies involving this area is obviously needed.

In conclusion, we have successfully shown in this study that both pons and vermis can be adequately visualized and measured in the transfontanel, mid-sagittal view during routine anatomical fetal surveys. The constructed nomograms may be helpful when evaluating anomalies of the metencephalon.

Further studies are required in order to examine the usefulness of these data in evaluating different developmental anomalies and their prognostic value.

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