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● *Review*

ROLE OF 3-D ULTRASOUND IN CLINICAL OBSTETRIC PRACTICE: EVOLUTION OVER 20 YEARS

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Abstract—The use of 3-D ultrasound in obstetrics has undergone dramatic development over the past 20 years. Since the first publications on this application in clinical practice, several 3-D ultrasound techniques and rendering modes have been proposed and applied to the study of fetal brain, face and cardiac anatomy. In addition, 3-D ultrasound has improved calculations of the volume of fetal organs and limbs and estimations of fetal birth weight. And furthermore, angiographic patterns of fetal organs and the placenta have been assessed using 3-D power Doppler ultrasound quantification. In this review, we aim to summarize current evidence on the clinical relevance of these methodologies and their application in obstetric practice. (E-mail: Araujojred@terra.com.br) © 2015 World Federation for Ultrasound in Medicine & Biology.

Key Words: **Doppler ultrasound, Fetus, Four-dimensional ultrasound, HDlive, Matrix array, Omniview, Spatiotemporal image correlation, Three-dimensional ultrasound, Volume calculation.**

INTRODUCTION

The current review evaluates the historical background underlying the role and clinical value of 3-D ultrasound (3-DUS). This review also illustrates that 3-DUS has achieved a recognized diagnostic role that goes beyond that of conventional 2-D ultrasound (2-DUS) and thus deserves to be included in routine practice. Health care providers should be informed about the established, increasing role being played by 3-DUS in obstetric practice and should be confident about administering a 3-DUS examination to their patients. However, health authorities are being required to make significant investments in advanced technology and to appropriately equip and digitalize modern obstetrics ultrasound laboratories.

To illustrate the established role of 3-DUS in obstetric practice, we provide data on its application in the study of fetal brain anatomy, fetal face, fetal echocardiography, fetal organ and limb volume and estimation of fetal birth weight, and we also examine 3-D power Doppler ultrasound (3-D-PD). Furthermore, we present several 3-DUS applications that include reslicing techniques such as Omniview, reverse-face/tilted/oblique view, spatiotemporal image correlation (STIC), B-flow, inversion mode and matrix array, virtual organ computer-aided analysis (VOCAL) volume calculation and recently developed lightening techniques.

BACKGROUND AND TECHNICAL ASPECTS OF 3-D ULTRASOUND

The first 3-DUS system was described by Baba et al. (1989). This system consisted of a 2-D probe attached to a mechanical arm that performed a scan over the maternal abdomen. With this scanning, several 2-D planes were collected and sent to a computer for generation of a 3-D image reconstruction. The great disadvantages of this system included the significant time required for performing the scan and poor image quality, which limited its use in clinical practice (Baba et al. 1989).

In the early 1990s, a group at National Cheng Kung University in Taiwan described the first visualization of fetal face, cerebellum and cervical spine using a convex

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volumetric probe on a Combison 330 ultrasound apparatus (Kretztechnik, Zipf, Austria), which was the first 3-DUS equipment used in clinical practice (Kuo et al. 1992). Nelson and Pretorius (1992) were among the first to visualize the fetal surface and the fetal spine (Steiner et al. 1995), and Merz et al. (1995) visualized an extensive series of congenital anomalies using both 2-DUS and 3-DUS. Merz et al. (1995) reported that 3-DUS enhanced prenatal detection of fetal anomalies in 62% of cases, was equivalent in 36% and was disadvantageous in only 3% of cases compared with 2-DUS. Three-dimensional ultrasound images are generated by changing the position of volume transducers to acquire a volume as a series of slices in different orientations. Integrated transducers are generally integrated with the scanner so that a set of volume data is immediately available after the volume is acquired, without the need for re-projection or post-processing (Nelson and Pretorius 1998).

A computer program creates a single 3-D data set based on the distance and angulation between the acquired 2-D ultrasound images. While the smallest unit of a 2-DUS image is a pixel, the smallest unit of a 3-DUS image is called a voxel. In a 3-DUS examination, the 2-DUS images are combined by computer to form an objective 3-D image of the anatomy and pathology. This image can then be viewed, manipulated and measured in three dimensions by the physician on the same or another computer. Also, a 2-D cross-sectional image can be generated in any orientation, without restriction, at an anatomic site, which may easily be associated with a previous or subsequent 3-D image. To avoid geometric distortions in the 3-D image that would lead to measurement errors, the locations and orientations of the acquired 2-D images must be accurately known. Four different 3-DUS imaging approaches have been pursued: mechanical scanners, free-hand techniques with position sensing, free-hand techniques without position sensing and 2-D arrays (Fenster and Downey 1996). The steps in a 3-DUS examination are data set acquisition, 3-D visualization and image interpretation and/or volume navigation and storage Three-dimensional ultrasound volumetric data can be acquired using linear, wedge, free-hand and/or rotational scans (Nelson and Pretorius 1998). The display technique for 3-D ultrasound imaging is subdivided into multiplanar, surface-based and volume-based rendering.

In multiplanar rendering, a 3-D voxel-based image must first be reconstructed. Then, the computer-user interface software enables selection of single or multiple planes for generating images similar to those of conventional 2-DUS, which are displayed simultaneously on the screen. A 3-D data set can be magnified, rotated or moved, thus allowing any plane within the acquired volume to be obtained (Merz et al. 2007). After some degree of manipulation, the fetus (or other structure of interest) may be viewed in a standardized manner, thus providing a good starting point for the examination. This is usually accomplished by manipulating the 3-D data set until the sagittal view is displayed in plane A (upper left), the transverse view in plane B (upper right) and the coronal plane in plane C (lower left) (Barra et al. 2013) (Fig. 1).

In surface-based rendering, the algorithm analyzes each voxel in the 3-D image and determines the structure to which it belongs. Once the tissues or structures have been classified and their boundaries identified, the boundary of interest is represented by a wire frame or mesh, and the surface is texture mapped with an appropriate color and texture to represent the anatomic structure (Lobregt and Viergever 1995; Neveu et al. 1994). Accurate and automatic segmentation of ultrasound data is essential for high-quality surface fitting, and segmentation based on signal void greatly simplifies the extraction of structural features. Baba et al. (1996, 1997) visualized fetal surfaces in near real time using simple thresholding to identify the fetal surface in the amniotic fluid.

The most common approach in 3-DUS is the ray-casting technique, in which the voxel intensity is propagated forward toward the viewing plane along each ray from back to front. Each voxel contributes to final image intensity in a manner that depends on shading and transparency values (Nelson and Pretorius 1998).

In the rendering mode, the voxels related to the amniotic fluid are removed from the 3-D data set and from the surface below the amniotic fluid, so that a region of interest delimited by straight and/or curved lines can be seen (Riccabona et al. 1997). Clipping planes producing a subcube in the volume can thus be obtained as well. Surface rendering mode can be further enhanced by a novel lightening HDlive technique (Fig. 2).

In addition, animation sequences such as rotation and gated "cine-loop" review assist volume visualization offered by real-time processing or pre-calculation (Nelson and Pretorius 1998).

In any case, to enhance diagnostic accuracy and prevent errors in diagnostic interpretation, especially in cases of uncontrolled rotation of an acquired volume to an odd angle by an inexperienced sonographer, standardization of the use of 3-D ultrasound was a primary clinical concern and aim during the development of this technique (Abuhamad et al. 2007; Benacerraf et al. 2005; Merz et al. 2007).

By examining its performance in the study of cerebral anatomy, cranial anatomy, cardiac structures and organ volumes, we illustrate the clinical value of 3-D/4-D ultrasound. We also describe how the technique has reached outstanding diagnostic accuracy in obstetric practice.

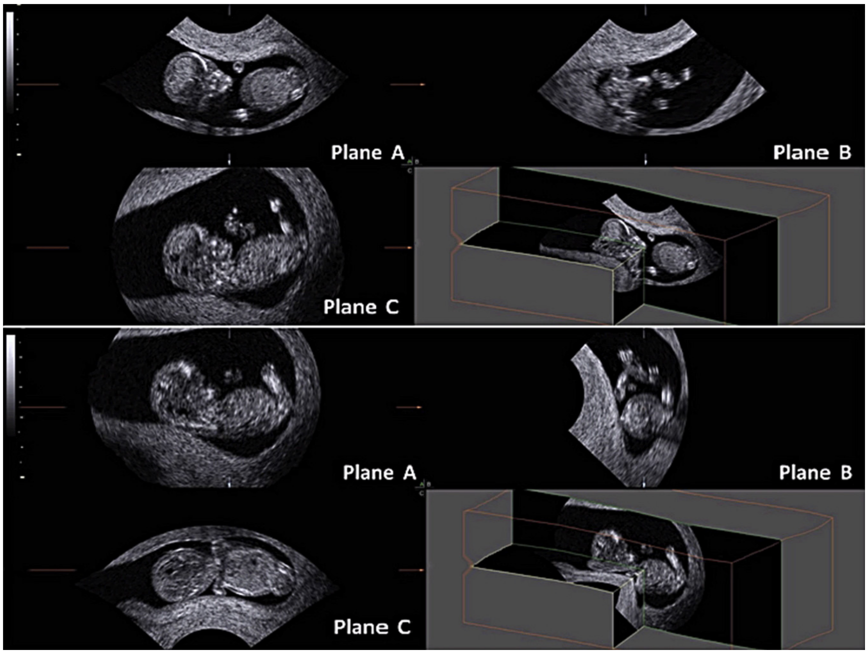

Fig. 1. Three-dimensional ultrasound in multiplanar mode in a first-trimester fetus. The acquired image acquired is at the top. After rotating and moving the 3-D data set, one can place the fetus in a standardized manner, with the sagittal plane in the A image, the transverse plane in the B image and the coronal plane in the C image. With the standardized image, it is possible to discern that the fetus is bending to its right, which can interfere with measurement of crown–rump length.

3-D ULTRASOUND AND THE STUDY OF FETAL BRAIN ANATOMY: "THE NEUROSONOGRAM"

Although the 2-DUS neurosonogram performed according to the guidelines of the International Society of Ultrasound in Obstetrics and Gynecology (ISUOG) represents the gold standard of care (ISUOG 2007), a growing body of evidence has now established the clinical role played in this application by 3-DUS, which has been suggested as a method that can overcome limitations associated with dependence on operator skills (Benacerraf et al. 2006). A fetal neurosonogram is performed by aligning the transducer with the sutures and fontanels of the fetal head (Timor-Tritsch and Monteagudo 1996).

In addition to the basic transthalamic, transventricular and transcerebellar axial views, evaluation of four

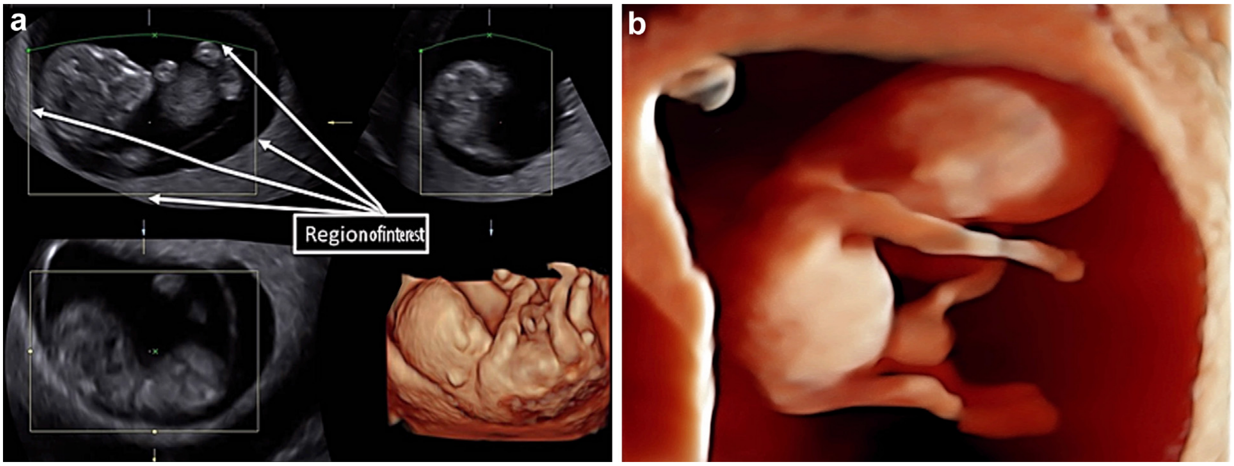

Fig. 2. (a) Multiplanar and rendering mode of a first-trimester fetus. In the rendering mode, the region of interest, which is delimited by lines in the multiplanar mode, is seen as it was viewed by the green line without the voxels related to amniotic fluid. (b) HDlive: Realistic image of an embryo at 10.2 wk of gestation using transvaginal scan with post-processing application of this novel lightening technique

coronal views (transfrontal, transcaudate, transthalamic and transcerebellar) and two sagittal views (midsagittal and parasagittal) has been recommended (ISUOG 2007). In recent years, 3-DUS has been effectively used to identify major brain structures and depict structures usually not displayed with the 2-D transabdominal axial approach (Chitty and Pilu 2009; Timor-Tritsch et al. 2012). Alternatively, acquisition of volume data sets starting from the axial view of the fetal head and off-line "navigation" using multiplanar reconstruction of planes can be employed to obtain the diagnostic planes and reduce operator dependence, which may potentially increase the rate of detection of central nervous system abnormalities (Rizzo et al. 2011a). The concept of automated volume ultrasound based on operator-independent retrieval of diagnostic 2-D planes from a 3-D volume requires initial, pre-determined standardization of organ-specific 3-D volumes. Similarly, 180° rotation along the y-axis in plane A, z-rotation and placement of the "reference dot" at the midpoint of the interhemispheric fissure are required (Abuhamad 2005). Monteagudo et al. (2000) examined 34 patients with a history of brain abnormality or suspected brain pathology and compared 2-D and 3-D transvaginal neurosonograms. Monteagudo et al. (2000) concluded that the key difference between the 2-DUS and 3-DUS studies was that the axial plane could be obtained only by 3-D reconstruction of the volume data sets; this is an advantage, because the axial plane is rarely seen with 2-D transvaginal technology. The planes obtained off-line from the 3-D volume were parallel and not oblique or at an angle, as is the case with the conventional 2-D transvaginal neurosonogram. Finally, when 2-DUS and 3-DUS studies of pathologic cases were compared, the important advantage offered by "navigating" inside the volumes generated by 3-DUS was the ability to follow the reference dot that identifies the same anatomic point on all three orthogonal planes, thus facilitating identification of the midline structure.

