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Visualization of caudothalamic groove at expert fetal neurosonography

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KEYWORDS: caudothalamic groove; cyst; fetus; germinal matrix; hemorrhage; neurosonography

CONTRIBUTION

What are the novel findings of this work?
Using a standardized methodology based on three-dimensional ultrasound imaging, the caudothalamic groove can be visualized consistently in normal fetuses undergoing targeted multiplanar neurosonography.

What are the clinical implications of this work?
If a fetal medicine specialist is familiar with the normal sonographic appearance of the caudothalamic groove, abnormal findings related to acquired intrauterine insults may be detected antenatally in high-risk fetuses, which could influence perinatal management.

ABSTRACT

Objectives *To describe the sonographic features of the caudothalamic groove in the third trimester of pregnancy in a group of structurally normal fetuses and to report a small series of cases with abnormal appearance of the caudothalamic groove at antenatal cranial ultrasound.*

Methods *This was an observational study conducted at two fetal medicine referral units in Italy. A non-consecutive cohort of pregnant women with a singleton non-anomalous pregnancy were recruited prospectively and underwent three-dimensional (3D) ultrasound assessment of the fetal brain at 28–32 weeks' gestation. At offline analysis, the ultrasound volumes were adjusted in the multiplanar mode, according to a standardized methodology, until the caudothalamic groove was visible in the parasagittal plane. To evaluate inter-observer agreement, two operators were asked independently to indicate if the caudothalamic groove was visible unilaterally or bilaterally on each volume and Cohen's kappa (κ) coefficient was calculated. The digital archives of the two centers were also searched retrospectively to retrieve cases with abnormal findings at the level of the caudothalamic groove on antenatal cranial ultrasound that were confirmed postnatally.*

Results *A total of 180 non-consecutive cases were included. At offline analysis of the 3D ultrasound volumes, the caudothalamic groove was identified in the parasagittal plane by both operators at least unilaterally in 176 (97.8%) cases and bilaterally in 174 (96.7%) cases. The κ-coefficient for the agreement between the two independent operators in recognizing the caudothalamic groove was 0.89 and 0.83 for one and both hemispheres, respectively. The retrospective search of our archives yielded five cases with an abnormal appearance of the caudothalamic groove at antenatal cranial ultrasound, including two cases of hemorrhage and three cases of cyst.*

Conclusions *The caudothalamic groove is consistently seen in normal fetuses on multiplanar neurosonography in the third trimester, and abnormal findings in this region may be detected antenatally.* © *2024 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

The caudothalamic (CT) groove is a sulcus of the germinal matrix of the brain, projecting from the floor of the lateral ventricles and located between the nucleus caudatus and the thalamus, approximately at the level of the foramen of Monro[1]. Antenatally, the germinal matrix is a highly

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vascularized and metabolically active tissue and represents a site of proliferation of the neuronal and glial cells that eventually migrate across the developing brain[2,3].

Owing to these features, the germinal matrix is a preferential site of acquired perinatal brain injury, and thus is commonly assessed in the parasagittal plane at neonatal cranial ultrasound[1,4–6]. Abnormal findings following different types of intrauterine insult, mainly inflammatory and/or clastic, have been described postnatally in this area of gray matter[3,7–11]. More specifically, the sonographic appearance of the CT groove is critical for the detection and differential diagnosis of acquired lesions in the germinal matrix, including cyst and hemorrhage[12].

The CT groove may also be identified before birth in a parasagittal view of the fetal brain (Figure 1)[13], but, to date, there is a lack of published data on its visualization at antenatal ultrasound. Such data could inform expert antenatal neurosonography, which is indicated in fetuses at risk for *in-utero* cerebral injury[14].

The aims of this study were as follows: to describe the sonographic features of the CT groove in the third trimester in a group of structurally normal fetuses; and to report a small series of cases with abnormal appearance of the CT groove at antenatal cranial ultrasound.

