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ORIGINAL ARTICLE

Sequential analysis of the normal fetal fissures with three-dimensional ultrasound: a longitudinal study

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ABSTRACT
Objective To perform a sequential analysis of the main cortical fissures in normal fetuses using 3D ultrasound.

Methods A cohort of patients with uncomplicated singleton pregnancies underwent three consecutive transabdominal scans at 19–21, 26–28 and 30–34 weeks. Volumes of the fetal head were acquired and searched in the multiplanar mode for the following cortical fissures: sylvian, parieto-occipital, calcarine, hippocampus and cingulate. A qualitative analysis of these sulci was performed in each volume by an experienced operator (A) and a trainee (B). By placing the dot on the sulcus in one plane, it was evaluated whether it was visible also in other planes.

Results Fifty patients were included in the study. At 19–21 weeks, the sylvian and parieto-occipital sulci were visualized on at least one plane by both operators in all cases. At 26–28 weeks, all fissures were visualized by both operators on at least one plane, with no significant difference between the performances of the two operators. At 30–34 weeks, a mild overall decline in the accuracy of identification of all the cerebral fissures was observed.

Conclusions 3D multiplanar mode allows a systematic evaluation of the cortical fissures in normal fetuses since midtrimester. © 2015 John Wiley & Sons, Ltd.

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INTRODUCTION
Ultrasound evaluation of the fetal cortex is considered challenging, particularly in the second trimester of pregnancy, mainly due to the poor development of the cortical sulci at this stage. Indeed, most operators are unfamiliar with the normal anatomy of the fetal cortex, which is subtle and continuously changing, and only a few papers have been published in literature on this topic.[1–12] As a result, most cortical abnormalities, which become evident in the third trimester of pregnancy, are overlooked at the anomaly scan even by expert operators. However, in a time when the diagnosis of most fetal abnormalities has been moved from the second to the first trimester of pregnancy, anticipating the diagnosis of cortical malformations from the third to the second trimester would be preferable, if possible. With the introduction of 3D technology, ultrasound evaluation of the fetal brain has become easier, even for less experienced operators. We believe there is now a concrete chance to get familiar with the normal anatomy of the fetal cortex since mid-trimester. The aim of the present study was to test the feasibility of a systematic evaluation of the main cortical sulci in a cohort of normal fetuses from 19 weeks onward through sequential analysis of a single volume dataset.

METHODS
This was a prospective study performed in our tertiary center ultrasound laboratories. A cohort of unselected patients with uncomplicated singleton pregnancies was recruited for the purpose of the study and written informed consent obtained. The study was found in accordance with the principles of Helsinki declaration and approved by the local ethics committee. Patients underwent three consecutive transabdominal scans at 19–21, 26–28 and 30–34 weeks of gestation. For each patient, three clusters of volumes were acquired at different stage of brain development, using a Voluson E8 (GE, Milan, Italy) and a Samsung Accuvix A30 (Samsung-Medison Co. Ltd. Seoul, Korea) equipped with a multifrequency volumetric transabdominal probe. A maximum quality sweep of 50° was set for each acquisition with the starting plane fixed in the standard axial plane used for the measurement of the biparietal diameter. Volume acquisition was repeated if the fetus was not still, in order to obtain a good quality volume. Both volume acquisition and offline analysis in the multiplanar mode were performed by an expert operator (A) and a trainee (B) with basic training in ultrasound. The static Volume Contrast Imaging mode of the GE 4D View software (9.0 version; Milan, Italy) or the HD Volume Imaging mode in the Samsung

machine was used for volume analysis. Thanks to these algorithms, the image quality of the reconstructed planed was greatly improved.[13] Volume datasets were searched in the multiplanar mode for the following cortical fissures: sylvian, parieto-occipital, calcarine, hippocampus and cingulate.

On each single volume, a qualitative analysis (visualized yes/no) of these sulci was independently performed by the two operators. For each fissure, the interobserver agreement in each plane and in each gestational period was calculated through Cohen's kappa coefficients and classified as poor ($K \leq 0.40$), moderate ($K = 0.41–0.60$), substantial ($K = 0.61–0.80$) and high ($K > 0.80$) using the criteria from Landis and Koch.[14]

By placing the dot on the sulcus in one plane, it was noted whether it was visible also in other planes. Volume acquisition was repeated if the fetus was not still, until a good quality volume was obtained and stored.