Viñals et al. (2007) reported that transfrontal 3-D acquisition of brain volume data sets is most advantageous for examining both the corpus callosum and the cerebellar vermis after 20 wk of gestation. Viñals et al. (2007) reported that the midsagittal plane was easily obtained in all cases, with diagnostic-quality images of the corpus callosum acquired in 93.1% and 99.0% of cases by two examiners, respectively. Bornstein et al. (2010a) performed off-line analysis using a transabdominal 3-D gray-scale and power Doppler volumes of the fetal brain acquired in 102 consecutive normal fetuses at 20 to 23 wk. Miguelote et al. (2012) compared the feasibility and reproducibility of 3-D volume reconstruction ultrasound when used for measuring corpus callosum length in 46 normal fetuses examined by 2-DUS and 3-DUS at 23 to 32 wk of gestation. Direct midsagittal views were obtained by either the transabdominal or transvaginal approach, and 3-D reconstructed midsagittal views were obtained by 3-D multiplanar manipulations and the volume contrast image through the C-plane (VCI-C) technique from volumes acquired in axial planes. VCI-C is a new approach that improves the contrast and resolution of the tissue compared with 2-DUS. It is able to yield measurements, margins and internal aspects of structures/tissues that are more precise (Ruano et al. 2004a) (Fig. 3).

Visentainer et al. (2010) established reference ranges for corpus callosum length and area in fetuses between 20 and 33 wk of gestation using 3-DUS. These authors reported that mean corpus callosum length increased from 21.7 to 38.7 mm between 20 and 33 wk of gestation and that mean corpus callosum area increased from 55.2 to 142.2 mm^2 between 20 and 33 wk of gestation. A strong correlation between corpus callosum length/area and gestational age ($R^2 = 0.7$ and 0.7) and biparietal diameter ($R^2 = 0.7$ and 0.6) was also documented.

Miguelotte et al. (2012) reported that the corpus callosum could be measured in 91% of transvaginal acquisitions, in 52% of transabdominal acquisitions, in 92% of multiplanar reconstructions and in 86% of VCI reconstructions obtained with the C-plane technique; they concluded that the success rate with respect to transvaginal acquisition was independent of gestational age and slightly dependent on gestational age for 3-D reconstruction techniques. Correa et al. (2006) evaluated the role of transabdominal 3-DUS in the assessment of the fetal brain and studied its potential for routine neurosonogram studies in 202 consecutive fetuses at 16 to 24 wk of gestation. Correa et al. (2006) found that the corpus callosum could be seen in 84% of patients, the fourth ventricle in 78%, the lateral sulcus (Sylvian fissure) in 86%, the cingulate sulcus in 75%, the cerebellar hemispheres in 98%, the cerebellar vermis in 92%, the medulla oblongata in 97% and the cavum vergae in 9%. The thalami and cisterna magna were identified in all cases. At or beyond 20 wk, an enhanced visualization rate was seen for the corpus callosum (97%), the supracerebellar cisterns (92%) and the third ventricle (93%).

Correa et al. (2006) concluded that multiplanar images obtained by transabdominal 3-DUS provide a simple, effective approach to detailed evaluation of fetal brain anatomy. This technique has the potential for use in routine scans for fetal abnormalities.

Studying fetal cerebral midline structures in 300 consecutive, normal women with low-risk pregnancies, Tonni et al. (2014) recently provided evidence that the application of a novel 3-DUS reslicing technique (Omniview, GE Medical System, Zipf, Austria) may facilitate

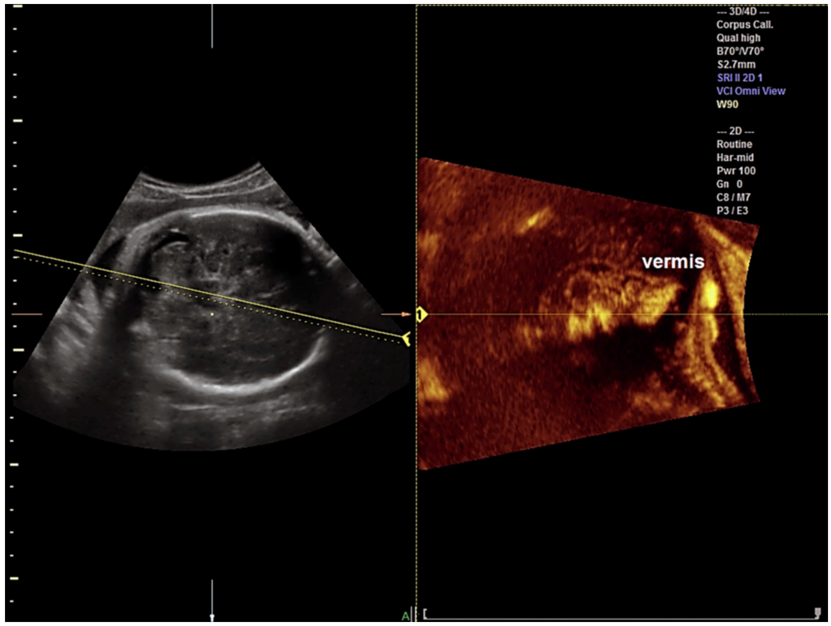

Fig. 3. Fetal neurosonogram using Omniview with volume contrast image in the C-plane (VCI-C). Yellow line is drawn in oblique direction through the posterior fossa enabling reconstruction of the cerebellar vermis in a normal fetus at second-trimester scan.

the evaluation of cerebral midline structures at second-trimester anatomic scan. Omniview is a new reslicing technique for 3-DUS/4-DUS that allows interrogation of volume data sets and simultaneous display of up to three independent planes of any given organ. It also allows simultaneous volume reconstruction of up to three independent planes through delineation of lines and angles in any direction. The volume can be sectioned freely by setting the ultrasound equipment to trace straight lines, curved lines or polylines, as selected on a menu. Omniniew or other commercially available software has the potential to facilitate the reconstruction and evaluation of 3-D volumes, thus compensating for limited operator expertise, and requires a short learning curve in training programs (Yeo et al. 2011a, 2011b). Tonni et al. (2014) reported that accurate off-line volume data sets of the corpus callosum and the posterior fossa were accurately reconstructed from the sagittal and axial planes in 98.5% and 96% of cases, respectively, with agreement rates of 0.96 and 0.91 for the midsagittal and axial planes, respectively, in cases involving pathology (Fig. 4).

The results obtained by Tonni et al. (2014) concur with those of Rizzo et al. (2011b), who first used this technology to reconstruct the sagittal and coronal planes of the brain in 106 normal fetuses at 18 to 24 wk of gestation. Midsagittal, parasagittal, transfrontal, transcaudate, transthalamic and transcerebellar planes were obtained, with visualization rates for brain structures of 72% to 96% using sagittal sections and 76% to 91% using coronal planes. The agreement rates between operators were 0.93 and 0.89 for the sagittal and coronal planes, respectively. Rizzo et al. (2011b) were also able to detect accurately all nine cases of cerebral pathology, including complete agenesis of the corpus callosum, borderline ventriculomegaly and classic Dandy–Walker malformation.

Brazilian researchers (Haratz et al. 2011) have evaluated the feasibility of fetal lateral ventricle (LV) volumetry in 30 fetuses at 20 to 36 wk of gestation, with ventricular width ranging from 10 to 30 mm. By comparing measurements performed by 3-DUS VOCAL with those obtained by magnetic resonance imaging (MRI), Haratz et al. (2011) found that 3-DUS volumetry of fetal LV by the VOCAL method correlates well with fetal MRI in fetuses with ventriculomegaly, and that this approach may be used as additional tool in patient counseling and prognosis prediction. VOCAL is a computer program installed on some commercial ultrasound machines that is used for volume calculation and employs poles demarcated with calipers. The angle of rotation depends on the ultrasound machine and varies from 6° to 30°. If 6° is chosen, the operator delimits 30 planes; with an angle of 30°, only 6 planes are delimited. Delimitation can be manual, automated or semi-automated. When the last plane is delimited, the system reconstructs the fetal organ and displays its volume. This method has been reported to be feasible and reproducible both *in vivo* and *in vitro* (Raine-Fenning et al. 2003; Ruano et al. 2005; Martins et al. 2007) and to correlate well with MRI and multiplanar methods (Ruano et al. 2004b). VOCAL has

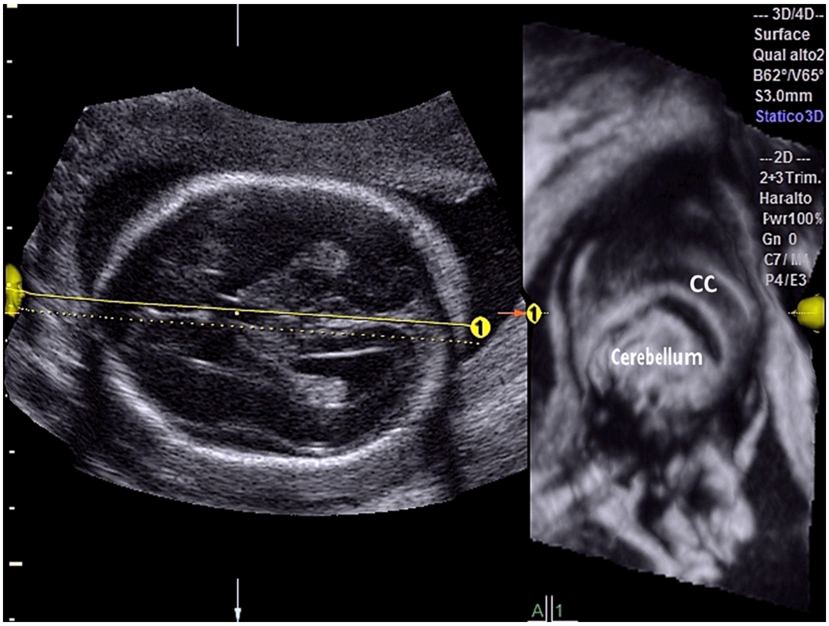

Fig. 4. Fetal neurosonogram using Omniview: Reconstruction of the corpus callosum (CC) in a normal fetus at 20 wk of gestation.

several advantages over the multiplanar method, as it is faster and allows corrections to be made in the area involved after completion of the final volume calculation (Peralta et al. 2006) (Fig. 5).

The calculation of fetal cerebellum in different ethnicities is an important application of VOCAL for constructing reference range in relation to gestational age. Such calculation has also improved the accuracy of prenatal diagnosis of cerebellar hypoplasia. Cerebellar hypoplasia may be found in fetuses with Down syndrome, intrauterine growth restriction (IUGR) and multiple genetic diseases (Rotmensch et al. 1997). In a longitudinal study of 52 fetuses from normal pregnancies, Araujo Júnior et al. (2007a) observed that the equation for fetal cerebellum volume as determined by Chang et al. (2000) for a Taiwanese population could not be applied

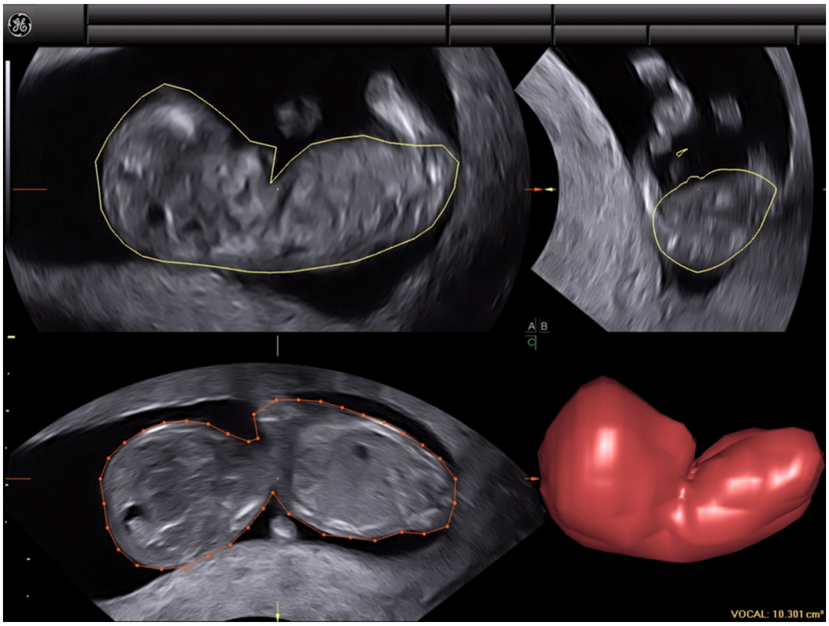

Fig. 5. Virtual organ computer-aided analysis (VOCAL) with a 30° rotation angle was used to calculate the volumes of the fetal head and trunk.

to a Brazilian population, thus confirming that ethnicity may potentially be a predisposing factor that may contribute to creating differences in fetal organ volume. Rutten et al. (2009) observed good intra- and inter-observer reliability when calculating cerebellar volume using both the multiplanar and VOCAL methods, as did Araujo Júnior et al. (2014a) in the calculation of volume of the fetal cisterna magna using VOCAL at 30° on the standard axial plane of the transverse diameter of the cerebellum.

In addition, when 3-DUS technology is used, the volume can be stored, compressed and then sent to a remote site for expert consultation for post-processing analysis that has been found to be accurate (Bornstein et al. 2010b; Rizzo et al. 2011c; Salman et al. 2011). Very recently, Passos et al. (2014) established reference ranges for fetal cisterna magna length and area by 3-DUS in the multiplanar mode in 224 normal pregnancies between 17 and 30 wk of gestation. The authors found that the mean length and area of the fetal cisterna magna ranged from 0.50 ± 0.10 to 0.79 ± 0.18 cm and from 0.95 ± 0.18 to 3.09 ± 0.62 cm^2, respectively.