METHODS

This observational study was conducted at two fetal medicine referral units in northern Italy (University Hospital of Parma, Parma and S. Orsola University Hospital of Bologna, Bologna). From January to October 2023, a non-consecutive cohort of pregnant women with a singleton pregnancy attending at either center for a third-trimester ultrasound scan was recruited prospectively to our study. Participants provided signed informed consent. The main indications for the referral scan were a personal or family history of congenital anomaly, placental insertion anomaly, increased risk of preterm birth and maternal conditions (e.g. diabetes, hypertensive disorder). The study was approved by the ethics committee of the University Hospital of Parma (reference: 845/2020/OSS/AOUPR). Inclusion criteria were maternal age ≥ 18 years and gestational age 28–32 weeks, with no evidence of fetal central nervous system (CNS) or extra-CNS structural anomaly on ultrasound, and with fetal biometry within the normal range. Patients were considered ineligible for the study or excluded if they presented with any of the following conditions: postnatal diagnosis of fetal structural or genetic abnormality, infectious disease during pregnancy, severe maternal obesity (body mass index $> 40\,kg/m^2$), fetal growth restriction and/or chronic drug consumption.

In all included cases, a three-dimensional (3D) ultrasound volume of the fetal brain was acquired by a fetal medicine specialist with expertise in fetal neurosonography using a high-end ultrasound machine (Voluson E10 and Expert 22 (GE Healthcare, Milwaukee, WI, USA) or Samsung Hera W10 (Samsung Medison Healthcare, Seoul, Republic of Korea)), equipped with a volumetric multifrequency transabdominal probe (4–8 MHz) and volumetric multifrequency transvaginal probe (6–12 MHz).

The fetal brain volume was acquired transabdominally, with a maximum quality sweep at an angle of 50–60°; in the case of cephalic fetal presentation, if the woman consented, the ultrasound volume was acquired

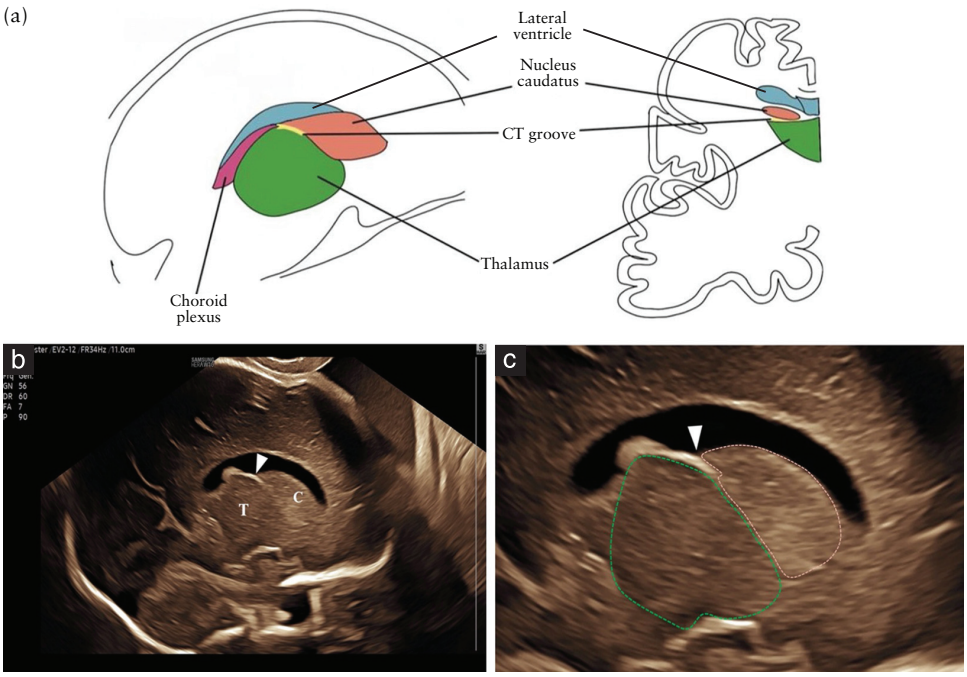

Figure 1 (a) Schematic representation of caudothalamic (CT) groove in fetal brain. (b,c) Two-dimensional transvaginal ultrasound images in parasagittal plane in normal fetus at 30 weeks' gestation, showing CT groove (arrowhead) located between nucleus caudatus (C) and thalamus (T).

transvaginally instead, with a maximum quality sweep at an angle of 120°. The standard midsagittal plane used for the demonstration of the corpus callosum was chosen as the starting plane for the volume acquisition, which was repeated until a good quality volume was obtained. The ultrasound volume was stored for subsequent offline analysis.