Starting from standard biparietal diameter (BPD) plane, the sylvian, parieto-occipital and calcarine fissures were first visualized in the axial plane.

The sylvian fissure was obtained in the standard BPD plane as the echogenic line outlining the insula (Figure 1a). In this plane, the sylvian fissure was observed only in the distal hemisphere, due to the shadowing of the cranial skull, however, it was bilaterally visible in the coronal plane (Figure 1b). In the sagittal plane, the sylvian fissure was visible as a reverse V-shaped sulcus (Figure 1c).

The parieto-occipital fissure was obtained in the standard BPD plane as a triangle-shaped structure close to the upper margin of the lateral ventricles (Figure 2a), simultaneously visible in the coronal plane as a lozenge-shaped structure bilateral to the cerebellum (Figure 2b). This fissure is close to the midline, therefore, it was visible on both hemispheres, in spite of the shadow cast of the skull bones, both in the axial and in the coronal planes (Figure 2a,b). In the sagittal plane, the parieto-occipital fissure was visible as the vertical portion of the L-shaped cuneus (Figure 2c).

The calcarine fissure was visible in the same axial plane as a triangle-shaped structure, very close to the parieto-occipital fissure, but more posterior (Figure 3a), and in the coronal plane as a lozenge-shaped structure bilateral to the cerebellum, very close to the parieto-occipital fissure, but more caudal (Figure 3b). Also, this structure is close to the midline and therefore visible on both sides of the fetal brain, both in the axial and in the coronal views (Figure 3a,b). In the sagittal plane, the calcarine fissure was visible as the horizontal portion of the L-shaped cuneus, the vertical portion being the parieto-occipital fissure, as previously mentioned (Figure 3c).

Leaving the standard BPD plane and scrolling through the coronal plane, the hippocampal fissure was achieved as a bilateral hook shaped structure at the level of the cerebral peduncles (Figure 4b) and simultaneously displayed on the sagittal plane as a curved declivous echogenic line (Figure 4a). Finally, scrolling in the sagittal plane towards the midline, the cingulate sulcus was recognizable as an echogenic structure superior and parallel to the body of the corpus callosum (Figure 5a) simultaneously visible on both cerebral hemispheres in the coronal plane (Figure 5b).

RESULTS

From May to November 2012, 50 patients with uncomplicated singleton pregnancies were included in the study. Details of the study population are reported in Table 1. Good quality volumes were obtained in all cases. A maximum of two volume acquisitions were performed for each patient with no additional time over the standard ultrasound evaluation.

Normal outcome was confirmed for each patient at postnatal 1–2 years follow-up through analysis of pediatric records and parental interview.