Examination of early brain development (7–12 wk of gestation) by 3-DUS using inversion mode rendering has been described by Kim et al. (2008). Inversion mode rendering is a technique that analyzes fluid structures and inverts gray-scale voxels; that is, formerly anechoic structures such as cardiac chambers, vessels and the stomach, bladder and renal pelvis become echogenic, whereas structures that are usually echogenic (such as bones) become anechoic (Gonçalves et al. 2004a; Lee at al. 2005). Inversion mode rendering allows reconstruction of cardiac chambers, aortic and ductal arches, abnormal venous connections and septal defects (Espinoza et al. 2005; Gonçalves et al. 2004a). Kim et al. (2008) recommended that this method not be used before 6 wk because of the limited amount of cerebral fluid present, nor after 12 wk because the choroid plexus is difficult to isolate after this point. Recently, in a work by Rolo et al. (2011), the development of fetal brain sulci and gyri was evaluated by 2-DUS and 3-DUS and by antenatal MRI. This study confirmed that although MRI is considered the most accurate method for detecting fetal gyrus and sulcus abnormalities (Ghai et al. 2006; Malinger et al. 2007), 3-DUS improves visualization of sulci and gyri compared with 2-DUS. Rolo et al. (2011) reported that the 3-DUS rendering mode may be useful for reaching a definitive diagnosis of abnormal cortical development and differentiation. Compared with MRI, 3-DUS is a faster and more economical procedure, may be more readily available and may be a valid alternative especially in cases of suspected fetal cortical anomalies that cannot be investigated with MRI.

Table 1 summarizes the most important articles on fetal neurosonograms obtained with 3-DUS.

3-DUS IN THE DIAGNOSIS OF CLEFT LIP AND CLEFT LIP/PALATE

Although facial clefting of the fetus can be prenatally diagnosed by 2-DUS, the introduction of 3-DUS together with the development of new software applications has led to new insights into the prenatal ultrasound study of the fetal palate. There is now a growing body of evidence that 3-DUS may enhance prenatal visualization of the fetal face and detection of facial clefting (Tonni et al. 2005), especially if 3-DUS is performed as a targeted examination to verify a suspected diagnosis of cleft obtained with 2-DUS (Martinez Ten et al. 2009). A number of techniques for fetal palate imaging have been developed. These include the “flipped-face” view (Platt et al. 2006), the “reverse-face” view (Campbell and Lees 2003), the Faure technique (Faure et al. 2007), “angle insonation” (Pilu and Segata 2007), “oblique-face” view (Martinez Ten et al. 2009) and retronasal triangle (Sepulveda et al. 2010). The last technique has been applied for imaging the fetal palate at the first-trimester scan. Faure et al. (2007), however, did not produce images involving facial clefting. Martinez-Ten et al. (2009) studied 60 fetuses between 20 and 33 wk of gestation, of which 10 had a cleft lip and palate initially detected by conventional 2-DUS at second-trimester scan. These authors reported that “oblique view” was the best method when the palate was involved (100%), whereas the “reverse-face” and “flipped-face” views were able to diagnose this area correctly in 71% and 86% of cases, respectively. The diagnostic challenge still remains, as involvement of the soft palate was regularly documented in only 14% of fetuses with defects of the secondary palate using either the “flipped-face” or “oblique-face” view.

Campbell and Lees (2003) found that although high-quality antenatal 2-DUS can readily diagnose clefts of the lips and of the alveolar ridge, 3-DUS may enhance sensitivity when the fetal face is examined in the frontal plane first and then the secondary palate is examined with the “reverse-face” view after secondary rotation through 180°. The reverse-face view is easy and fast, as it requires only 2–3 min to obtain the frontal view of the face with complete visualization of the palate. The reverse-face view may potentially provide an unobstructed view of the palatal area, nasal cavity and orbits and, thus, offers unique diagnostic information about the condition of the secondary palate. Tonni et al. (2005) reported that the best time for ultrasound-based screening for facial cleft varies between 18 and 23 wk of gestation, which

Table 1. Reference, study population, GA, prenatal US technique and clinical findings in cases of fetal 3-D neurosonograms

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Monteagudo et al. (2000)	34 fetuses with brain pathology		3-D TVUS neurosonogram vs 2-D TVUS	Axial plane only from 3-D reconstruction; planes were parallel and not oblique or at angle; reference dot indicates the same anatomic landmark in all three orthogonal planes when "navigating" within the volume
Correa et al. (2006)	202 healthy fetuses	16–24	3-D TA neurosonogram	CC detected in 88%; Sylvian fissure in 86%; cingulated sulcus in 87%; cerebellar vermis in 92%; cerebellar hemispheres in 98%; medulla oblongata in 97%
Viñals et al. (2007)	60 healthy fetuses	20–33	Visualization of cerebral midline structures by 2-D vs. 3-D multiplanar and VCI-C plane vs. transfrontal plane	Midline plane in 88% of multiplanar, 82% of VCI-C and 87% of transfrontal plane; CC and cerebellar vermis by 3-D median planes were highly correlated; primary and secondary fissures of cerebellar vermis detected in 13%–26% of multiplanar, 18%–35% of VCI-C and 52%–79% of transfrontal plane
Bornstein et al. (2010a)	102 healthy fetuses	20–23	TA 3-D gray-scale and power Doppler	93%–99% midsagittal visualization of CC
Rizzo et al. (2011b)	106 healthy fetuses	18–24	3-D neurosonogram using OmniView reslicing technique in midsagittal, parasagittal, transcaudate, transthalamic, transcerebellar planes	Rates of visualization of brain structures: 72%–96% using sagittal planes, 76%–91% using coronal planes Inter-observer agreement rates of 0.93 and 0.89 for sagittal and coronal planes, respectively Nine cases of brain pathology correctly identified
Visentainer et al. (2010)	70 healthy fetuses	20–33	Reference range of CC length and area	CC length and area increased from 21.7 to 38.7 mm and from 55.2 to 142.2 mm^2, respectively, from 20 to 33 wk Strong correlation between CC length and area with gestational age (R^2 = 0.7 and 0.7, respectively) and biparietal diameter (R^2 = 0.7 and 0.6, respectively)
Miguelotte et al. (2012)	46 healthy fetuses	23–32	Measurement of CC by 2-DUS TA/TV vs. 3-DUS reconstructed midsagittal vs. VCI-C from volume data sets acquired in axial planes	CC measured in 52% and 91% by TA and TV US vs. 86% in VCI-C and 92% in multiplanar
Haratz (2011)	30 fetuses with increasing LV	20–36	Measurement of LV volumetry using VOCAL vs. MRI	Good agreement between LV volumetry using VOCAL and MRI measurement; ICC = 0.928 (95% CI: 0.876; 0.958); Bland–Altman plots confirmed the high correlation (mean of differences: 1.62 cm^3, standard deviation: ±8.41 cm^3
Araujo Júnior et al. (2014a)	224 healthy fetuses	17–29	Measurement of CM volumetry using VOCAL with a 30° angle	CM volume ranged from 0.73 ± 0.25 to 3.79 ± 1.10 cm^3 between 17 and 29 wk, respectively Correlation was observed between fetal cisterna magna volume and GA (R^2 = 0.67) Good reliability and intra-observer agreement were observed, with ICC = 0.92 (95% limits of agreement: –49.7; 48.4)
Tonni et al. (2014)	300 fetuses	19–23	3-D neurosonogram of cerebral midline anatomy using OmniView reslicing technique in midsagittal and transcerebellar planes	CC and cerebellar vermis in 98.5% and 96% of cases from sagittal and axial planes, respectively. Five pathologic cases accurately detected with agreement rates of 0.96 and 0.91 for midsagittal and axial planes, respectively

CC = corpus callosum; CI = confidence interval; CM = cisterna magna; GA = gestational age; LV = lateral ventricle; MRI = magnetic resonance imaging; ICC = inter-observer correlation coefficient; TA = transabdominal; TV = transvaginal; US = ultrasound; VCI-C = volume contrast imaging C-plane; VOCAL = virtual organ computer-aided analysis.

corresponds to the proposed standard period for second-trimester anomaly scan.

Three-dimensional ultrasound has been found to yield a more precise visualization of the fetal primary and secondary palate, thus allowing differentiation of the position and extent of the cleft, especially in cases in which 2-DUS is limited by acoustic shadowing (Martinez Ten et al. 2009; Tonni et al. 2005). Wang et al. (2007) reported that 2-DUS plus 3-DUS markedly improved prenatal detection of cleft palate (from 22.2% to 88.9%) compared with 2-DUS alone.

Despite the widespread use of ultrasound, little is known about impact of a surface ultrasound image of the abnormal fetal face on parents. After birth, a questionnaire was systematically given to parents whose child had had a 3-D examination for lip and cleft palate during pregnancy. The results indicated that 3-DUS not only improved diagnosis of cleft lip/cleft lip and palate, but also led to a better understanding and acceptance of the malformation than 2-DUS. The parental impact of 3-DUS is positive and supporting, which suggests that it be regularly used in cases of isolated fetal lip and cleft palate (Escalon et al. 2010). Furthermore, Tonni and Lituania (2012) provided evidence that 3-DUS reconstructing techniques such as Omniview or other available software may be used to study the fetal hard and soft palate, although future prospective studies with consecutive patients are necessary to determine whether the routine application of this novel reslicing software will increase prenatal diagnosis of facial cleft, especially in cases of isolated cleft palate (Figs. 6, 7).

Furthermore, Tonni and Grisolia (2013) recently reported that the soft palate and the uvula can best be reconstructed with 3-DUS rendering in the surface mode, with further post-processing using HDlive, a new lightening technique for designing surfaces in which the operator sets various light parameters to obtain depth effects through lightening and shading of the images (Kagan et al. 2011). With this application, the visualization of embryonic and fetal development structures becomes more feasible, and the sonographer can thus monitor normal and altered gestational development in an enhanced manner (Hata 2013; Hata et al. 2012a) (Fig. 8).

Tonni et al. (2013) reported on the accuracy of Omniview in reformatting the retronasal triangle in 100 low-risk and 50 high-risk first-trimester fetuses. The authors reported that adequate volume data sets were captured in 98% of cases, and the retronasal triangle was reformatted in 96% of cases by off-line analysis. The secondary palate was successfully assessed in 93% of cases. An abnormal retronasal triangle was detected in two cases of lethal aneuploidy in the coronal plane, with a false-positive rate of 1.3%.

Table 2 summarizes the most important on assessment of fetal cleft lip and cleft lip/palate using 3-DUS.

Role of 3-DUS in the study of cranial sutures and fontanels

Despite the enormous progress that has been made in prenatal diagnosis with 2-DUS over the last few decades, visualization of sutures and fontanels remains difficult. Since identification of craniosynostosis may

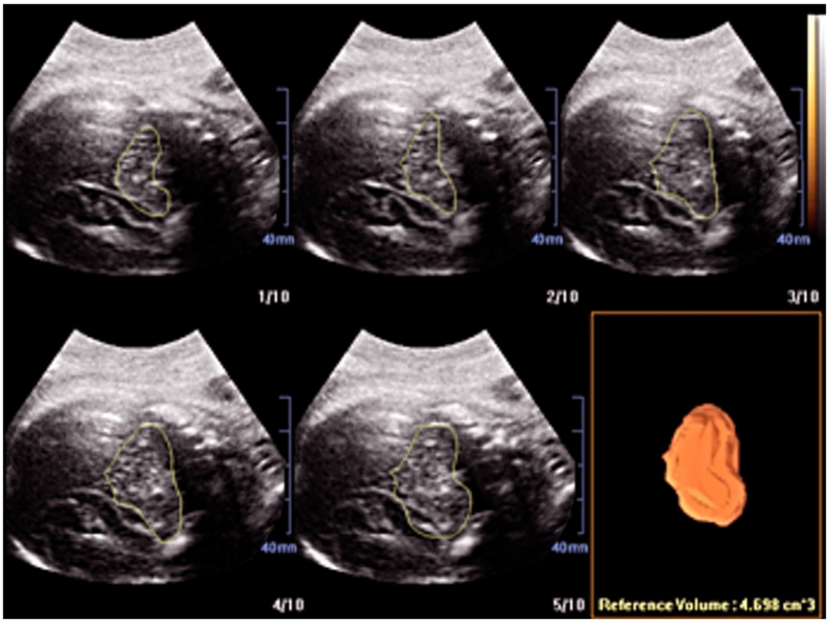

Fig. 6. Fetal neurosonogram. Fetal cerebellum volume was calculated at 20 wk of gestation using extended imaging virtual organ computer-aided analysis (XI VOCAL) with 10 sequential planes.