At offline analysis, the ultrasound volumes were adjusted in the multiplanar mode until the CT groove was visible in the parasagittal view. In detail, the following technique was adopted systematically to demonstrate the CT groove (Figure 2, Videoclip S1): (1) In the midsagittal plane, the dot was placed on the roof of the third ventricle, just below the cavum septi pellucidi; (2) in the corresponding coronal plane, the dot was moved laterally on either side following the upper hyperechogenic edge of the thalamus and placed on the connection point between the thalamus and the posterior border of the nucleus caudatus; (3) in the parasagittal plane, the normal CT groove appeared on either side as a hyperechogenic indentation between the nucleus caudatus anteriorly and the thalamus posteriorly; (4) to evaluate interoperator agreement, the two members of the study group in charge of offline analysis of the 3D ultrasound volumes (E.d.P. and E.C.) were asked independently to indicate if the CT groove was visible unilaterally or bilaterally on each volume.

The digital archives of the two centers were also searched retrospectively using the following keywords: 'intracranial hemorrhage', 'intracranial cyst', 'subependymal lesion', 'germinal matrix hemorrhage' and 'germinal matrix cyst'. The ultrasound volumes or videoclips of the fetal brain obtained in cases with postnatal confirmation of such lesions were retrieved from the database and analyzed. In these cases, the appearance of the CT groove was evaluated qualitatively.

Continuous variables are reported as median (interquartile range) and categorical variables as *n* (%). Cohen's kappa (κ) was used to assess interobserver reliability for the unilateral or bilateral visualization of the CT groove. Predefined criteria for interpreting Cohen's κ were used: 0.0–0.20, poor agreement; 0.21–0.40, fair agreement; 0.41–0.60, moderate agreement; 0.61–0.80, substantial agreement; and 0.81–1.0, almost perfect agreement[15]. Statistical analysis was performed using SPSS version 21.0 (IBM Corp., Chicago, IL, USA) and Jamovi version 1.6.23 (www.jamovi.org). $P < 0.05$ was considered to indicate statistical significance.

RESULTS

Over the study period, 180 non-consecutive cases fulfilling the inclusion criteria were recruited prospectively. The demographic characteristics of the study population are shown in Table 1. A 3D volume of the fetal brain was acquired transvaginally in 138 fetuses and transabdominally in the remaining cases owing to breech presentation ($n = 36$) or unwillingness to undergo a transvaginal scan ($n = 6$). At offline analysis of the 3D ultrasound volumes, the CT groove was identified in the

Table 1 Demographic and obstetric characteristics of 180 women with normal singleton pregnancy

Characteristic	*Value*
Maternal age (years)	34.0 (29.0–38.0)
Caucasian	128 (71.1)
Prepregnancy BMI (kg/m^2)	23.4 (21.3–27.9)
Nulliparous	106 (58.9)
GA at ultrasound (weeks)	30.3 (29.1–31.8)
BMI at enrolment (kg/m^2)	26.3 (23.9–30.2)
Fetal head circumference (mm)	282 (270–294)
Cephalic presentation	138 (76.7)

Data are given as median (interquartile range) or *n* (%). BMI, body mass index; GA, gestational age.