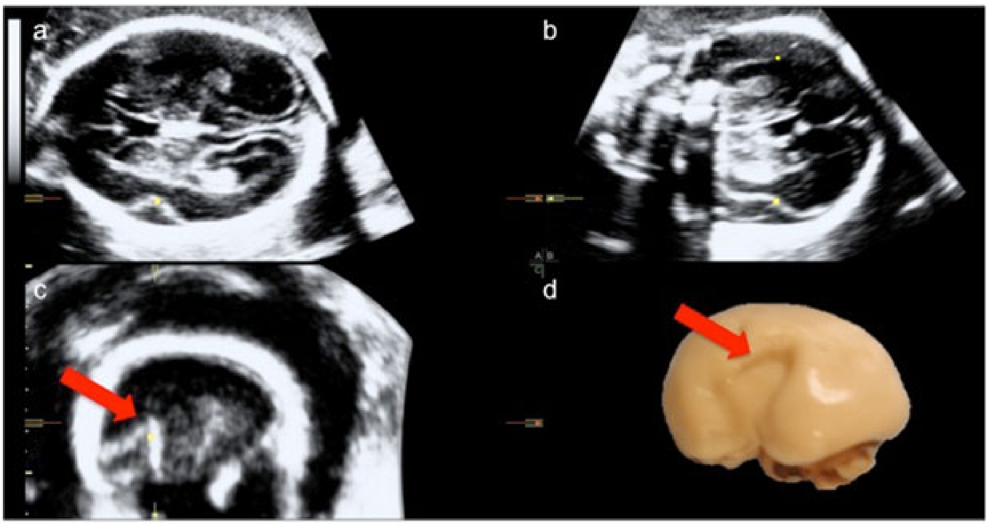

Figure 1 Demonstration of the Sylvian fissure in the multiplanar mode and corresponding anatomic specimen in a normal fetus at 20 weeks. (a) In the axial plane, the sylvian fissure appears as the echogenic line outlining the insula (yellow dot) only visible in the distal hemisphere; (b) in the coronal plane, it is visible as the curved vertical line in both hemispheres (yellow dots); (c) in the sagittal plane, it is visible as the reverse V-shaped sulcus (yellow dot, red arrow); and (d) corresponding anatomic specimen with the Sylvian fissure highlighted in the sagittal plane (red arrow)

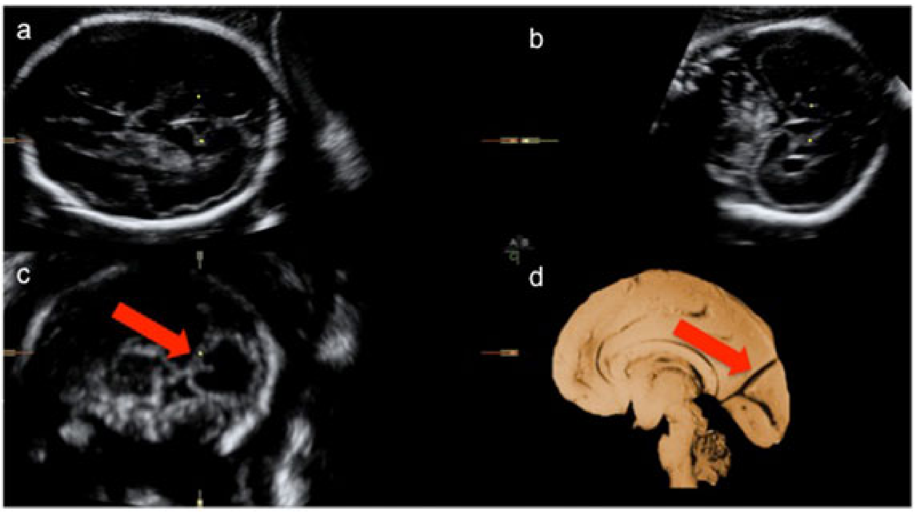

Figure 2 Demonstration of the parieto-occipital fissure in the multiplanar mode and corresponding anatomic specimen in a normal fetus at 26 weeks. (a) In the axial plane, the parieto-occipital fissure appears bilateral as the triangle-shaped structure close to the upper margin of the lateral ventricles (yellow dots); (b) in the coronal plane, it is visible in both hemispheres as the lozenge-shaped structure bilateral to the cerebellum (yellow dots); (c) in the sagittal plane, it is visible as the vertical portion of the L-shaped cuneus (yellow dot, red arrow); and (d) corresponding anatomic specimen with the parieto-occipital fissure highlighted in the sagittal plane (red arrow)

The sylvian fissure was visualized in all cases by both operators in the axial and coronal planes at every gestational age. The visualization of this fissure in the sagittal plane was more difficult, with an interobserver agreement that was poor at 19–21 weeks, substantial at 30–34 weeks, but perfect at 26–28 weeks, with 100% of cases recognized by both the operators.

Similarly, the parieto-occipital fissure was fully identified by both operators in at least one plane (axial plane) at every gestational age. Again, 26–28 weeks was the period with the best interobserver agreement, with a $k = 1$ in all planes.

For the calcarine fissure, the interobserver agreement at 19–21 weeks was high only in the axial plane, but poor in the other planes; whereas, at 26–28 weeks, it was high in the coronal and in the sagittal planes and moderate in the axial plane. Visualization of this fissure at 30–34 weeks was more difficult, with an inter-observer agreement that was moderate in all planes.