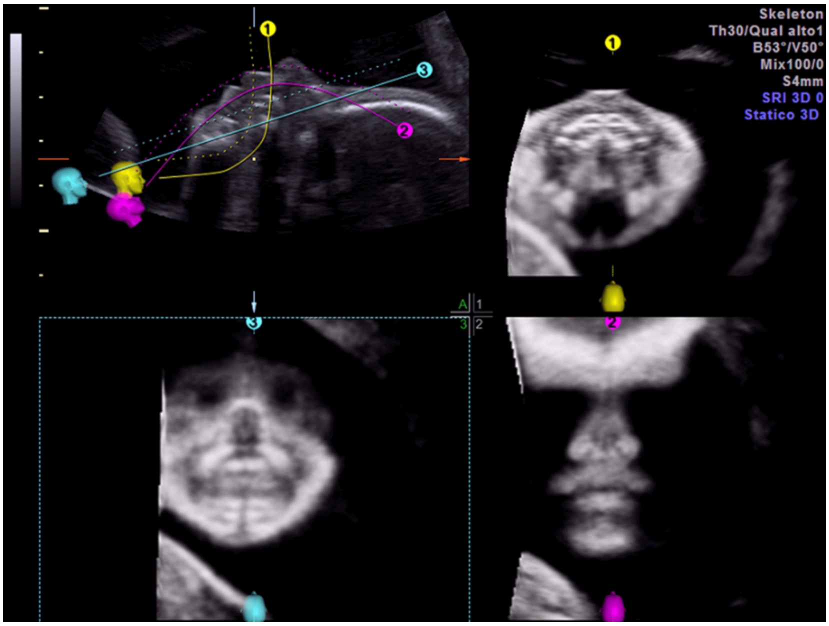

Fig. 7. Assessment of the fetal face and palate using Omniview in a normal fetus at the second-trimester scan.

be important in prenatal screening within families with a history of a syndrome associated with craniosynostosis, correct prenatal diagnosis is essential. In a study by Dikkeboom et al. (2004) of 120 fetuses at four different gestational ages, both the surface mode and maximum mode proved equally effective at revealing fetal sutures and fontanels throughout gestation. The sagittal suture and posterior fontanel were more difficult to display, whereas the metopic suture and anterior fontanel were best seen in sagittal scan. The posterior fontanel often could not be seen in any of the scan modes; however, if a 3-DUS scan of the back of the head was included, the posterior fontanel, the lambdoid sutures and possibly even the sagittal suture could be evaluated more clearly. In addition, when comparing the accuracy of 2-DUS and 3-DUS in the study of cranial sutures and fontanels

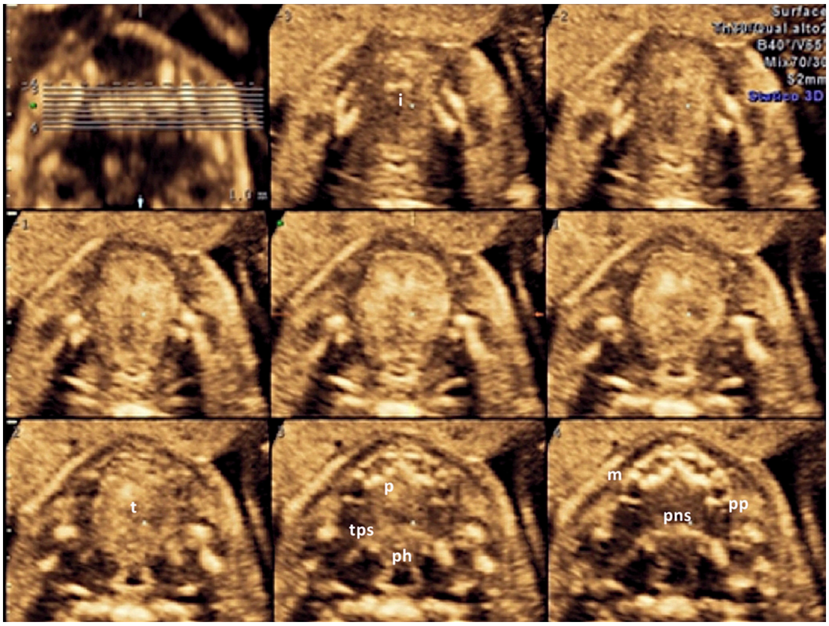

Fig. 8. Visualization of fetal hard and soft palates in a normal fetus with tomographic ultrasound imaging at second-trimester scan. (i, interpalatal suture; m, maxillary process; ph; pharynx; p, hard palate; pp, ptherygoid process; pns, posterior nasal spine; transverse posterior spine; t, tongue)

Table 2. Reference, study population, GA, prenatal 3-D ultrasound technique and clinical findings in the detection of orofacial clefting

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Campbell et al. (2005)	8 fetuses with suspected clefting		3-DUS "reverse face view"	Fetal lip and alveolar ridge examined by 3-D surface rendering in the frontal plane and face rotated through 180° on the vertical axis to examine secondary palate
Tonni et al. (2005)	1,856 low-risk pregnancies	19–23	3-DUS	Fetal profile visualized in 100%, 87% at first glance using 3-DUS; 2 cases of CL/CLP detected
Platt et al. (2006)	50 healthy fetuses		3-DUS "flipped face" view	Fetal face examined with fetus in supine position; static 3-D volume acquisition, 90° rotation; cut plane directed in a plane from chin to nose; volume of cut plane then scrolled from chin to nose to examine in sequential order the lower lip, mandible, alveolar ridge, tongue, upper lip, maxilla and hard and soft palate; 100% visualization rate
Pilu and Segata (2007)	15 healthy fetuses 1 fetus with CLP	19–28 33	3-DUS 'angled insonation"	To avoid acoustic shadowing from alveolar ridge, secondary palate insonated at 45° angle in sagittal plane; 3-DUS used to reconstruct axial and coronal planes
Martinez-Ten et al. (2009)	50 healthy fetuses, 10 fetuses with CLP	20–33	"Oblique face" view Comparison with ''reverse face'' and ''flipped face'' views	Face first imaged in midsagittal plane; an axial plane to include the palate and perpendicular to this surface then obtained; profile outlined in a cranial-to-caudal direction; coronal plane to be scrolled and rotated through whole length and width of palate obtained "Oblique face" correctly identified normal palate in 86% of cases; cleft involving the hard palate identified in 100% of cases; cleft of soft palate identified in only 14% of 7 cases, with cleft of secondary palate that was correctly considered normal in 26% in "oblique face" view
Tonni and Lituania (2012)	-	Second and third trimester	"Omniview" volume reconstruction	Pictorial essay illustrating clinical value of reformatting 3-DUS volume data sets in cases of orofacial clefting

3-DUS = 3-D ultrasound; CL = cleft lip; CLP = cleft lip and cleft palate; GA = gestational age.

at 15–16 wk of gestation, Ginath et al. (2004) maintained that 3-DUS appears to be a better method than 2-DUS for displaying the sagittal suture (50 [100%] vs. 35 [70%], $p < 0.001$) (Fig. 9).

3-DUS AND FETAL ECHOCARDIOGRAM

The prenatal detection of congenital heart disease (CHD) still represents one of the most difficult challenges for the sonographer during a routine second- or third-trimester scan. One of the main difficulties in the study of the fetal heart by conventional 2-DUS is obtaining and interpreting the outflow tracts of the major arteries. The RADIUS trial found that physicians in non-tertiary care centers were unable to detect CHD in a low-risk population of approximately 15,000 women (Crane et al. 1994). The problem can be described as follows: although the four-chamber view has been used for a number of years as the primary screening image for detection of CHD, inclusion of the right and left outflow tracts increases the detection of cardiac malformations from 30% to 80%–90%. Nelson et al. (1996) and Deng and Rodeck (1996) were among the first to develop a new gating method for 3-DUS and 4-DUS reconstruction of clinically useful cardiac images based on real-time conventional 2-DUS. Fetal heart rate and time points in the cardiac cycle were determined and used to synchronize image data for reprojection into a volume at the appropriate phase of the cardiac cycle. These authors found that rearrangement of those phased 3-D images into a cyclic sequence allowed dynamic and spatial relationships among chambers, myocardium, valves and great vessels. Three-dimensional ultrasound allows the examiner to obtain a volume of data that can be manipulated along the x- and y-axes using reference points from the four-chamber view, the five-chamber view and the three-vessel view at the bifurcation of the pulmonary arteries and from the three-vessel view at the transverse aortic arch and trachea (DeVore et al. 2004; Yagel et al. 2001). This can be accomplished by 3-D multiplanar imaging of the fetal heart, by static 3-D (no cardiac motion) or by STIC technique. STIC is a software application that permits acquisition of data sets for fetal heart and vessel volume, and the images can be viewed in either the multiplanar or the rendering mode. STIC offers several potential advantages, primarily that of allowing the study of cardiac anatomy and function during a single cardiac cycle and removal of motion artifacts of the rapidly beating fetal heart (Deng and Rodeck 2006; Deng et al. 2000). Meyer-Wittkopf et al. (2001) collected gated 3-D volume

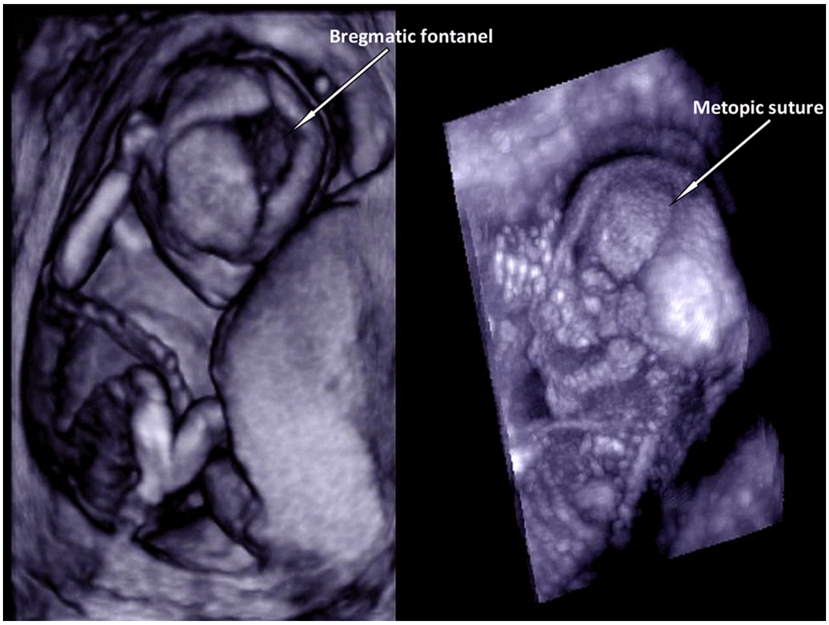

Fig. 9. Maximum surface rendering mode revealing cranial sutures and fontanels in a normal fetus at first-trimester scan.

data sets to test the feasibility of 3-D freehand echocardiographic assessment of ventricular volumetry in 29 healthy fetuses and 22 fetuses with CHD and found that both fetuses with CHD and those without CHD had exponential increases in cardiac volume during gestation. Wang et al. (2002) reported that among the basic cardiac views in 23 normal fetuses in the anterior spine position, 3-DUS improved the visualization of pulmonary outflow and provided a reliable alternate technique for clinical use compared with 2-DUS. Furthermore, real-time 3-DUS is a useful method for rendering dynamic 3-D surface views and reformatting cross-sectional views and provides useful information especially using the subcostal/subxiphoid window (Deng et al. 2000, 2002a).

Spatiotemporal image correlation can be implemented by minimum projection mode, a rendering algorithm that allows the visualization of vessels and cystic anatomic structures located in different scanning planes. Minimum projection mode facilitates the visualization of normal and abnormal vascular connections to the fetal heart at the level of the three-vessel view. This technique has proved to be useful in prenatal diagnosis of conotruncal anomalies and in assessment of the spatial relationships of abnormal vascular connections in the upper mediastinum (Espinoza et al. 2004).

In addition, obtaining diagnostic planes by means of STIC is less dependent on operator experience; less time is required to perform the examination; the analysis can be performed after the patient leaves; the structures can be evaluated using the rendering mode; and both morphology and function can be studied (Bennasar et al. 2010a, 2010b; DeVore et al. 2003; Gonçalves et al. 2003; Viñals et al. 2003). Finally, the volumes can be sent via the Internet to reference centers that specialize in fetal echocardiography (Viñals et al. 2005) (Figs. 10–12).

A volume data set is obtained in the 3-D static mode or using four dimensions to observe the 3-D heart contracting during one complete cardiac cycle. The diagnostic power of the 4-D echocardiogram derives not only from improved reformatted cross-sectional images of 4-D data sets that are virtually free of motion artifacts, but also from display of 3-D/4 D images that resemble direct views at surgery (Deng and Rodeck 2004). By reformatting standard four-as well as five-chamber and three-vessel and trachea views from color STIC data sets, Chaoui et al. (2004) obtained diagnostic accuracy in 88.5% of healthy fetuses and in 88.8% of pathologic fetuses. However, unfavorable imaging windows/angles and volume were observed in fetuses examined after 29 wk of gestation. Real-time 3-DUS had a high sensitivity for detecting CHD (93%) and a low specificity (45%), with a high rate of “undetermined” responses and false-positive artifacts between four reviewers using a single volume scan (Sklansky et al. 1999, 2005). Using the reconstructed image, the sonographer can evaluate intracardiac anatomy at different depths and can recreate casts of blood flow through the chambers and major vessels (Deng et al. 2002b; DeVore 2005). Color Doppler STIC enables volume data sets to be acquired from the fetal heart for display as a cine loop of a single cardiac cycle. Moreover, color Doppler STIC has the potential to simplify visualization of the outflow tract and improves evaluation of the location and extent

