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Tela-choroidea-to-anterior-cerebral-artery distance (TACAD): novel marker on color Doppler to identify fetuses with complete or partial agenesis of corpus callosum

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KEYWORDS: agenesis of corpus callosum; anterior cerebral artery; color Doppler; fetal neurosonography; pericallosal artery; tela choroidea

CONTRIBUTION

What are the novel findings of this work?
We present a novel tool, the tela-choroidea-to-anterior-cerebral-artery distance (TACAD), which allows objective assessment of the position and course of the anterior cerebral artery (ACA) relative to the tela choroidea in the midsagittal view of the brain on color Doppler. We provide reference ranges for TACAD based on measurements in normal fetuses and demonstrate that TACAD is shorter in fetuses with complete or partial agenesis of the corpus callosum.

What are the clinical implications of this work?
TACAD enables objective assessment of the abnormal course of the ACA in fetuses with agenesis of the corpus callosum.

ABSTRACT

Objectives *To assess objectively the course of the anterior cerebral artery (ACA) by measuring its distance to the tela choroidea in the midsagittal view, and to compare this distance in normal fetuses with that in those with agenesis of the corpus callosum (ACC), a condition known to be associated with an abnormal course of the ACA.*

Methods *The tela-choroidea-to-anterior-cerebral-artery distance (TACAD) was measured in the midsagittal view of the brain on color Doppler, between the anterior border of the tela choroidea and the ACA at the level of the callosal genu. Reference ranges in relation to gestational age were established in a prospective, cross-sectional study of 253 normal healthy fetuses between 19 and 36 weeks of gestation. The study group included fetuses with complete ACC (n = 28) or partial ACC (n = 18).*

Results *TACAD of normal fetuses showed an increase during the second half of pregnancy, with a mean value of 10.1 mm and 14.2 mm at 22 and 30 weeks of gestation, respectively. All (28/28) fetuses with complete ACC and 83% (15/18) of those with partial ACC had significantly shorter TACAD, with mean values of 3.9 mm and 6.6 mm, respectively.*

Conclusions *TACAD is a measurement that is simple to obtain during fetal color Doppler neurosonography, which enables quantification of the course of the ACA and pericallosal artery. TACAD is shorter in fetuses with complete or partial ACC than in normal fetuses and provides an objective, quantifiable value, rather than merely descriptive information.* © *2023 The Authors. Ultrasound in Obstetrics & Gynecology published by John Wiley & Sons Ltd on behalf of International Society of Ultrasound in Obstetrics and Gynecology.*

INTRODUCTION

Agenesis of the corpus callosum (ACC) is one of the most common congenital brain anomalies, with an estimated prevalence of 2.56 per 10 000 in the general population[1]. Despite the relatively high prevalence, its antenatal diagnosis remains challenging[2,3]. In complete (cACC) and partial (pACC) ACC, indirect signs in the axial plane, such as absence or abnormal shape of the cavum septi pellucidi (CSP), have been reported, in addition to colpocephaly and dilated interhemispheric fissure and third ventricle[2,4–7]. Detection of these signs

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leads subsequently to targeted fetal neurosonography, including assessment in the coronal and sagittal planes, as suggested by the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) guidelines on the sonographic examination of the fetal central nervous system[8,9]. In the midsagittal plane, one of the reported features of ACC is an abnormal course of the anterior cerebral artery (ACA) demonstrated on color Doppler[6,10]. However, this sign is difficult to describe clearly, as its assessment is often subjective. We believe that there is a need for an objective assessment of the ACA position and course in the anterior brain, which can be achieved through the addition of a measurement in the midsagittal plane. The aims of the present study were to present a new parameter, the tela-choroidea-to-anterior-cerebral-artery distance (TACAD), establish reference ranges for this marker in the second half of gestation and assess its clinical value by comparing measurements in fetuses with cACC and pACC with the reference ranges.

METHODS

Study design and ultrasound examination

This was a prospective, cross-sectional study of healthy fetuses and a retrospective study of fetuses with cACC or pACC that underwent corpus callosum (CC) evaluation in two prenatal centers in Germany (Center for Prenatal Diagnosis Munich, Munich and Center for Prenatal Diagnosis and Human Genetics, Berlin). At our centers, the routine comprehensive scan after 20 weeks of gestation includes transabdominal visualization of the CC. In most cases, the CC was visualized directly in the midsagittal plane on two-dimensional ultrasound, and the ACA and pericallosal artery (PCA) were displayed in the midsagittal plane using high-definition color Doppler flow with the pulse-repetition frequency set at 0.6–0.8 kHz (Figure 1). The color box size was selected to be as narrow as necessary to optimize the image frame rates while capturing essential image information. In cases in which direct visualization was not feasible, three-dimensional reconstruction without color Doppler was achieved.