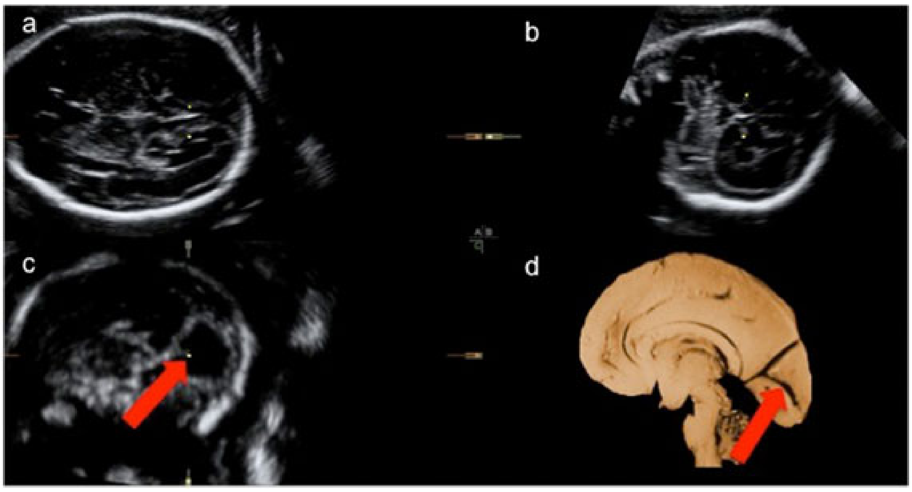

Figure 3 Demonstration of the calcarine fissure in the multiplanar mode and corresponding anatomic specimen in a normal fetus at 26 weeks. (a) In the axial plane, the calcarine fissure appears bilateral as the triangle-shaped structure, very close to the parieto-occipital fissure, but more posterior (yellow dots); (b) in the coronal plane, it is visible in both hemispheres as the lozenge-shaped structure bilateral to the cerebellum, very close to the parieto-occipital fissure, but more caudal (yellow dots); (c) in the sagittal plane, it is visible as the horizontal portion of the L-shaped cuneus (yellow dot, red arrow); and (d) corresponding anatomic specimen with the calcarine fissure highlighted in the sagittal plane (red arrow)

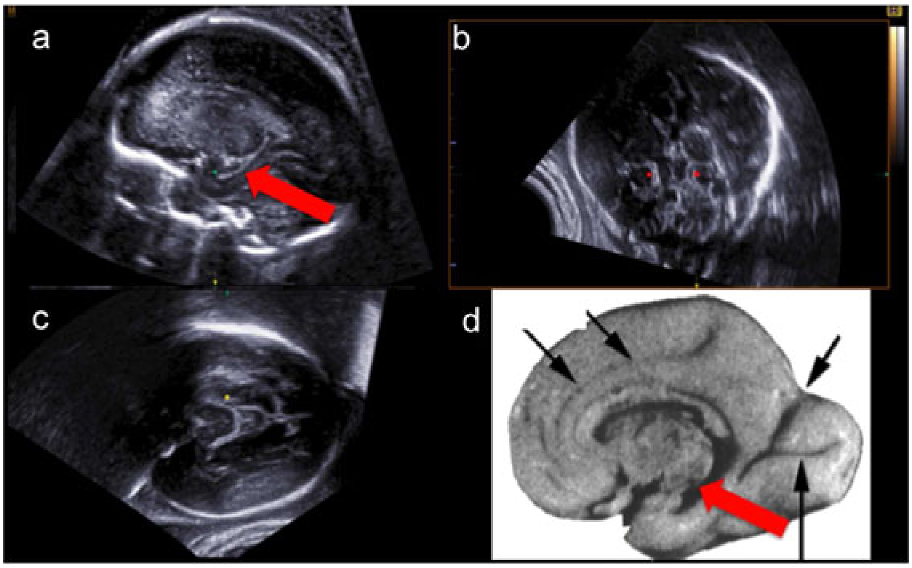

Figure 4 Demonstration of the hippocampal fissure in the multiplanar mode and corresponding anatomic specimen in a normal fetus at 27 weeks. (a) In the sagittal plane, the hippocampal fissure appears as the curved declivous echogenic line (green dot, red arrow); (b) in the coronal plane, as the bilateral hook-shaped structure at the level of the cerebral peduncles (red dots); (c) in the axial plane, it is visible as the curved line close to the thalami (yellow dot); and (d) corresponding anatomic specimen with the hippocampal fissure highlighted in the sagittal plane (red arrow), the cingulate, the parieto-occipital and the calcarine fissures are also visible (black arrows)

For the hippocampus, the rate of visualization on the axial plane was null in all the three gestational time frames. However, more in detail, the inter-observer agreement at 19–21 weeks was high in the axial plane and moderate in the other planes. At 26–28 weeks, it was high in the axial and coronal planes, but poor in the sagittal plane. At 30–34 weeks, it was high in the axial plane and poor in the other planes.