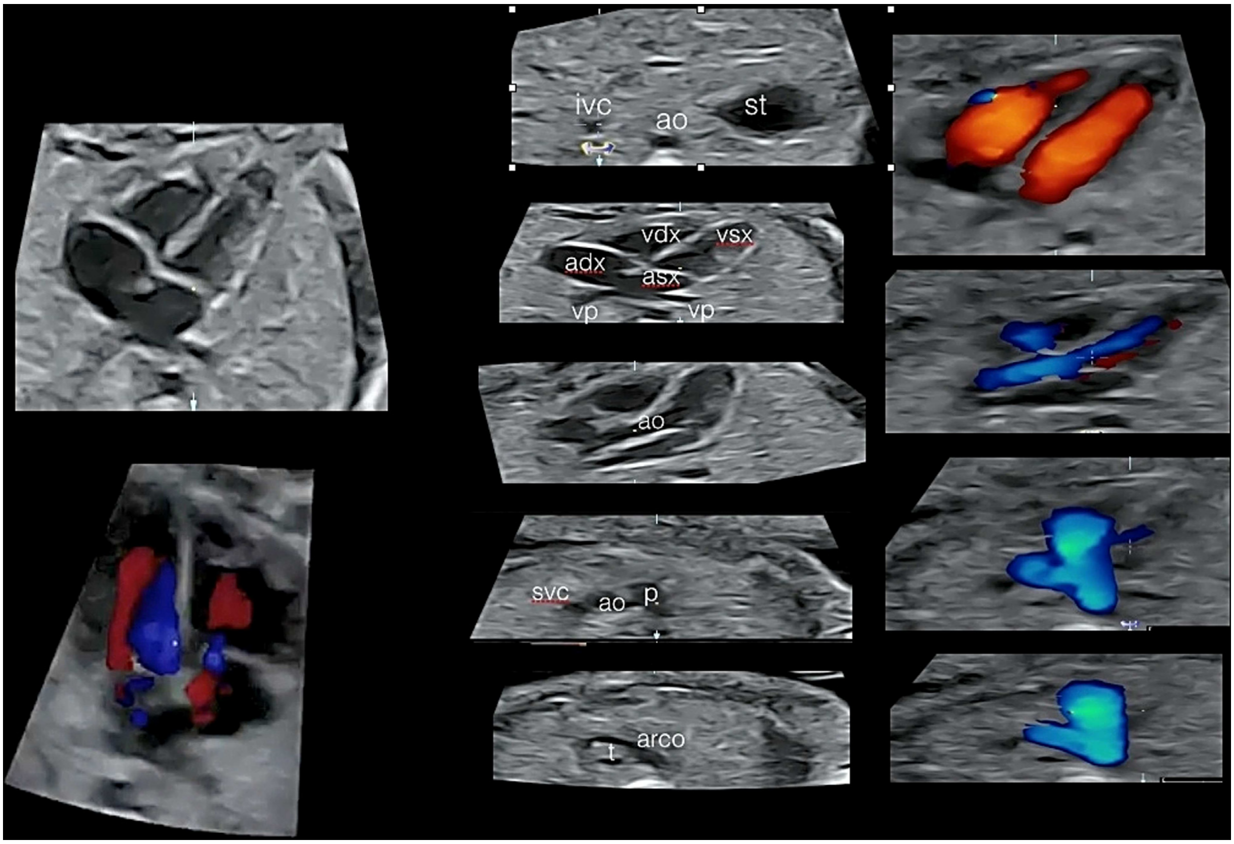

Fig. 10. Fetal echocardiogram using spatiotemporal image correlation (STIC) with HD flow revealing the situs solitus, the four-chamber view and the great artery outflow tract. ao = aorta; arco = ductal arch; adx = right atrium; asx = left atrium; ivc = inferior vena cava; p = pulmonary artery; st = stomach; vdx = right ventricle; vp = pulmonary vein; vsx = left ventricle.

of ventricular septal defects, as well as 3-D evaluation of regurgitation jets and venous streams at the level of the foramen ovale (Gonçalves et al. 2004c). Limitations on this application may include its inability to be used in early or late gestation because of low signal discrimination. In addition, insonation perpendicular to the structures of interest does not image color Doppler signals and should be avoided during volume acquisition (Chaoui et al. 2004).

Gonçalves et al. (2004b) were the first to illustrate that 4-D gray-scale and power Doppler STIC can be used to systematically visualize the abnormal relationship of the outflow tracts in fetuses with transposition of the great arteries, with volume acquisition requiring only clear visualization of the apical four-chamber view during 2-D ultrasonography for 7.5 to 15 s. Yagel et al. (2005) confirmed the accuracy of 4-D color Doppler ultrasound using STIC in the assessment of fetal ventricular septal defects. Gonçalves et al. (2005b) established the clinical usefulness of STIC 4-D data sets and addressed the necessity for appropriate training in a study evaluating the agreement between two independent observers and the reproducibility of STIC technique to display standard cardiac views of the left and right ventricular outflow tracts by analyzing 20 volume data sets of satisfactory quality. Acar et al. (2005) studied 60 fetuses between 22 and 34 wk of gestation using a matrix-array transducer based on both Biplane and Live 3-D imaging. In 16 fetuses, the fetal heart had morphologic abnormalities (hypoplastic left ventricle in 4, tetralogy of Fallot in 2, Ebstein anomaly in 2, rhabdomyomas in 2, hypoplastic right ventricle in 1) or myocardial dysfunction (5 fetuses). Real-time 3-D echocardiograms were performed with a cardiac matrix probe (2–4 MHz). Acar et al. (2005) concluded that real-time 3-D echocardiography is a feasible and non-time-consuming method, allowing multiplanar scanning and new inside 3-D views of the fetal heart. Virtual casting of the fetal heart using Live 3-D volume data sets processed by a semi-automated program have enabled clear recognition of the sequential connections and spatial relationships in 84% of cases with specialist interaction (McDonald et al. 2005). In addition, virtual cast view of the whole heart provides more straightforward guidance for detailed multiplanar assessment than the usual 3-D surface display (Deng and Rodeck 2006).

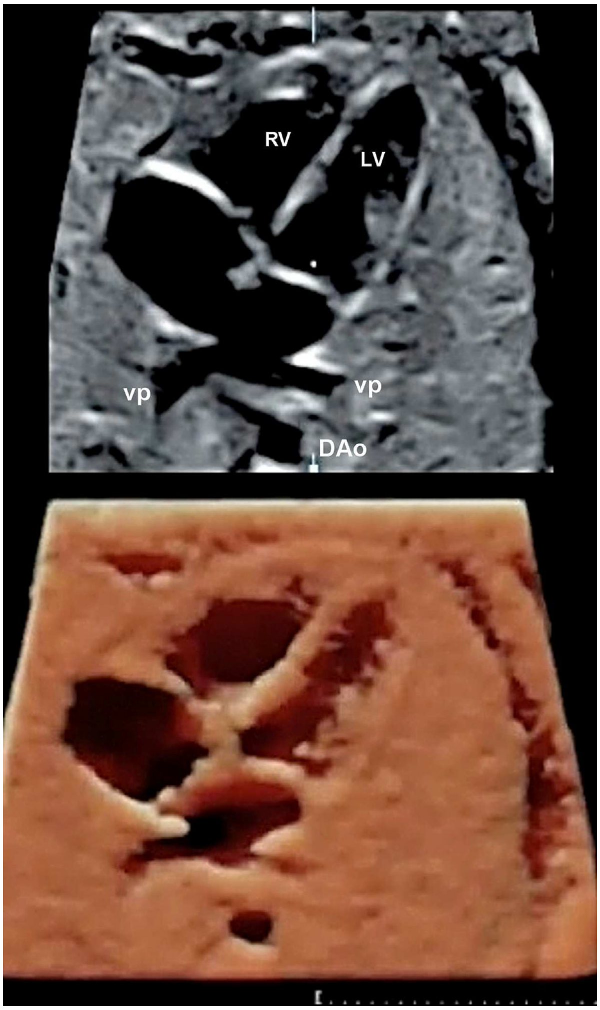

Fig. 11. Fetal echocardiogram using spatiotemporal image correlation (STIC). The four chamber view with pulmonary veins draining into the left atrium is rendered in the upper panel; same image after post-processing with HDlive. DAo = descending aorta; LV = left ventricle; RV = right ventricle; vp = pulmonary vein.

Notwithstanding, limitations to accurate cardiac gating by STIC still exist and are due mainly to fetal heart rate variations during volume acquisition (7–15 s) (Deng et al. 2003). In fact, the necessity for gating is determined by a direct volume scan; direct volume scan refers to any volume scan in which a volume of interest is scanned with sufficient imaging volume coverage, imaging volume rate (*i.e.*, temporal resolution) and spatial resolution (Deng and Rodeck 2006).

DeVore and Polanko (2005) reported that examination of the outflow tracts of the fetal heart (four-chamber, five-chamber and three-vessel and trachea views) could be identified with the use of TUI (tomographic ultrasound imaging) technology in fetuses between 13 and 40 wk of gestation and that fetuses with tetralogy of Fallot, transposition of the great vessels and pulmonary stenosis all

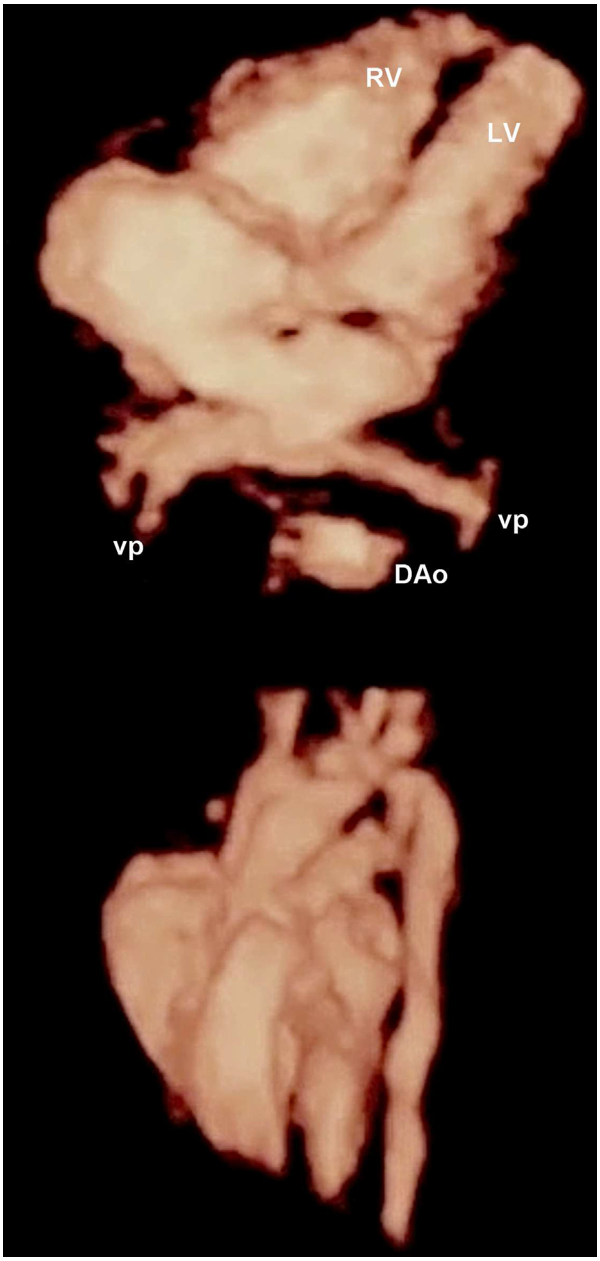

Fig. 12. Fetal echocardiogram using STIC (spatiotemporal image correlation). The four-chamber view and great artery outflow tract are seen using post-processing HDlive. DAo = descending aorta; LV = left ventricle; RV = right ventricle; vp = pulmonary vein.

exhibited abnormal cardiac anatomy on TUI. TUI is a post-processing software application that enables any acquired 3-D volume data set (obtained in either gray scale, color Doppler or STIC) to be automatically sliced and displayed as multiple images on the screen (DeVore et al. 2005; Espinoza et al. 2006; Gonçalves et al. 2006). With the TUI application, a 3-D volume can be split into as many as nine images, and the interslice distance (0.5–10 cm) can be selected to suit the volume being investigated. Using 4-D volume acquisition with STIC, color Doppler imaging and off-line TUI analysis from a standardized starting plane (four-chamber view, starting from a simple 2-D cardiac landmark), Turan et al. (2009) reconstructed the four-chamber view; the cardiac axis, size and symmetry; the atrioventricular valves; the major arteries; and the descending aorta in 89.7%–99.1% of cases at 11 to 13 wk of gestation. Four-dimensional fetal echocardiography with STIC can be used with VOCAL (with 15°–30° of angle rotation) and the inversion mode to assess fetal heart function. Through this application, mean stroke volume was found to range from 0.78 cm^3 at midgestation to 5.5 cm^3 at term, whereas the ejection fraction remained fairly stable through gestation (Messing et al. 2007), and right and left heart stroke and cardiac output increased with gestational age, with mean values of 0.02 mL, 0.01 mL, 2.39 mL/min and 1.80 mL/min at 12 wk; 0.30 mL, 0.32 mL, 43.46 mL/min and 46.72 mL/min at 20 wk; and 2.07 mL, 2.67 mL, 284.71 mL/min, and 365.99 mL/min at 34 wk, respectively (Molina et al. 2008). An exponential increase in stroke volume and cardiac output was observed, whereas ejection fraction remained nearly constant (Simioni et al. 2011). To compare 2-DUS and 3-DUS echocardiography, Tonni et al. (2009) assessed the feasibility of including volumetric 3-D reconstruction of cardiac anatomy and Doppler angiography of the major vessels in routine second-trimester pregnancy scans in a low-risk pregnancy population. Tonni et al. (2009) reported that visualization of the pulmonary veins, ductus venosus and inferior vena cava was significantly improved by 3-DUS compared with 2-DUS. The authors concluded that echocardiographic examination using 3-DUS may be included in routine second-trimester scans. A different conclusion was drawn by Wanitpongpan et al. (2008), who observed that use of STIC by general obstetricians to check normality of fetal cardiac structures at 17–21 wk of gestation has marginal clinical effectiveness compared with 2-D scanning by a fetal echocardiologist, suggesting that technical improvement by operators is necessary to expand the use of 3-DUS in fetal cardiac screening program. Xiong et al. (2012a; 2012b) found that the image quality of real-time 3-D echocardiograms is similar to that of images acquired by STIC from the sagittal view and superior to that obtained by STIC from the four-chamber view and that real-time 3-D echocardiograms have no motion artifact, which has the potential to improve the rate of detection of fetal ventricular septal defects.

Notwithstanding, STIC and VOCAL can be used to calculate cardiac volume, and Uittenbogaard et al. (2010a, 2010b), Herberg et al. (2011) and Hamill et al. (2011) reported that imaging of fetal cardiac structures and volumetry, using STIC and VOCAL, is a reliable and accurate method for calculating volumes of 30 mL upward, both *in vivo* and *in vitro*. Although caution should be exerted in the calculation of cardiac structures in both the pediatric and adult settings, Rolo et al. (2013) have reported the mean area of the tricuspid and mitral valves to range from 0.19 to 0.20 cm^2 at 18 wk and from 0.93 to 1.06 cm^2 at 33 wk of gestation, respectively. In addition, the calculated reference range for the fetal interventricular septum has been found to correlate with gestational age (r = 0.81) and to increase from 0.47 cm^2 at 18 wk to 2.42 cm^2 at 33 wk of gestation, respectively (Nardozza et al. 2013). Very recently, Araujo Júnior et al. (2014b) reported that 4-D fetal echocardiography in the rendering mode allows visualization of the virtual planes of the interatrial and interventricular septa and of the atrioventricular valve annulus.