All examinations were performed using high-resolution ultrasound equipment (Voluson E8 or Voluson E10 machine; GE Healthcare, Zipf, Austria) with convex transabdominal probes. Transvaginal assessment of the head, including the CC, was performed in select normal cases and all abnormal cases. Ultrasound images were stored in the ultrasound system as well as in an image archiving system (Viewpoint®; GE Medical Systems), both of which allow offline measurements. As a standard requirement of our institutions, all patients provided signed informed consent for the fetal examination and agreed to the storage of digital images for quality control and later data evaluation. This study was approved by the ethics committee of the Ludwig-Maximilians-University, Munich, Germany (Nr. 282-13).

Normal fetuses

Healthy patients referred for antenatal screening ultrasound or growth follow-up performed between 19 and 36 weeks of gestation were included prospectively. Only fetuses that underwent transabdominal examination and had good-quality imaging data were recruited. Stored images of the brain demonstrating the CC and PCA in the midsagittal view were used for offline evaluation. Measurements were collected from women with a singleton pregnancy and a structurally normal, appropriate-for-gestational-age fetus, showing no cerebral or extracerebral abnormality. Pregnant women with chronic diseases affecting fetal growth were not included in the study. Additionally, pregnancies with adverse outcome (prematurity or small-for-gestational-age neonate) were excluded retrospectively. For reliable CC evaluation, only images with optimal imaging characteristics (i.e. thin abdominal wall and dorsoposterior fetal position) were considered for the study. Three-dimensional reconstructed images and cases with transvaginal images of the brain were not considered.

Fetuses with cACC or pACC

The study group included fetuses with cACC or pACC examined between January 2014 and December 2020 in the two prenatal centers. Only fetuses with transabdominal images of the brain in the midsagittal view with color Doppler were considered. All cases were confirmed either by postnatal diagnosis or magnetic resonance imaging (MRI) examination. Images from the first diagnosis or the first examination with stored color Doppler data were included in the study. In this study, pACC was defined as a short anteroposterior length of the CC, measuring < 3rd centile of the reference ranges[7,11], and at least one missing part of the four components of the CC according to the ISUOG guidelines[9]. In general, these fetuses were detected due to abnormality in the transventricular axial plane, including the previously reported CSP ratio[7]. Fetuses with microcephaly and a short CC and fetuses with a thin or thick CC were excluded from further evaluation.

Measurement technique

TACAD was measured in the midsagittal view between the most anterior, lowest edge of the tela choroidea and the A3 segment of the ACA in its course around the genu, at the point at which it branches into the PCA, making TACAD the longest distance between the anterior aspect of the tela choroidea and the ACA (Figure 1). To establish the reference ranges, TACAD was correlated with gestational age. In cases with cACC and pACC, the furthest distance to the ascending branch of the ACA was considered (Figure 2). In cases with pACC, the length of the CC was recorded. All measurements were performed offline by one examiner (K.K.), who was unaware of the origin of the images (normal *vs* abnormal cases). In both control and ACC groups, gestational age