Finally, for the cingulate fissure at 19–21 weeks, the rate of visualization on the axial plane was null in all the three gestational time frames. More in detail, the inter-observer agreement was high for the axial, substantial for the coronal

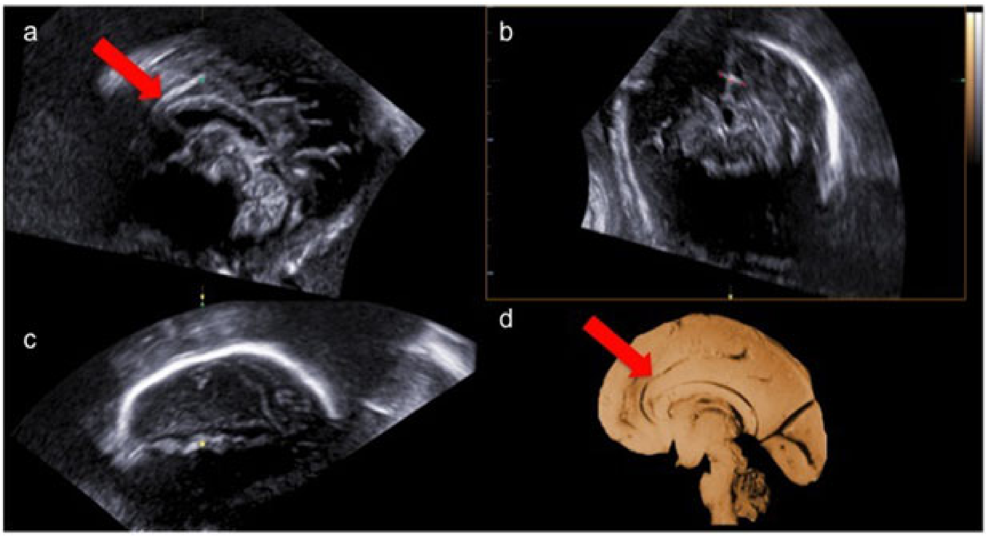

Figure 5 Demonstration of the cingulate fissure in the multiplanar mode and corresponding anatomic specimen in a normal fetus at 27 weeks. (a) In the sagittal plane, the cingulate fissure appears as the echogenic structure superior and parallel to the body of the corpus callosum (blue dot, red arrow); (b) in the coronal plane, it is visible as the bilateral triangle-shaped structure close to the midline (red dots); (c) in the axial plane, it is visible as the curved line close to the midline (yellow dot); and (d) corresponding anatomic specimen with the cingulate fissure highlighted in the sagittal plane (red arrow)

Table 1 Details of the study population

Mean maternal age (years), mean ± *SD*	34.9 ± 5.02
Maternal ethnicity, *n* (%)	
White	40 (80)
Black	2 (4)
Asiatic	8 (16)
Parity, n (%)	
0	23 (46)
1	20 (40)
2	7 (14)
>2	0
Mean maternal body mass index, mean ± *SD*	25.4 ± 3.23
Mean gestational age at first observation (weeks), mean ± *SD*	20 ± 1.76
Mean gestational age at second observation (weeks), mean ± *SD*	27 ± 2.41
Mean gestational age at third observation (weeks), mean ± *SD*	32 ± 2.02

and poor for the sagittal plane. At 26–28 weeks, it was substantial in the axial, poor in the coronal and high in the sagittal plane. At 30–34 weeks it was poor in the axial and coronal but high in the sagittal plane.

All results are summarized in Table 2.