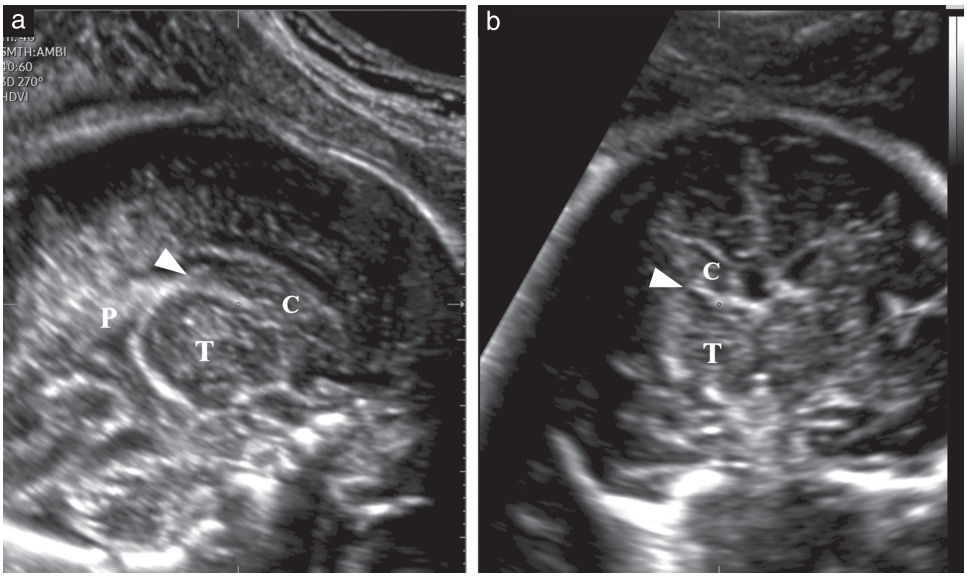

Figure 2 Three-dimensional transabdominal ultrasound images in normal fetus at 28 weeks' gestation, showing caudothalamic groove (arrowhead) in parasagittal (a) and coronal (b) planes. Choroid plexus (P) is also visible in (a). C, nucleus caudatus; T, thalamus.

parasagittal plane by both operators at least unilaterally in 176 (97.8%) cases and bilaterally in 174 (96.7%) cases. The κ-coefficient for the agreement between the two independent operators in recognizing the CT groove was 0.89 and 0.83 for one and both hemispheres, respectively. Non-visualization of the CT groove in four cases was mainly due to suboptimal image quality in the reconstructed parasagittal plane.

The retrospective search of our archives yielded five cases with an abnormal sonographic appearance of the CT groove at antenatal cranial ultrasound (Figures 3–5, Table 2), which was confirmed by postnatal magnetic resonance imaging (MRI) (Figure 6). The abnormal findings included one case of bilateral hemorrhage (Case 1), one case of bilateral cyst (Case 2), one case of unilateral hemorrhage (Case 3) and two cases of unilateral cyst (Cases 4 and 5). 3D volumes were available for Cases 1 and 4 (Figures 3 and 4, respectively), while in two fetuses (Cases 2 and 3), the abnormal appearance of the CT groove was noted on a sonographic video showing a parasagittal view of the brain (Figure 5a,c).

Table 2 Clinical details of cases with abnormal appearance of caudothalamic groove

Case	*GA at diagnosis (weeks)*	*Type of anomaly*	*Associated findings*
1	24	Bilateral hemorrhage	*COL-4* mutation
2	34	Bilateral cyst	CMV infection
3	28	Unilateral hemorrhage	Severe IUGR/ alloimmune thrombocytopenia
4	21	Unilateral cyst	CMV infection
5	27	Unilateral cyst	Severe IUGR

CMV, cytomegalovirus; GA, gestational age; IUGR, intrauterine growth restriction.

DISCUSSION

Our study shows that antenatal visualization of the CT groove is feasible in normal fetuses on third-trimester ultrasound by fetal medicine specialists with advanced skills in neurosonography. To the best of our knowledge, this is the first time that abnormal findings at antenatal ultrasound involving the CT groove due to an acquired intrauterine brain injury (i.e. hemorrhage or cyst) have been described.

In the neonate, the CT groove is considered to be a crucial landmark for the sonographic identification of acquired perinatal brain injury, particularly for the differential diagnosis between anomalies involving the subependymal germinal matrix and those arising from the contiguous structures (e.g. choroid plexus, periventricular zone), which carry a different prognosis[1]. At neonatal sonography, the CT groove appears as a hyperechogenic V-shaped area with homogeneous echogenicity[4,5].