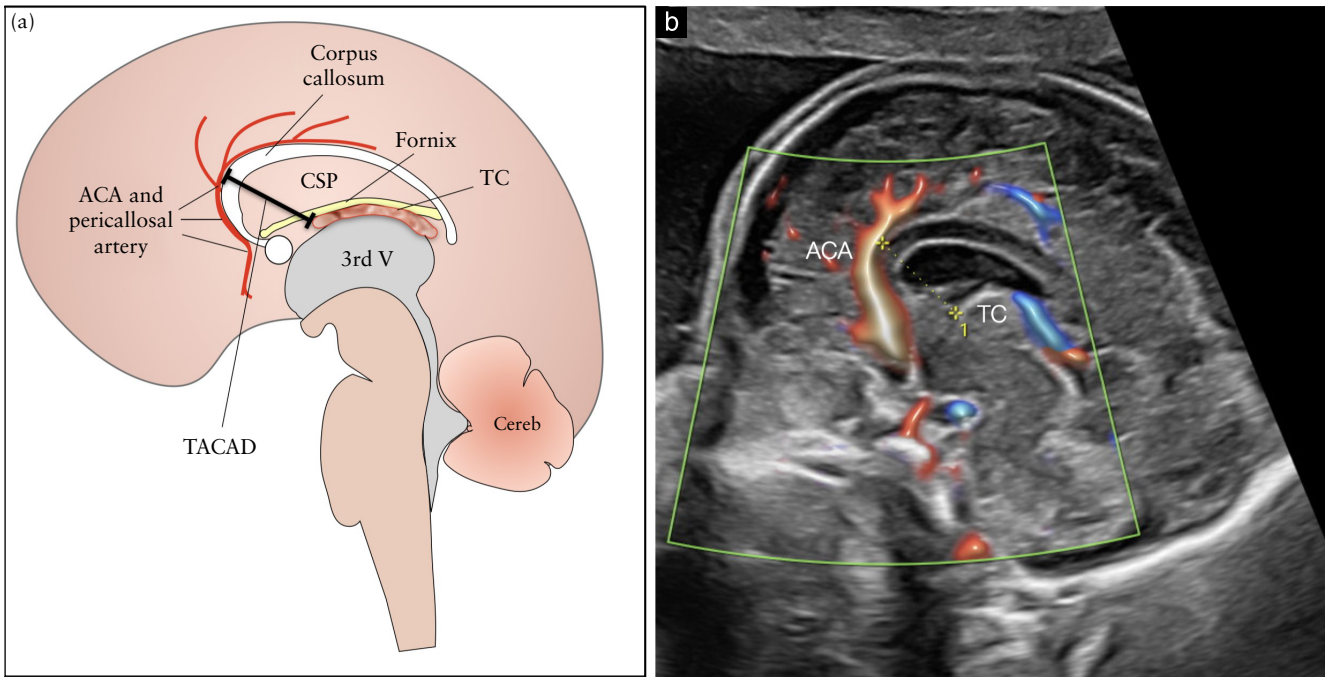

Figure 1 Schematic drawing (a) and corresponding color Doppler ultrasound image (b) in midsagittal view of fetal brain, showing corpus callosum with pericallosal branch of anterior cerebral artery (ACA). Tela-choroidea-to-anterior-cerebral-artery distance (TACAD) is measured as distance between anterior edge of echogenic tela choroidea (TC) and far branch of ACA. 3rd V, third ventricle; Cereb, cerebellum; CSP, cavum septi pellucidi.