The application of inversion mode or B-flow imaging to 4-D rendering of the outflow tracts results in “digital casts” displaying the spatial relationships and connections between the great arteries and ventricular chambers. These details cannot be visualized with conventional 2-DUS (Gonçalves et al. 2005a; Hata et al. 2008). It has also been found that with B-flow, extracardiac vessels such as the aorta, pulmonary artery, ductus arteriosus, inferior vena cava and ductus venosus can be detected on reconstructed images. Four-dimensional echocardiography with B-flow imaging and STIC detected the “digital casts” of the outflow tracts of major arteries and veins draining into the heart and permitted evaluation of fetal extracardiac hemodynamics in the second and third trimesters of pregnancy (Hongmei et al. 2012; Zhang et al. 2010). B-Flow visualizes blood flow in gray scale, and because it is not a Doppler method, no velocities are measured. In B-flow imaging, digitally encoded, wide-band pulses are transmitted and subsequently reflected off moving blood cells. The returning echoes are decoded and filtered to enhance sensitivity, so that moving scatter can be detected and blood can be distinguished from tissue. The most useful diagnostic aspect of 4-D echocardiography with B-flow is its ability to distinguish the boundary between flowing blood and vessel wall with precision (Deane 2000). Volpe et al. (2010) reported that 4-DUS with B-flow imaging and STIC can facilitate visualization and detailed examination of the anatomic features of the interrupted aortic arch, including visualization of the neck vessels, thus supplying additional information with respect to 2-DUS.

In the manufacture of matrix array transducers, a laser is used to cut the piezoelectric crystal into many equal-sized square elements, forming an element matrix. These elements are located in the tip of the transducer so that they are in close contact with the surface of the body for easy transmission and reception of ultrasound pulses. Each single element can fire an ultrasound beam any direction. By appropriately defining the ultrasound beam for each single element, it is possible to build up a pyramidal volumetric ultrasound beam, with an opening angle between 6° and 100°. The recently available matrix-array transducer allows the simultaneous visualization of two planes, oriented in different directions, with the same degree of resolution. Images are displayed on a screen divided into two parts: the original plane is on the left-hand side, whereas on the right-hand side is one of the different scanning planes that the sonographer can visualize using a different orientation of the ultrasound beam in the space (axial planes, sagittal planes or rotation) (Fig. 13a, b)

Dense matrix-array live 3-D ultrasound technology provides real-time temporal resolution of about 25 Hz (volume/s) (Deng and Rodeck 2006; Deng et al. 2002a, 2003; Sklansky et al. 1999). Echocardiographic examinations of 151 fetuses, including 4 with suspected CHD, were carried out by Xiong et al. (2009) using a matrix probe with live xPlane imaging. The fetal heart was acquired in the four-chamber view, with the fetal spine at 6 o'clock and the apex at 12 o'clock. After the reference line on the primary image plane (four-chamber view) was moved, a secondary image plane cutting across the reference line was displayed on the right side of the screen. By default, the secondary plane was rotated +90° with respect to the reference plane. The interventricular septum was visualized successfully in 150 (99.3%) cases using live xPlane imaging, including 82 (54.3%) cases with the spine posterior and 68 (45.7%) cases with the spine anterior. The interventricular septum was visualized in all fetuses with CHD (Xiong et al. 2009).

Yuan et al. (2011) determined the feasibility and reliability of real-time xPlane imaging to assess simultaneously the four-chamber view and a view of the left ventricular outflow tract (LVOT) in 145 fetuses between 11 and 37 wk of gestation, including 29 fetuses with CHD. The four-chamber view was assessed in three positions: subcostal (apex at 3 or 9 o'clock), apical (apex at 12 or 6 o'clock) and fetal heart apex midway between the subcostal and apical positions. By use of the rotation function with the four-chamber view as the reference plane, the LVOT was simultaneously displayed on the secondary image plane and visualized successfully in 95.1% of cases after 14 wk of gestation (Yuan et al. 2011). Xiong et al. (2013) described a relatively simple method of visualizing the ductal and aortic arch views using live xPlane imaging. Evaluation of the ductal arch in the detection of conotruncal anomalies by live xPlane imaging was assessed in 200 fetuses, of which 152 were normal, 27 presented with conotruncal anomalies and 21 exhibited another CHD. An abnormal view of the ductal arch was obtained in 92.6% of fetuses with conotruncal anomalies compared with fetuses with no CHD (23.8%).

In addition, the use of 4-D echocardiography and telemedicine may be of help in the off-line analysis of fetal cardiac volume data sets by remote consultation at tertiary care centers (Viñals et al. 2005, 2008, 2011; Yagel et al. 2011); volumes can be studied and analyzed by sectional planes in a median time of 11.0 min (range: 2.5–30.0 min) and with a median confidence score of 4.0 (range: 1.0–5.0) between experts (Adriaanse et al. 2012).

Very recently, Yeo and Romero (2013) developed a fetal intelligent navigation echocardiography (FINE) method for rapid, simple and automatic examination of the fetal heart using diagnostic planes according to the American Institute of Ultrasound in Medicine (AIUM) practice guideline (AIUM 2011). After seven anatomic cardiac structures of the fetal heart have been recognized, the system automatically rotates, aligns, dissects and scales volume data sets to display nine cardiac diagnostic planes simultaneously in a single template. However, as complex anatomy of the fetal heart may require additional interrogation of a given diagnostic plane, a novel tool has also been developed (VIS-Assistance). This software allows operator-independent sonographic navigation and exploration of surrounding structures in a cardiac diagnostic plane of interest; it also provides automatic labeling of diagnostic planes, side of the fetus and cranial and caudal ends. The time needed to observe all nine VIS-Assistance video clips is 15 min 27 s.

The FINE method has been tested on 51 volume data sets of normal fetal hearts (19.5–39.3 wk of gestation) and in 4 cases of proven CHD (coarctation of aorta, tetralogy of Fallot, transposition of great vessels and pulmonary atresia with intact ventricular septum), respectively. However, even if the FINE method were able to reveal evidence of abnormal cardiac anatomy in all four cases with pathology, Yeo and Romero (2013) recommend using the FINE method as an aid for examination of the fetus in low-risk populations rather than for diagnosis of specific CHDs.

Table 3 summarizes the most important articles on fetal echocardiography by 3-DUS/4-DUS.

3-DUS IN ASSESSMENT OF FETAL ORGAN VOLUME AND ESTIMATION OF BIRTH WEIGHT

The assessment of fetal organs was one of the first applications of 3-DUS in obstetrics. This application was first described in mid-1995 in an article published by a group at the Department of Obstetrics and Gynecology, National Cheng Kung University of Medicine,

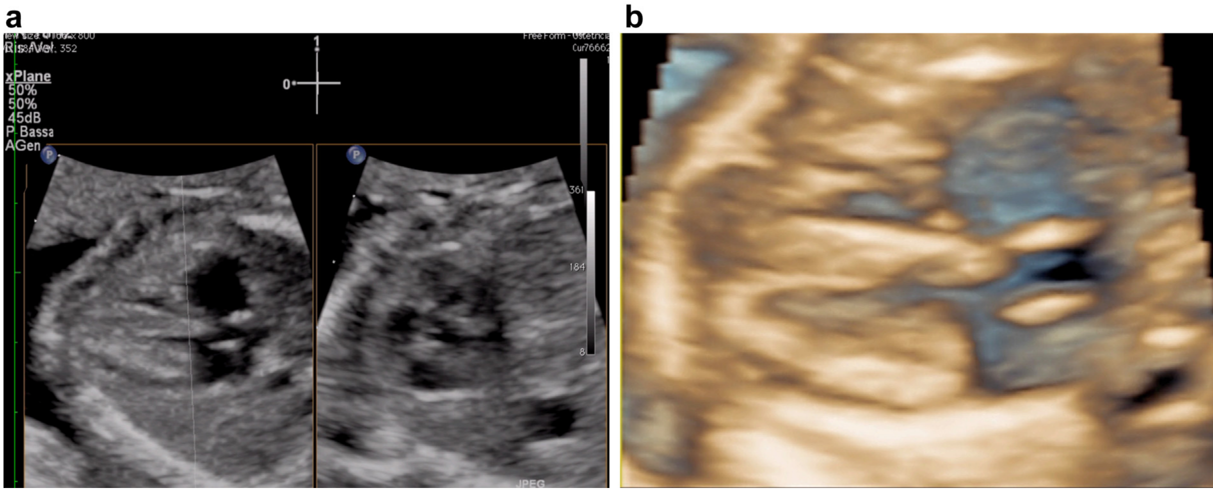

Fig. 13. (a) Fetal echocardiogram using matrix array probe: Normal four-chamber view and great artery outflow tract by means of xPlane imaging. Note that the vertical line is drawn straight to cross the right ventricle, the tricuspid valve, the interventricular septum, the mitral valve and the left ventricle, respectively. (b) Four-dimensional sonogram revealing the four-chamber view.

Tainan, Taiwan (Chang et al. 1997a, 1997c). Because fetal organs are irregular in shape, the use of an ellipsoid formula (length × width × height × 0.523)—the only one possible with 2-DUS—leads to considerable errors in calculation of the 3-D volumes of such organs. The ellipsoid formula (length × width × height × 0.523), is traditionally used in conventional ultrasound in obstetrics and gynecology to assess the volumes of several structures such as the uterus and ovaries (which are regular structures) (Leonhardt et al. 2014). However, when the volume of an irregular structure needs to be calculated, the accuracy of 2-DUS is lower than that of 3-DUS, as reported in an *in vitro* study (Riccabona et al. 1996). In an *in vivo* study, Araujo Júnior et al. (2007b) assessed fetal lung volumes in 51 normal fetuses between 20 and 35 wk of gestation by comparing 3-D (VOCAL) and 2-D (ellipsoid: length × width × height × 0.523) techniques. These authors observed that calculation using 2-DUS overestimated lung volumes compared with those calculated with the 3-D VOCAL technique. In addition, inclusion of a new constant value in the 2-D volume calculation technique (right fetal lung volume: length × width × height × 0.152, left fetal lung volume: length × width × height × 0.167) led to substantial overlapping agreement between the 2-D- and the 3-D volume calculation techniques (Araujo Júnior et al. 2008). Notwithstanding, the main objective of these pioneering studies was to determine a new constant to be incorporated into the 2-D ultrasound formula to increase its accuracy, because 3-DUS was an expensive and limited method at that time (Chang et al. 1997a, 1997c). In these pioneering studies, the authors used the multiplanar mode, which was the first technique developed for assessing fetal organ volumes. Multiplanar mode allows assessment of the volume of a given structure based on three orthogonal planes (axial, coronal and sagittal) that constitute the 3-D image. After selection of a plane, the external surface of the structure is delineated and the area is determined while simultaneously, on another plane, the cursor is moved for a new area calculation. The interval between slices is selected by the operator and usually ranges from 1.0 to 3.0 mm. Once the measurements have been established, the software calculates areas and provides the volume automatically. In comparison to the multiplanar mode, VOCAL allows the structure to be analyzed by rotation around a given axis, with the consecutive planes being displayed on the screen. The boundaries of the structure are delimited with the cursor, being the structure bounded on its outer surface by manual or sphere modes. The rotation angle, selected by the operator, may be 6°, 9°, 15° or 30° (GE ultrasound equipment) or 12°, 18° or 30° (Samsung ultrasound equipment). If a rotation angle of 6° is selected, 30 consecutive planes will be determined, whereas if a rotation angle of 30° is selected, only 6 consecutive planes will be determined. Once the rotational process has ended, the software automatically calculates the volume with a 3-D rendering of the structure displayed on the screen. Multiplanar and/or VOCAL techniques have been used to assess different fetal structures such as lungs (Kalache et al. 2003), placenta (Nowak et al. 2008), gestational sac (Nardozza et al. 2010b) and cerebellum (Rutten et al. 2009). The main advantages of the VOCAL technique over the multiplanar technique are the shorter time needed to perform the

Table 3. Reference, study population, and GA, prenatal US technique and clinical findings in case of fetal 3-D/4-D echocardiogram

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Chaoui et al. (2004)	34 healthy and 27 fetuses with CHD	18–35	STIC with color Doppler	Four-chamber, five-chamber and three-vessel and trachea views could be obtained in 31/35 healthy and 24/27 fetuses with CHD
Messing et al. (2007)	100 healthy and 6 fetuses with CHD	20^{+5}–40	STIC with VOCAL (15°) and inversion mode	LVED ranged from mean of 0.53 cm^3 at midgestation to mean of 3.96 cm^3 at term; LVES ranged from mean of 0.17 cm^3 at midgestation to 1.56 cm^3 at term; RVED ranged from mean of 0.68 cm^3 at midgestation to mean of 5.44 cm^3 at term; RVES ranged from mean of 0.26 cm^3 at midgestation to 2.29 cm^3 at term
Molina et al. (2008)	140 healthy fetuses	12–34	STIC with VOCAL (30°)	Left and right stroke volume and cardiac output increased exponentially with gestation, from respective mean values of 0.02 mL, 0.01 mL, 2.39 mL/min and 1.80 mL/min at 12 wk to 0.30 mL, 0.32 mL, 43.46 mL/min and 46.72 mL/min at 20 wk and 2.07 mL, 2.67 mL, 284.71 mL/min and 365.99 mL/min at 34 wk
Turan S et al. (2009)	107 low-risk pregnancies	11–13^{+6}	(1) Four-chamber view; (2) STIC with color Doppler; (3) TUI; (4) Fetal cardiac anatomy	Minimum of three 3-D volumes obtained for each patient, transabdominally in 91.6%; fetal motion artifact required acquisition of more than three volumes in 20%; median time for TUI off-line analysis was 100 s (range: 60–240 s); individual anatomic landmarks identified in 89.7%–99.1%; Visualization of all structures in one panel observed in 91 patients (85%)
Simioni et al. (2011)	265 healthy fetuses	20–34^{+6}	STIC with VOCAL (30°)	Left and right SV and CO increased exponentially with gestation and EF remained fairly stable through gestation; mean left and right SV increased from 0.211 and 0.220 mL at 20 wk to 1.925 and 2.043 mL, respectively, at 34 wk; Mean left and right CO increased from 30.25 and 31.52 mL/min at 20 wk to 268.49 and 287.80 mL/min, respectively, at 34 wk; both left and right mean EF remained constant at around 0.63 with advancing gestational age
Espinoza et al. (2010)	90 healthy fetuses and with CHD	18–26	Accuracy of 7 centers in assessment of CHD using STIC	Overall, median (range) sensitivity, specificity, positive and negative predictive values and false-positive and -negative rates for identification of fetuses with CHD were 93% (77%–100%), 96% (84%–100%), 96% (83%–100%), 93% (79%–100%), 4.8% (2.7%–25%), and 6.8% (5%–22%), respectively; most frequent CHDs were conotruncal anomalies (36%); excellent intercenter agreement (κ = 0.97)
Yeo et al. (2011b)	50 healthy fetuses	15^{+3}–40	Four-chamber view and “swing technique” (FAST) echo for visualization of standard diagnostic planes of fetal echocardiography from data set volumes obtained with STIC and resliced with OmniView	Ductal arch, pulmonary artery, three-vessel and trachea and five-chamber views, long-axis view of the aorta and four-chamber view were generated in 100% of cases (except for the three-vessel and trachea view, which was seen in 98%); swing technique was able to generate three-vessel and trachea view, five-chamber view and/or long-axis view of the aorta, four-chamber view and stomach in 100% of normal cases
Yeo et al. (2011a)	50 healthy fetuses	15^{+3}–40^{+4}	STAR technique: Three dissecting lines through the four-chamber view of the heart contained in a STIC volume data set to display cardiac outflow tract. Line 1: Ventricular septum en face with both great vessels (pulmonary artery anterior to the aorta) Line 2: Pulmonary artery with continuation into the longitudinal view of the ductal arch Line 3: Long-axis view of the aorta arising from the left ventricle	STAR technique was able to generate intended planes in all 50 normal cases; in abnormal cases, STAR technique allowed identification of ventricular septal defect, revealed great vessel anomalies and displayed views that deviated from what was expected from the examination of normal hearts