The germinal matrix, which is located at the level of the CT groove, is considered to be the source of

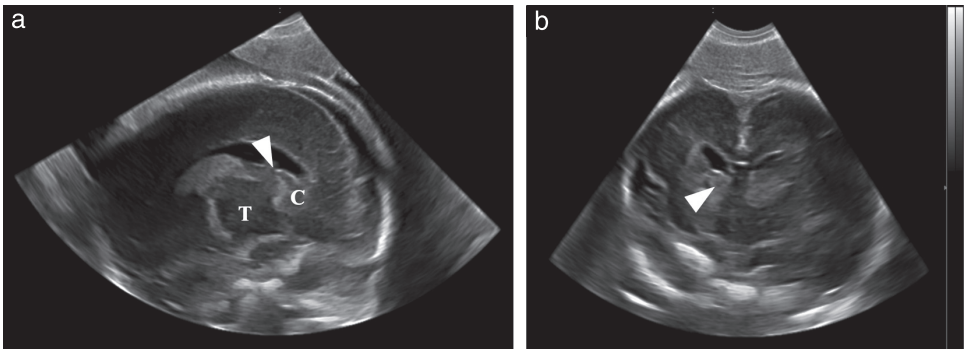

Figure 3 Three-dimensional ultrasound images at 24 weeks' gestation in fetus with *COL-4* mutation (Case 1), showing hemorrhage (arrowhead) of germinal matrix in parasagittal (a) and coronal (b) planes. C, nucleus caudatus; T, thalamus.

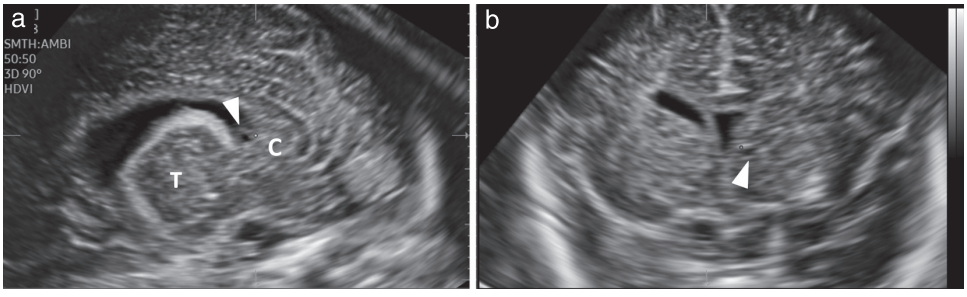

Figure 4 Three-dimensional ultrasound images at 21 weeks' gestation in fetus with cytomegalovirus infection (Case 4), showing small cyst (arrowhead) of germinal matrix in parasagittal (a) and coronal (b) planes. C, nucleus caudatus; T, thalamus.