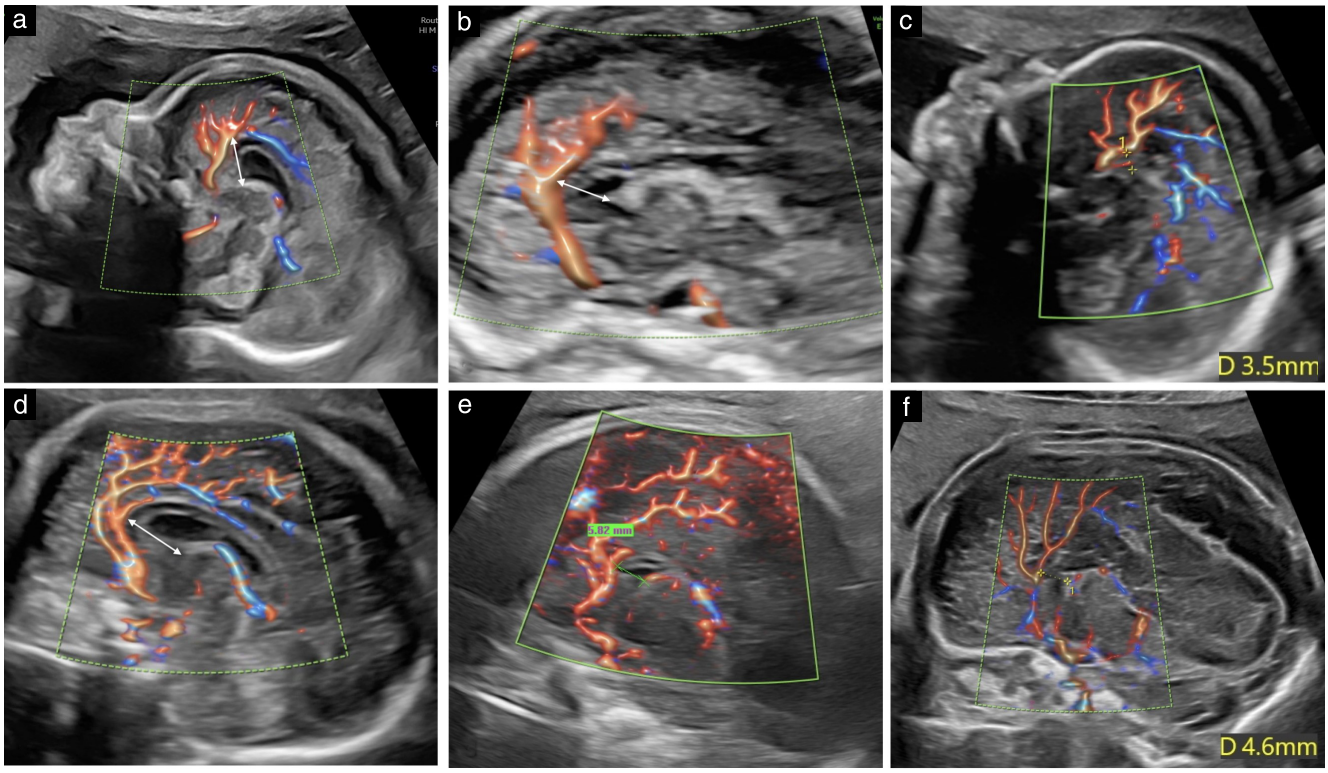

Figure 2 Color Doppler ultrasound images showing tela-choroidea-to-anterior-cerebral-artery distance (TACAD), indicated by double-headed arrows or calipers. (a,d) TACAD in two normal fetuses at 22 (a) and 29 (d) weeks of gestation. (b,e) Shorter TACAD in two fetuses with partial agenesis of corpus callosum at 23 (b) and 28 (e) weeks of gestation. (c,f) Shortest TACAD in two fetuses with complete agenesis of corpus callosum at 22 weeks of gestation.

at examination, result of genetic testing, if available, and outcome were collected. Additionally, presence of associated intracranial or extracranial anomaly or syndromic condition was recorded for ACC cases.

Statistical analysis

Regression analysis was applied to assess the relationship between TACAD and gestational age. The cACC and pACC study groups were compared with the reference group by transforming TACAD values into *Z*-scores and using Kruskal–Wallis one-way ANOVA. The cACC and pACC study groups were compared using the Mann–Whitney *U*-test. $P < 0.05$ was considered statistically significant. Intraobserver variability assessment for systematic error was performed on 30 arbitrarily chosen images and was calculated by having one operator perform two measurements in the same image one day apart. Intraobserver agreement was quantified by calculating the mean difference between two measurements and using Bland–Altman 95% limits of agreement (LOA). Statistical analysis was performed using the statistical packages GraphPad Prism 4 and GraphPad InStat for Windows (GraphPad Software, San Diego, CA, USA).

RESULTS

Normal fetuses and reference range

The normal population consisted of a total of 253 pregnancies, examined between 19 and 36 weeks of gestation, which were included for the calculation of the TACAD reference range. In the normal population, TACAD increased with advancing gestation, with the best-fit curve being a second-order polynomial in relation to gestational age, with the following formula: $\text{TACAD (mm)} = -0.01871 \times \text{GA}^2 + 1.484 \times \text{GA} - 13.45$ (SD = 1.036; $R^2 = 0.7554$) (Figure 3). No intraobserver variability was found, with a mean difference between measurements of 0.0133 mm. The Bland–Altman 95% LOA of −0.619 to 0.645 mm confirmed reliable reproducibility and absence of systematic error. The mean and median values of TACAD during the study period were 11.5 mm and 11.1 mm, respectively. The calculated mean value at 22 weeks of gestation, when the screening ultrasound is generally performed, was 10.1 mm, increasing to 12.5 mm and 14.2 mm at 26 and 30 weeks of gestation, respectively.

Fetuses with cACC or pACC

The study population with ACC included a total of 46 fetuses, consisting of 28 with cACC and 18 with pACC. CC length in fetuses with pACC ranged between 8.5 mm and 27.7 mm (mean, 15.3 mm; median, 14.7 mm). In the whole ACC study group, 12/46 (26%) fetuses had associated additional intracerebral or extracerebral anomalies and 15/46 (33%) patients opted for termination of pregnancy.