DISCUSSION

Our study has shown that a systematic evaluation of the cortical fissures can be easily performed with 3D ultrasound in normal fetuses since midtrimester. In particular, a nice demonstration of the main fissures was achieved in most cases, as early as 19 weeks, also by the less experienced operator. A good inter-observer agreement was obtained for each fissure on at least one plane in each gestational age, with the exception of the calcarine fissure at 30–34 weeks. This is probably due to the difficulty to recognize this fissure among others in a more complex brain. The best inter-observer agreement was obtained for all fissures at 26–28 weeks, therefore this appears to be the best period to study the fetal sulci. Indeed, at 19–21 weeks, the fetal cortex is still immature; whereas, at 30–34 weeks, the quality of the image is often impaired by the ossification of the fetal skull, and the complexity of the fetal brain makes it more difficult to distinguish each fissure. Concerning the planes, the sylvian, parieto-occiptial and the calcarine fissures were best visualized in the axial view, the hippocampus in the coronal and the cingulate in the sagittal plane.

Evaluation of the fetal cortex is challenging, and even expert operators are often unfamiliar with normal fetal brain anatomy throughout pregnancy. Although severe conditions, cortical abnormalities are therefore easily overlooked at routine anomaly scan. The reasons for this are twofold. First, the anatomy of the developing brain is rapidly changing, making difficult to establish standard references. Second, the early stage of development of the fetal sulci in the second trimester has discouraged operators from trying to make a diagnosis of cortical abnormalities at this stage of pregnancy. As a result, the fetal cortex has remained mostly unexplored at ultrasound. For the same reasons, only a few papers have been published in literature on this topic.[1–12] Magnetic Resonance Imaging (MRI) is considered the gold standard for the evaluation of the fetal cortex, especially in the third trimester.[15–24] Recently, a rapid technologic enhancement and the introduction of 3D ultrasound have allowed to obtain a multiplanar reconstruction of the fetal head very similar to that obtained with MRI. Three-dimensional ultrasound is particularly useful in the evaluation of the fetal brain, as previously demonstrated.[25] Indeed, the multiplanar mode permits a simultaneous visualization of the same structure in the three planes, making easier to locate it in the space. Moreover, the enhancement Volume Contrast Imaging or HD Volume Imaging modes now allow achieving excellent quality images, often even better than those obtained with 2D ultrasound.[13] Finally, it takes only a few seconds to acquire a good volume of the fetal head, and elaborating the same volume, all the main fetal fissures can be sequentially and easily demonstrated in a few minutes. Other Authors have previously attempted to demonstrate the fetal fissures with 3D multiplanar mode.[6–8] However, there are some elements of novelty in our study. First, we analyzed the fetal brain at a very early stage of development (19 weeks). Indeed, mainly due to medical-legal reasons related to pregnancy termination, the anomaly scan is performed in most countries before 22 weeks of gestation. Second, we asked a trainee with basic training in ultrasound to elaborate volume datasets and locate the main cortical sulci. We ideally believe that at least the insula and the parieto-occipital fissures should be recognized even by less experienced operators and sonographers at routine anomaly scan. Indeed, these sulci can be easily demonstrated also with 2D ultrasound. We decided not to measure fetal fissures in our study, as previously reported by other Authors,[8] because in our opinion, it would be very difficult to standardize such measures. The aim of the present study was not to create reference ranges for normal fetuses, but rather to demonstrate that a good visualization of the main fetal sulci is feasible and reproducible since mid-trimester by sequential analysis of a single volume dataset. In particular, the Sylvian and the parieto-occipital fissure were recognized with no effort even by the less experienced operator as early as 19 weeks. Conversely, an early demonstration of the other fetal fissures was more challenging, and should be attempted at mid-trimester only in dedicated settings or when brain abnormalities are suspected.

An interesting finding of our study was that the best visualization of the fetal sulci was obtained between 26 and 28 weeks. This is somehow surprising. Cohen-Sacher *et al.*[1] have previously demonstrated that the first cortical sulci can be observed in normal fetuses at 18 weeks. Subsequent development of the fetal cortex goes on until term, but all the main cortical fissures are already present by 30–32 weeks.[1]

The explanation for the poor visualization we had in late gestational weeks probably lies in the transabdominal approach. We decided not to use the transvaginal approach in our study because we wanted to keep the evaluation of

Table 2 **Performances of operator A and operator B in the sonographic demonstration of the fetal sulci at different gestational weeks by 3D ultrasound**