(*Continued*)

Table 3. (*Continued*)

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Rolo et al. (2013)	328 healthy fetuses	$18–33^{+6}$	STIC in rendering mode	Mean areas of tricuspid and mitral valves ranged from 0.19 ± 0.08 and 0.20 ± 0.10 cm^2 in the 18th wk to 0.93 ± 0.31 and 1.06 ± 0.39 cm^2 in the 33rd wk, respectively
Nardozza et al. (2013)	328 healthy fetuses	$18–33^{+6}$	STIC in rendering mode	Interventricular septum area exhibited correlation with gestational age (r = 0.81); mean increased from 0.47 ± 0.10 cm^2 in 18th wk to 2.42 ± 1.13 cm^2 in 33rd wk of gestation

CHD = congenital heart disease; CO = cardiac output; EF = ejection fraction; LVED (RVED) = left (right) ventricle at end diastole; LVES (RVES) = left (right) ventricle at end systole; STIC = spatiotemporal image correlation; STAR = simple targeted arterial rendering; TUI = tomographic ultrasound imaging; SV = stroke volume; TUI = tomographic ultrasound imaging, VOCAL = virtual organ computer-aided analysis.

procedure (Ruano et al. 2006b) and the minor corrections required on the external surface area at the end of the volume calculation process (Peralta et al. 2006). Chang et al. (2002c) estimated a time between 10 and 15 min to calculate the fetal upper-arm volume using the multiplanar mode with a 3.0-mm interval between slices. The main advantage of the multiplanar method is its application in all 3-DUS equipment since their first generation (Combison 530, Kretztechnik, Zipf, Austria) (Chang et al. 1997b).

The VOCAL method has been used to assess fetal volume in the first trimester (Araujo Júnior et al. 2008; Barra et al. 2013; Martins 2008; Martins et al. 2009) as well to calculate volumes of diverse fetal organs such as the cerebellum, brain, lungs, heart, adrenals and kidneys (Araujo Júnior et al. 2007a, 2007b, 2007c, 2008; Chang et al. 2002a, 2003c; Peralta et al. 2006; Roelfsema et al. 2004; Tedesco et al. 2009; Turan et al. 2012; Werneck Britto et al. 2009). More recently, a new method for assessing fetal organ volume was made available in 3-DUS equipment produced by Samsung (Seoul, Korea), namely, the extended imaging virtual organ computer-aided analysis (XI VOCAL) technique. This method consists of delimiting from 5 to 20 sequential plane areas on the screen (multislice view). When the operator delimits the last area, the system automatically calculates the volume and reconstructs the structure (Guimaraes Filho et al. 2007a). XI VOCAL has been applied to assess not only fetal heart volume (Barreto et al. 2012), but also the gestational sac, yolk sac, embryo and placenta (Araujo Júnior et al. 2010; Cheong et al. 2010; Nardozza et al. 2010b; Araujo Júnior et al., 2011c) and has been found to have *in vitro* reproducibility (Barreto et al. 2010) (Fig. 14).

Three-dimensional ultrasound has been reported to be more accurate than 2-DUS in calculating pulmonary volume (Riccabona et al. 1996). This is of great importance in the prenatal diagnosis of pulmonary hypoplasia, a condition associated with high rates of neonatal morbidity and mortality. Pulmonary hypoplasia has an incidence of 11 to 14 per 10,000 live births in the general population (Laudy and Wladimiroff 2000) and is characterized by reduced numbers of pulmonary cells, bronchial trees and alveoli, with consequent decrease in lung size and weight (Lauria et al. 1995).

Fetal lung volumetry, in normal and high-risk conditions for pulmonary hypoplasia, has been obtained with both the multiplanar and VOCAL methods (Gerards et al. 2006; Ruano et al. 2006b), even though VOCAL has several advantages over the multiplanar method. These consist of the ability to include smaller portions of the lungs extending below the dome of the diaphragm and the possibility of modifying the contour along each plane (Peralta et al. 2006). In addition, VOCAL has been more accurate than the multiplanar method in calculating lung volume in fetuses with congenital diaphragmatic hernia (Ruano et al. 2006b). Using the VOCAL method at 30° of rotation, Peralta et al. (2006) and later Werneck Britto et al. (2009) found that mean fetal lung volume increased with gestation from 0.6 to 4.6–6.3 mL at 12 wk to 20.5–30 mL at 32 wk and from 9–12.5 cm^3 at 24 wk to 22–31.8 cm^3 at 32 wk. Furthermore, Ruano et al. (2009) reported that the ratio of observed/expected total fetal lung volume, as measured by 3-DUS, was the most accurate predictor of pulmonary hypoplasia and pulmonary hypertension and, thus, perinatal mortality.

Fetal renal malformations are frequently detected in ultrasound examinations during routine prenatal scan, and assessment of fetal kidney volume can help predict abnormal renal function and improve prenatal care and/or postnatal management. Yu et al. (2000) assessed fetal kidney volume using the multiplanar method in 152 normal pregnancies at 20 to 40 wk of gestation. Mean fetal kidney volume ranged from 1.49–1.8 mL at 20 wk to 1.63–1.8 mL at 40 wk. Calculating fetal kidney volume using VOCAL with a 30° angle of rotation, Tedesco et al. (2009) determined that the mean volume ranged from

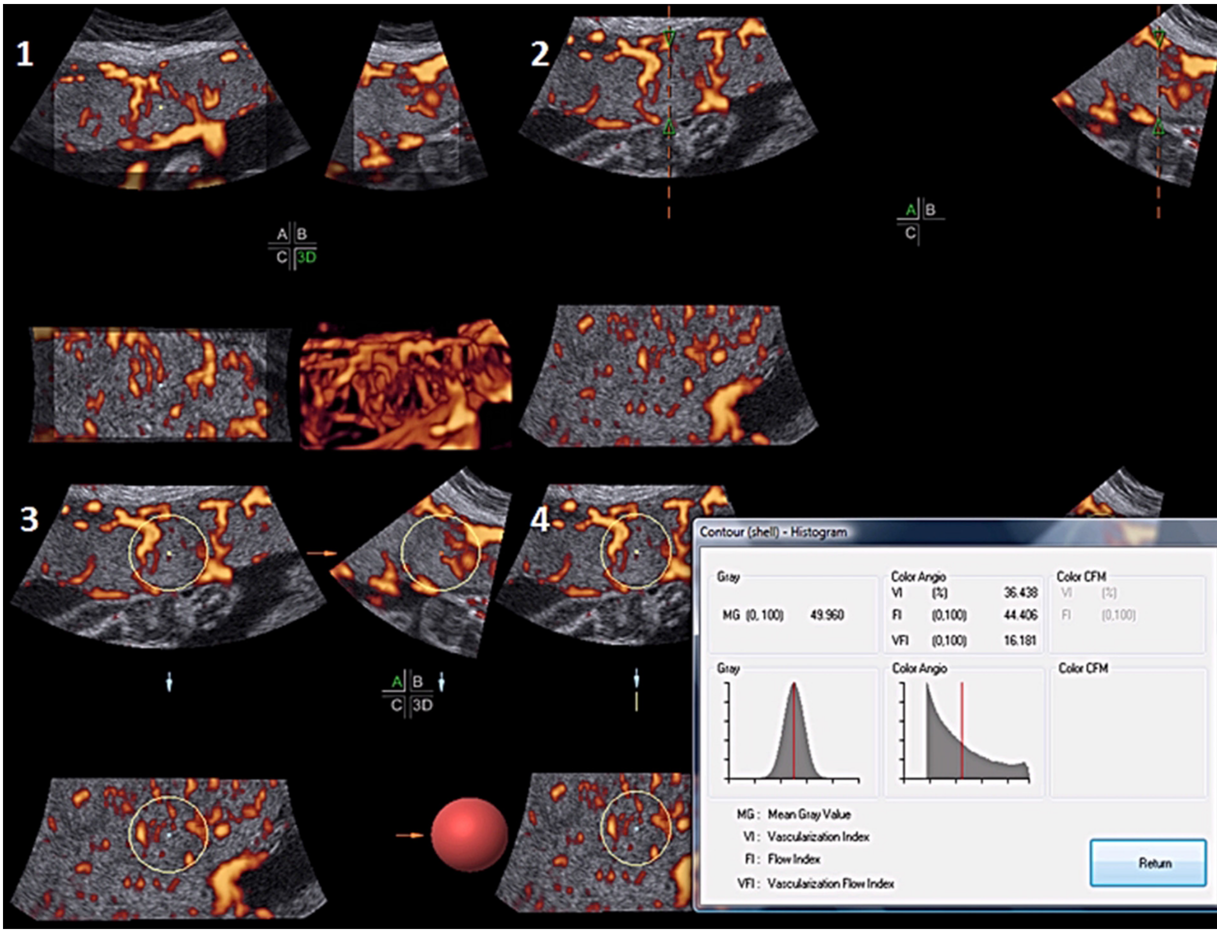

Fig. 14. Power Doppler ultrasound of the placenta using the "vascular biopsy" technique. The calipers are positioned at the level of the basal and chorionic plate of the placenta. The software automatically calculates the values of the vascular indices.

4.5 cm^3 at 24 wk to 12.1 cm^3 at 34 wk, with no statistically significant differences between the two fetal kidneys.

The same results (4.0 cm^3 at 20 wk to 44.9 cm^3 at 40 wk) were reported by Yoshizaki et al. (2013). Chang et al. (2003) observed that fetal liver volume assessed by 2-DUS (craniocaudal × anteroposterior and laterolateral × 0.42) was significantly smaller than the volume determined by 3-DUS (multiplanar method). Furthermore, measurements of fetal liver volume obtained by 3-DUS are more reproducible than those obtained by 2-DUS. The new constant of 0.55 was determined by polynomial regression, so that fetal liver volume obtained with 2-DUS is similar to that obtained with 3-DUS. The constant of 0.42 was determined by Gimondo et al. (1995) in 327 fetuses at 20 to 40 wk of gestation using 2-DUS.

Boito et al. (2003) assessed fetal liver volume with the multiplanar method and its relation to umbilical venous flow and maternal glycosylated hemoglobin (HbA1c) in pregnancies complicated by diabetes mellitus type I. Data on 32 fetuses of diabetic mothers were compared with those for a control group. Boito et al. (2003) observed a statistically significant difference in fetal liver volume between fetuses of diabetic mothers and controls (mean: 45.9 mL vs. 38.3 mL, respectively). Dos Santos Rizzi et al. (2010) determined reference ranges for fetal liver volume using 3-DUS with a new multiplanar method. These authors completed a longitudinal study involving 250 fetal liver volume measurements taken during 53 normal pregnancies at 27 to 38 wk. Mean fetal liver volume ranged from 43.5 cm^3 at 27 wk to 130.5 cm^3 at 38 wk. The new multiplanar technique had good intra- and inter-observer reliability.

Abnormalities in fetal growth are a major worldwide public health problem that has significant impact on both industrialized countries and developing nations. In 2004, the World Health Organization (WHO) estimated that of the 130 million children born each year, about 20 million are considered underweight. Of the 4 million neonatal deaths that occur each year, 60%–80% are in the range of low birth weight (LBW); these children are more likely to die, have perinatal injury, have poor neonatal development, develop infections and exhibit cognitive deficits (Lawn et al. 2005). Two-dimensional ultrasound is used for estimating fetal weight in millions of pregnant women each year. Unlike birth weight, which is measured directly, calculation of fetal weight is imprecise because it depends on the skill of the examiner in obtaining two or more measurements of the fetus, which are then used to calculate the weight. This process can be both time consuming and expensive in obstetric practice. One systematic review of 11 different methods for estimating fetal weight concluded that large random errors are an important obstacle to the confident use of estimation of fetal weight in clinical practice, because 95% confidence intervals exceeded 14% of actual birth weight in reported studies (Dudley 2005).