TACAD was below the 5th centile in 43/46 (93%) cases with ACC, including 28/28 (100%) cases with cACC and 15/18 (83%) cases with pACC. The mean TACAD in

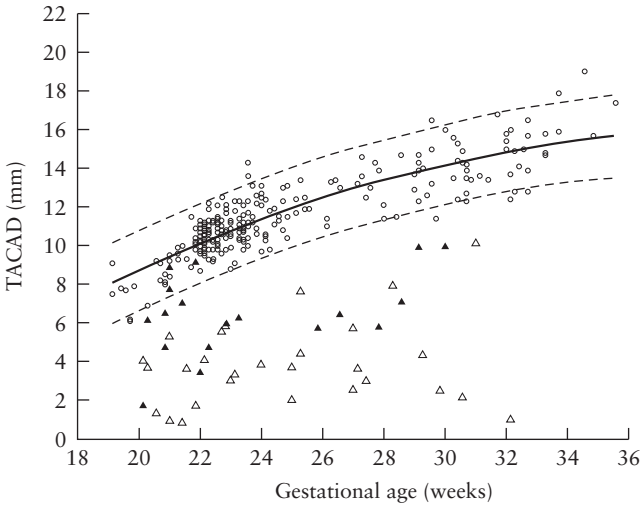

Figure 3 Individual tela-choroidea-to-anterior-cerebral-artery distance (TACAD) values in normal fetuses (○) and fetuses with partial (▲) or complete (△) agenesis of corpus callosum across gestation. Reference range (median (——) and 5th and 95th centiles (- - - -)) based on normal population is shown in relation to gestational age.

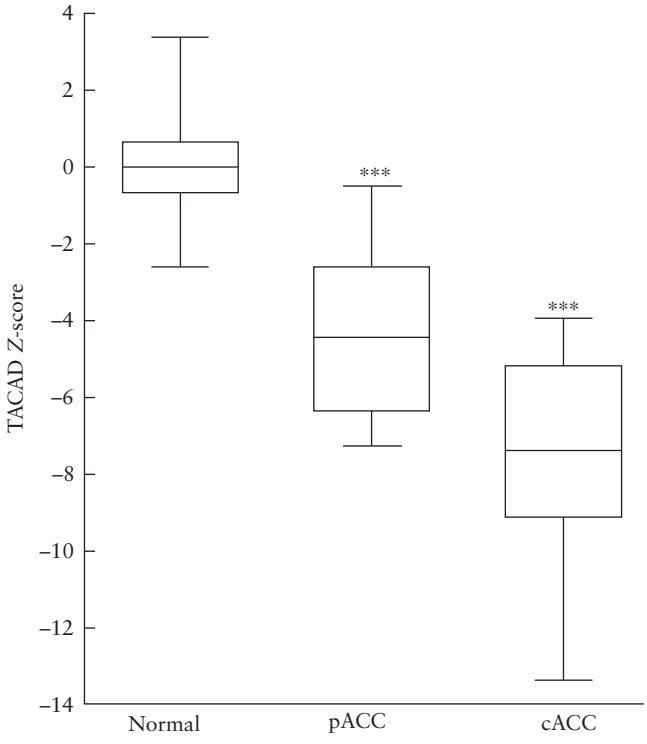

Figure 4 Box-and-whiskers plot of tela-choroidea-to-anterior-cerebral-artery distance (TACAD), expressed as *Z*-score, in normal fetuses and in fetuses with partial (pACC) or complete (cACC) agenesis of corpus callosum. Box and internal line show median and interquartile range, and whiskers represent range. Asterisks represent statistically significant difference in TACAD *Z*-score compared with normal population ($P < 0.001$).

the whole study group with ACC was 4.9 mm, measuring 3.9 mm in the cACC and 6.6 mm in the pACC subgroups. The calculated TACAD *Z*-scores in fetuses with cACC and pACC were significantly lower compared with those of normal fetuses ($P < 0.001$), and there was also a significant difference in TACAD *Z*-score between the cACC and pACC subgroups ($P < 0.001$) (Figure 4). Additionally, we performed a separate evaluation of cases detected before 24 weeks of gestation, which included 14 and 12 fetuses with cACC and pACC, respectively. A significant difference in TACAD *Z*-score was also observed between this subgroup and the normal group ($P < 0.001$).