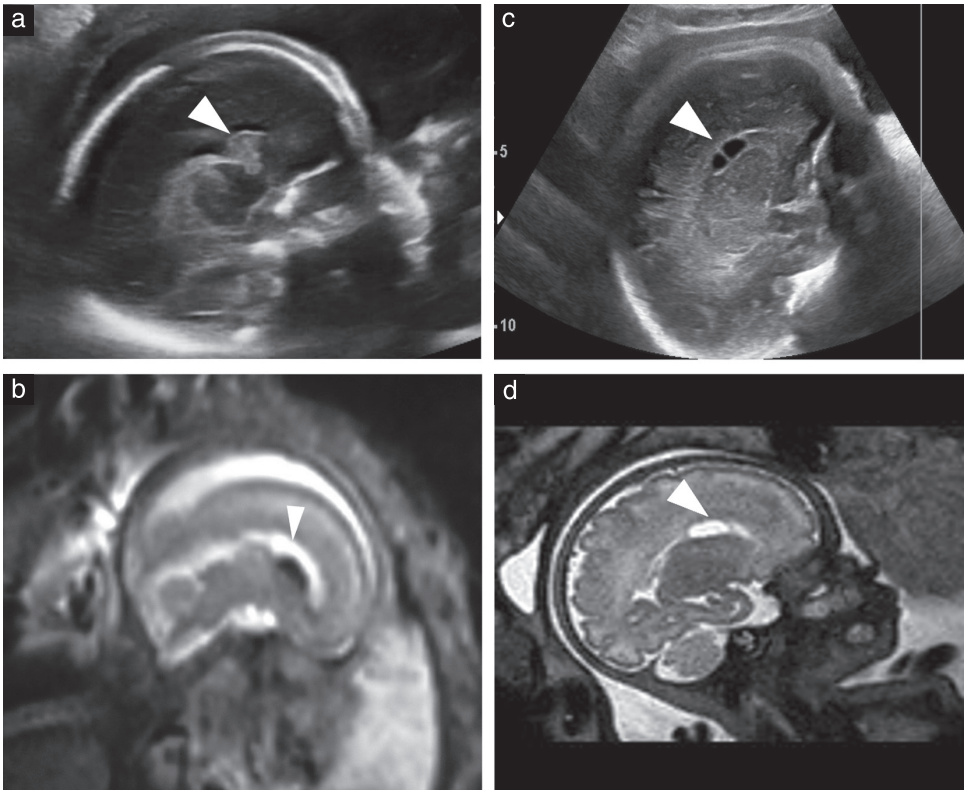

Figure 5 (a) Two-dimensional (2D) ultrasound image in parasagittal plane in fetus at 28 weeks' gestation (Case 3), showing hemorrhagic lesion (arrowhead) of germinal matrix; this was confirmed on antenatal magnetic resonance imaging (MRI) in same plane at same gestational age (b). (c) 2D ultrasound image in parasagittal plane in fetus at 34 weeks (Case 2), showing multiple cystic lesions (arrowhead) of germinal matrix; this was confirmed on antenatal MRI in same plane at same gestational age (d).

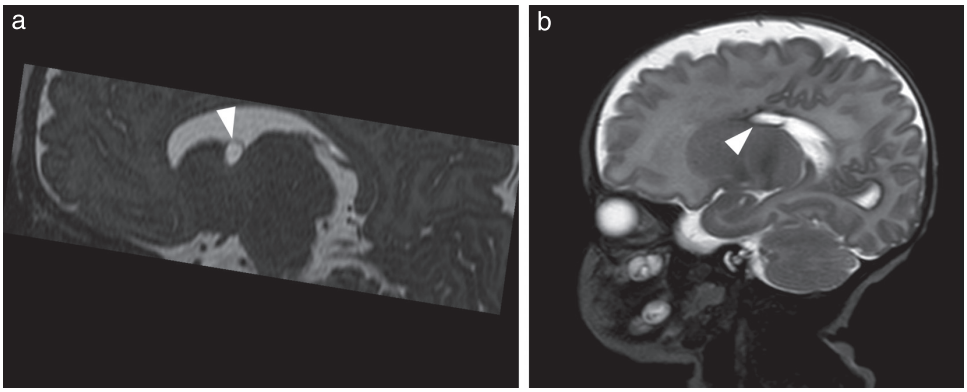

Figure 6 (a) Postnatal follow-up of Case 4. Three-dimensional T2-weighted magnetic resonance imaging (MRI) (balanced steady-state free precession sequence with driven equilibrium radio frequency reset pulse (DRIVE)), showing cystic lesion (arrowhead) of germinal matrix at level of caudothalamic groove in parasagittal plane. (b) Postnatal follow-up of Case 1. T2-weighted MRI showing hemorrhagic lesion (arrowhead) of germinal matrix at level of caudothalamic groove in parasagittal plane.

cerebral excitatory neurons, and generates precursors of oligodendroglia and astrocytes as well as late-migrating gamma-aminobutyric acidergic (GABAergic) neurons that will go on to populate both the cerebral cortex and the thalamus. It is also a highly vascularized zone consisting of thin-walled vessels[3,16,17]. A postmortem fetal MRI study demonstrated that the volume of the germinal matrix increases until 23 weeks, decreases rapidly at 28 weeks, with a small remnant located along the ventral tips of the frontal horns anteriorly to the CT groove between 28 and 32 weeks, and is nearly completely involuted by 36 weeks[18].