	Sylvian				Parieto-occipital				Calcarine				Hyppocampus				Cingulate			
Plane	Operator A	Operator B	Cohen *k* (95% CI)	*P*	Operator A	Operator B	Cohen *k* (95% CI)	*P*	Op A	Op B	Cohen *k* (95% CI)	*P*	Operator A	Operator B	Cohen *k* (95% CI)	*P*	Operator A	Operator B	Cohen *k* (95% CI)	*P*
19–21 gestational weeks																				
Axial	100	100	1	<0.001	100	100	1	<0.001	0	0	1	<0.001	0	0	1	<0.001	0	0	1	<0.001
Coronal	100	100	1	<0.001	66.7	39.4	0.511 (0.313–0.709)	<0.001	69.7	27.3	0.262 (0.107–0.417)	0.006	66.7	36.4	0.449 (0.255–0.643)	<0.001	48.5	30.3	0.634 (0.432–0.836)	<0.001
Sagittal	100	75.7	0.038 (0.032–0.109)	0.570	66.7	39.4	0.511 (0.313–0.709)	<0.001	69.7	27.3	0.262 (0.107–0.417)	0.006	66.7	36.4	0.449 (0.255–0.643)	<0.001	100	66.7	0.039 (0.035–0.113)	0.468
26–28 gestational weeks																				
Axial	100	100	1	<0.001	100	100	1	<0.001	60.6	36.4	0.545 (0.345–0.745)	<0.001	0	0	1	<0.001	63.6	54.5	0.795 (0.628–0.962)	<0.001
Coronal	100	100	1	<0.001	100	100	1	<0.001	100	100	1	<0.001	100	100	1	<0.001	100	72.7	0.040 (0.034–0.112)	0.529
Sagittal	100	100	1	<0.001	100	100	1	<0.001	100	100	1	<0.001	100	72.7	0.040 (0.034–0.112)	0.529	100	100	1	<0.001
30–34 gestational weeks																				
Axial	100	100	1	<0.001	100	100	1	<0.001	69.7	45.4	0.535 (0.331–0.739)	<0.001	0	0	1	<0.001	63.6	30.3	0.388 (0.202–0.574)	0.001
Coronal	100	100	1	<0.001	100	78.8	0.135 (0.107–0.376)	0.057	78.8	60.6	0.595 (0.375–0.815)	<0.001	75.7	39.4	0.348 (0.166–0.532)	0.001	75.7	42.4	0.372 (0.184–0.560	0.001
Sagittal	75.7	63.6	0.719 (0.517–0.921)	<0.001	100	78.8	0.135 (0.107–0.376)	0.057	78.8	60.6	0.595 (0.375–0.815)	<0.001	75.7	30.3	0.238 (0.089–0.387)	0.009	100	100	1	<0.001

CI, confidence interval.

the fetal brain easy, not time consuming. However, the calcification of the fetal skull, the lower position of the fetal head and the decrease of the amniotic fluid probably make the transvaginal approach more convenient at 34 weeks. Moreover, even if MRI probably remains the best tool for the visualization of the fetal brain in the third trimester of pregnancy, this technique has some limitation in the second trimester, due to fetal movements and small size of the fetal head.

We acknowledge some limitations in the present study. First, only a few cases were recruited and our data should be confirmed on larger series. Second, a good quality volume is necessary to evaluate fetal fissures, especially at 20 weeks, and this is not always possible depending on maternal body mass index. However, we obtained good volume datasets in all our patients. In the selected cases, when the fetus is in vertex position, transvaginal scan could overcome visualization issues in the majority of cases.

In conclusion, we have demonstrated that a good visualization of the main fetal fissures can be easily achieved at midtrimester in normal fetuses even by less experienced operators with 3D ultrasound. Further research is needed to establish if abnormal cases can be identified at this stage of pregnancy.

WHAT'S ALREADY KNOWN ABOUT THIS TOPIC?

- The fetal cortex in the second trimester has remained mostly unexplored at ultrasound.
- It has been demonstrated that 3D ultrasound is particularly useful in the evaluation of the fetal brain.

WHAT DOES THIS STUDY ADD?

- We have demonstrated that a good visualization of the main fetal fissures can be easily achieved at midtrimester in normal fetuses even by less experienced operators with 3D ultrasound.

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