DISCUSSION

This study shows that TACAD can be used for objective quantification of the position and course of the ACA relative to the tela choroidea. The tela choroidea is a c-shaped structure in the center of the head, which courses over the thalami. Due to its high vascularization, the tela choroidea appears hyperechogenic on ultrasound, which makes it suitable as a landmark (Figures 1 and 2). This study demonstrates that, in the second half of gestation, the reported increase in CC length[11] is accompanied by an increase in TACAD and, in cases with ACC, TACAD is significantly shorter, owing to an abnormal ACA course (Figures 3 and 4).

The abnormal course of the ACA was first described as one of the diagnostic signs to confirm ACC on X-ray and pneumoencephalography[12,13]. The study by Zellweger[12] was one of the first to describe the clear pattern of the abnormal course of the ACA on angiography. This approach was abandoned with the advent of CT and MRI. Later, absence of a normal PCA on neonatal ultrasound was reported as a possible additional sign of ACC[14].

To date, the literature on vascularization of the fetal brain has been relatively limited[15]. Few studies have reported on visualization of the PCA in normal and abnormal fetuses, focusing mainly on the anatomy, variations and its course in anomalies such as holoprosencephaly[6,16–20]. This study reports on TACAD, a simple measurement that can be performed on color Doppler in fetuses with cACC and pACC. This parameter enables an objective assessment of the abnormal course of the ACA using the tela choroidea as a clear echogenic landmark in the midsagittal view of the head. The tela choroidea can also be well-displayed in cases of cACC without CSP[21]. The abnormal course of the ACA on fetal ultrasound has been described as an additional feature in cACC[4] and pACC[5,10]. In normal fetuses, the ACA continues as the PCA, which runs along the CC[16] (Figures 1 and 2a,d). In cACC, the ACA ascends vertically without forming the loop of the PCA[5,6] (Figure 2c,f), while, in pACC, the loop of the PCA is partly present, but abruptly interrupted[5,10] (Figure 2b,e). This study shows that, in fetuses with ACC, the abnormal ACA course can be detected objectively based on a short TACAD, which is shorter in cases with cACC than in those with pACC (Figure 4).

The strengths of this study are the large number of fetuses examined and the advent of TACAD, a new measurable parameter that facilitates objective description of the aberrant course of the ACA in cases with cACC or pACC. Since the tela choroidea can already be seen at 13 weeks of gestation, we are confident that it can be of help in the early assessment of the developing CC, as was recently reported[22]. Furthermore, both the ACA and the tela choroidea are well recognizable structures in the midsagittal plane on color Doppler ultrasound and, in the near future, may be used as part of artificial-intelligence-based assessment of normal and abnormal fetal brain anatomy. Machine learning has recently been applied with success in suspecting brain anomalies in the axial view[23].

This study also has some limitations. Major variations in ACA anatomy have been reported among normal fetuses[16], which are likely to be present in fetuses with CC anomalies and which have not been well researched yet. A further limitation is that, in all reported cases, the diagnosis of cACC and pACC was achieved prior to color Doppler assessment. An additional source of bias to be mentioned is that a true blinded study could not be achieved because the course of the ACA already appeared abnormal at the time of TACAD measurement. However, the main aim of the study was to describe quantification of the commonly reported abnormal course of the ACA on color Doppler[5,6,10]. Even if the finding of abnormal TACAD in the second half of pregnancy may be of minor clinical relevance, future studies of this measurement throughout the late-first and early-second trimesters may reveal it as a useful marker of abnormal CC development, at a time when ACC is usually undetected.

In conclusion, we propose a new parameter, TACAD, and present reference ranges for it in the second half of pregnancy. In normal fetuses, TACAD measures 10 mm at 22 weeks of gestation and increases to 14 mm at 30 weeks. An abnormal course of the ACA in children with ACC was first described more than 70 years ago[12] and reported as an interesting additional marker on antenatal ultrasound[5,6,10]. In this study, we quantified this observation by introducing TACAD, which is short in both cACC (mean, 3.9 mm) and pACC (mean, 6.6 mm) and hope that this measurement may be of help in suspicious cases. Further studies are needed to confirm our observation and find out whether this parameter can be used in the early-second trimester before a CC anomaly is usually detected. In the near future when machine learning is used more routinely in antenatal ultrasound assessment, landmarks and measurements such as those proposed in this paper will be needed for an objective assessment of the relationship of the analyzed structures, which today are still assessed subjectively.

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