Owing to its characteristics as a highly vascularized and metabolically active tissue, this area of gray matter is the preferential site of acquired perinatal brain injury that may derive from hypoxia, hemorrhage or infection/inflammation (e.g. cytomegalovirus)[17–20]. Destructive lesions of the germinal matrix typically occur

in preterm neonates more frequently within the first week after birth. Hemorrhagic or cystic lesions mostly arise at the level of the CT groove and may extend into the lateral ventricle and the periventricular brain parenchyma[20,21]. In the preterm neonate, thorough assessment of the CT groove is performed routinely on transfontanellar ultrasound, with the aim of detecting abnormal findings that may be overlooked in clinically asymptomatic neonates[1,21].

Although destructive lesions at the level of the CT groove are detected more frequently in high-risk neonates, the Developing Human Connectome Project showed that, in a large population of healthy full-term neonates ($n = 500$), lesions at the level of the CT groove may be present in up to 10% of cases at postnatal imaging[22]. Similar findings were observed in a larger study of 3186 full-term healthy neonates; the authors found that cystic lesions were the most common cranial ultrasonographic findings in this population ($n = 119$ (3.7%)) and that the CT groove was the most common site of injury[23]. On this basis, we are entitled to suspect that an abnormal appearance of the CT groove in the neonate may be an isolated and transient CNS finding without overt clinical implications.

However, it is plausible that a proportion of these lesions detected incidentally in the neonate may result from brain insults occurring during the antenatal period. Owing to increased expertise in fetal cranial ultrasound and improvements in ultrasound technology, major advances have occurred in the context of antenatal neurosonography[24]. Most intrauterine clastic lesions of the brain can be detected antenatally using advanced neurosonography[24]. Previous work has shown that detailed fetal neuroimaging by multiplanar sonography can accurately identify white-matter lesions (e.g. cystic periventricular leukomalacia) following intrauterine transfusion in a population of fetuses with severe red blood cell alloimmunization[25]. Thus, sonographic assessment of the CT groove and evaluation for abnormal findings at this level during advanced neurosonography in fetuses at higher risk of acquired perinatal brain injury seems appropriate.

Our study has demonstrated that, using a standardized methodology based on 3D ultrasound, the CT groove is visualized consistently in normal fetuses undergoing targeted multiplanar neurosonography. Moreover, if the fetal medicine specialist is familiar with the normal sonographic appearance of this anatomical area, abnormal findings of the CT groove related to acquired intrauterine insults may be detected antenatally in high-risk fetuses undergoing expert cranial ultrasonography, and this may have an impact on perinatal assessment and management[26]. In particular, additional investigations, including exome sequencing, TORCH screening and MRI, should be considered, with the aim of understanding the etiology and improving antenatal counseling in these cases[27,28].

The main strengths of our study are the novelty of the topic, the large number of normal cases included and the prospective study design. The standardized methodology used by two expert operators for the analysis of 3D ultrasound volumes and the assessment of the CT groove represents an additional strength. Finally, the use of 3D ultrasound technology is expected to accelerate the learning curve for recognizing the CT groove at antenatal neurosonography. However, the small number of pathological cases and the retrospective methodology used to retrieve these cases should be acknowledged as the main limitations of our study.

In conclusion, we have shown that a systematic evaluation of the normal CT groove is feasible and reproducible at antenatal cranial ultrasound during the third trimester of pregnancy. Furthermore, our study showed that abnormal findings of the CT groove due to intrauterine insult may be detected antenatally. Our findings may assist fetal medicine specialists when performing expert sonographic assessment of the fetal brain.

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SUPPORTING INFORMATION ON THE INTERNET

The following supporting information may be found in the online version of this article:

Videoclip S1 Transabdominal 3D ultrasound acquisition in third-trimester fetus and offline analysis showing caudothalamic groove in coronal and sagittal planes.