An alternative approach for quantifying soft tissue (fat and muscle) may be assessment of fetal limb volume using 3-DUS (Khoury et al. 2009). In the late 1990s, Chang et al. (1997b) assessed the accuracy of fetal thigh volume determined by 3-DUS when using the multiplanar method to predict fetal birth weight in 100 Taiwanese women with singleton pregnancies for whom delivery was expected to occur within 48 h. These authors found that the formula based on the calculation of fetal thigh volume was superior to 2-DUS formulas in predicting birth weight. However, the multiplanar mode was time consuming (10–15 min) and exhibited acoustic shadows near the bone joints on the edges of the limbs, which hinders the practical use of this approach in routine obstetric care. Chang et al. (2002c) also described the first reference range for fetal limb volume by 3-DUS in a cross-sectional study of 206 Taiwanese women with singleton at 20 to 40 wk. Fetal upper-arm volume was measured with the multiplanar method (3.0-mm interval between planes), with the mean volume ranging from 6.31 mL at 20 wk to 74.63 mL at 40 wk. Employing this approach, Chang et al. (2003b) later reported that mean fetal thigh volume ranged from 8.99 mL at 20 wk to 128.89 mL at 40 wk. Accurate estimation of fetal birth weight plays a key role in planning best obstetric–perinatal care when dealing with prematurity, IUGR and/or increased fetal growth rate. Song et al. (2000) developed a modified multiplanar approach based on the use of three standard planes (lengthwise midpoint of the femur and two other points at a distance of 4 mm from its proximal and distal ends). The authors found that their method was less time consuming (2 min) and superior to 2-DUS in predicting fetal birth weight. Lee et al. (2001) proposed the term *fractional limb volume*, defined as 50% of the volume of the central portion of the limb, upper arm and/or thigh containing the highest amount of soft tissue. The authors also assessed the accuracy of this new model in predicting birth weight in 100 singleton pregnancies with delivery estimated to occur within 4 d. Lee et al. (2001) reported that a formula based on abdominal circumference and fractional thigh volume was more accurate (within 5% of actual weight) in predicting birth weight than the approach proposed by Hadlock et al. (1985).

Schild et al. (2008) used both 2-DUS and 3-DUS measurements to predict birth weight in fetuses ≤1600 g in 150 singleton pregnancies with delivery expected to occur within 7 d. The organs evaluated by 3-DUS were the thigh and abdomen, as measured in the multiplanar mode. The model based on biparietal diameter, head circumference, abdominal circumference, femur length and thigh and abdomen volumes proved to be superior to the approach based solely on 2-DUS measurements with biparietal diameter, head circumference, abdominal circumference and femur length as previously described (Campbell and Wilkin 1975; Salomon et al. 2011). The 3-DUS measurements were taken in the same manner as 2-DUS measurements, but adjustments in the orthogonal axes were made according to Lima et al. (2012).

Nardozza et al. (2010c) were unable to find statistically significant differences between 2-DUS and 3-DUS calculations using three different models based on 3-D fetal thigh volume, 3-D upper-arm volume or both, after examining 81 Brazilian singleton pregnancies with delivery expected to occur within 48 h. Nonetheless, when 2-DUS and 3-DUS measurements were grouped together, a better estimation of fetal birth weight compared with that obtained with 2-DUS ultrasound measurements alone was obtained (Nardozza et al. 2010a). In addition, Beninni et al. (2010) reported that VOCAL with 30° rotation angle and multiplanar mode with 3.0-mm plane interval produced significant results in estimating fetal birth weight, and both generated formulas from these methods can be used interchangeably.

Using 2-DUS for standard fetal biometry and 3-DUS for fractional thigh volume, Yang et al. (2011) was able to predict 69.5% and 95.3% of birth weights to within 5% and 10% of actual birth weight, respectively. Lee et al. (2009b) reported that mean fractional upper-arm volume ranged from 1.9 mL at 18 wk to 48.8 mL at 42 wk, whereas mean fractional thigh volume ranged from 3.4 mL at 18 wk to 115.8 mL at 42 wk of gestation. In the same manner, Yang et al. (2011) was able to predict 69.5% and 95.3% of birth weights within 5% and 10% of actual birth weight, respectively.

Using a newly developed technique based on XI VOCAL, Cavalcante et al. (2011) found that the fetal upper-arm volume in a Brazilian population ranged from 4.59 cm^3 at 20 wk to 53.87 cm^3 at 40 wk. In a clinical series of 425 healthy pregnancies, Araujo Júnior et al. (2011a) were able to determine a reference range for fetal thigh volume (8.0 cm^3 at 20 wk to 122.1 cm^3 at 40 wk).

Table 4. Reference, study population, GA, prenatal US technique and clinical findings in cases of fetal organ volumes by 3-DUS

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Chang et al. (1997c)	50 healthy fetuses	20–30	Fetal heart volume using multiplanar method with 1.0-mm interval	Fetal heart volume was higher by 2-DUS than by 3-DUS; obtained new constant (0.45) to be incorporated into 2-D ellipsoid formula
Chang et al. (1997c)	55 healthy fetuses	20–31	Fetal liver volume using multiplanar method with 2.0-mm interval	Fetal liver volume was smaller by 2-DUS than by 3-DUS; obtained new constant (0.55) to be incorporated into 2-D ellipsoid formula
Yu et al. (2000)	152 healthy fetuses	20–40	Fetal renal volume using multiplanar method with 1.0-mm interval	Mean of fetal right kidney ranged from 1.49 mL at 20 wk to 1.63 mL at 40 wk; mean of fetal left kidney ranged from 1.8 mL at 20 wk to 17.1 mL at 40 wk.
Peralta et al. (2006)	650 healthy fetuses	12–30	Fetal heart and lung volumes using VOCAL method with 30°	Mean left and right fetal lung volumes increased with gestation, from 0.6 and 0.6 mL at 12 wk to 4.6 and 6.3 mL at 20 wk and 20.5 and 30.0 mL at 32 wk; fetal heart volume increased with gestational age, with mean values of 3.09 mL at 20 wk, 9.18 mL at 26 wk and 24.89 mL at 34 wk
Araujo Júnior et al. (2007a)	52 healthy fetuses	20–32	Fetal cerebellum volume using VOCAL method with 30°	Equation for fetal cerebellum volume determined by Chang et al. (2000) in Taiwanese population cannot be applied to Brazilian population
Werneck Brito et al. (2009)	61 healthy fetuses	24–32	Fetal lung volume using VOCAL method with 30°	Mean fetal right lung volume ranged from 12.5 cm^3 at 24 wk to 31.8 cm^3 at 32 wk of gestation; mean fetal left lung volume ranged from 9.2 cm^3 at 24 wk to 22.0 cm^3 at 32 wk of gestation
Tedesco et al. (2009)	57 healthy fetuses	24–34	Fetal renal volume using VOCAL method with 30°	Mean fetal right kidney volume ranged from 4.5 cm^3 at 24 wk to 12.1 cm^3 at 34 wk; no significant difference between both fetal kidney volumes.
Barreto et al. (2012)	303 healthy fetuses	20–34	Fetal heart volume using XI VOCAL method with 10 planes	Fetal heart volume increased with gestational age, with mean values of 3.09 mL at 20 wk, 9.18 mL at 26 wk and 24.89 mL at 34 wk
Yoshisaki et al. (2013)	213 healthy fetuses	20–40	Fetal renal volume using VOCAL method with 30°	Mean fetal right kidney volume ranged from 4.0 cm^3 at 20 wk to 44.9 cm^3 at 40 wk; mean fetal left kidney volume ranged from 4.2 cm^3 at 20 wk to 44.3 cm^3 at 40 wk

2-DUS (3-DUS) = 2-D (3-D) ultrasound; VOCAL = virtual organ computer-aided analysis; XI VOCAL = extended imaging virtual organ computer-aided analysis.

Nardozza et al. (2012) compared the multiplanar (5.0-mm plane interval) and XI VOCAL (5°, 10°, 15° and 20° rotation) techniques for assessing fetal limb volumes in 40 normal fetuses at 20 to 40 wk of gestation, but did not observe any statistically significant differences.

Tables 4 and 5 summarize the most important articles concerning the assessment of fetal organ volume and estimation of fetal birth weight using 3-DUS.

THREE-DIMENSIONAL POWER DOPPLER ULTRASOUND

Ever since it was first described more than a decade ago, 3-D-PD quantification has generated great interest among researchers (Pairleitner et al. 1999) because of its potential for assessing the flow/vascularity of an entire organ or tissue (Martins et al. 2010) with a noninvasive, relatively simple, tolerable technique that eliminates use of contrast and exposure to radiation (Miyague et al. 2013a). In a 3-D-PD examination, both the number of red voxels and their intensity are related to the number of moving cells; therefore, the quantification offered by this technique could be used as a tool for assessing perfusion. Quantification of 3-D-PD signals in a determined region of interest is performed with three indices: vascularization index (VI) = ratio of color voxels to all voxels in a given volume, flow index (FI) = the average color intensity of all red voxels in the analyzed volume and vascularization flow index (VFI) = a combination of the two, which is calculated as (VI × FI)/100. Besides the theoretical potential, a correlation between these indices and true perfusion has been found in both *in vitro* and *ex vivo* models (Jones et al. 2009, 2010; Morel et al. 2010; Raine-Fenning et al. 2008a). Despite the great scientific interest in these indices, as evidenced by the more than 200 articles published in the field of obstetrics and gynecology alone (Alcazar 2008; Martins 2010; Martins and Raine-Fenning 2010; Martins et al. 2007, 2010), their use has generally not been considered in clinical practice because of their serious limitations (Martins et al. 2011; Nandi et al. 2014; Nastri et al. 2013). The most important of these limitations is their strong dependence on attenuation (Miyague et al. 2014), machine settings (Martins et al.

Table 5. Reference, study population, GA, prenatal US technique and clinical findings in cases of fetal limb volumes by 3-DUS

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Liang et al.(1997)	105 singleton Taiwanese pregnancies	48 h before/at birth	Fetal upper-arm volume using multiplanar method with 3.0-mm interval	Determined new formula using fetal upper-arm volume that was better than 2-DUS formulas in predicting birth weight
Chang et al. (1997b)	100 singleton Taiwanese pregnancies	48 h before/at birth	Fetal thigh volume using multiplanar method with 3.0-mm interval	Determined new formula using fetal thigh volume that was better than 2-DUS formulas in predicting birth weight
Song et al. (2000)	84 singleton Korean pregnancies	48 h before/at birth	Fetal thigh volume using modified multiplanar method with 4.0-mm interval	Formula for fetal thigh volume using new multiplanar method was better than 2-DUS formulas in predicting birth weight and less time consuming (2 min)
Lee et al. (2001)	100 singleton American pregnancies	4 d before/at birth	Fetal fractional thigh volume (50% of volume of central portion of limb, which contains the highest amount of soft tissue)	Best birth prediction obtained with formula that associated abdominal circumference and fractional thigh volume; This new model was compared with Hadlock et al. (1985) formula in 30 fetuses and predicted birth weight more accurately than Hadlock et al. formula in 20/30 fetuses within 5% of real weight
Nardozza et al. (2010c)	81 singleton Brazilian pregnancies	48 h before/at birth	Fetal thigh and upper-arm volumes using multiplanar method with 5.0-mm interval	Formulas using fetal thigh, upper arm and both limbs did not differ from 2-DUS formulas
Araujo Júnior et al. (2011a)	425 healthy fetuses	20–40	Fetal thigh volume using XI VOCAL method with 10 planes	Mean fetal thigh volume ranged from 8.0 cm^3 at 20 wk to 122.1 cm^3 at 40 wk
Cavalcante et al. (2011)	425 healthy fetuses	20–40	Fetal upper-arm volume using XI VOCAL method with 10 planes	Mean fetal upper-arm volume ranged from 4.59 cm^3 at 20 wk to 53.87 cm^3 at 40 wk
Lee et al. (2009b)	303 healthy fetuses	18–42	Fetal fractional thigh and upper-arm volumes (50% of volume of central portion of limb, which contains the highest amount of soft tissue)	Mean fractional upper-arm volume ranged from 1.9 mL at 18 wk to 48.8 mL at 42 wk; Mean fractional thigh volume ranged from 3.4 mL at 18 wk to 115.8 mL at 42 wk
Lee et al. (2009a)	87 singleton American pregnancies	4 d before/at birth	Fetal fractional thigh and upper-arm volumes (50% of volume of central portion of limb, which contains the highest amount of soft tissue)	Fractional thigh volume was most highly correlated prenatal parameter of percentage body fat of all single-parameter models and this parameter alone explained 46.1% of variability in percentage body fat

2-DUS = 2-D ultrasound; XI VOCAL = extended imaging virtual organ computer-aided analysis.

2010; Raine-Fenning et al. 2008b) and sampling volume (Kudla and Alcazar 2010). Because of such limitations, full standardization of the method would be required, but almost impossible to achieve because of the large number of parameters requiring adjustment without error. Even worse, these indices are highly dependent on attenuation (Jones et al. 2009; Miyague et al. 2014; Raine-Fenning et al. 2008a), which limits comparison between patients. Additionally, there are important concerns about reproducibility, particularly when the entire organ cannot be assessed and only a sample can be examined (*i.e.*, the placenta from a third-trimester pregnancy) (Martins and Nastri 2011; Martins et al. 2010, 2012); such variability could be explained by several factors including variability in movement, sampling region and even the phase in the cardiac cycle during 3-D-PD acquisition (Miyague et al. 2013b). This approach is undergoing refinement with respect to 3-D-PD, particularly in the volumetric pulsatility index (Alcazar and Kudla 2012; Martins et al. 2013; Welsh et al. 2012b) and in fractional moving blood volume (Soares et al. 2013; Welsh et al. 2012a). It is believed that such refinements will be able to overcome limitations in the original 3-D-PD indices; however, these indices are still not ready to be used in clinical practice. There is evidence that the abnormalities revealed by umbilical Doppler represent pathologic vascular modifications in the villous tree of the placenta only in advanced stages of impaired placental function (Fok et al. 1990; Trudinger et al. 1987). Therefore, reduced intraplacental blood flow may precede increased umbilical resistance by several weeks, as far as the detection of this condition is concerned (Jaffe and Woods 1996; Yagel et al. 1999). For these reasons, the development of new techniques for screening placental insufficiency at a much earlier stage are of great interest (Guimaraes Filho et al. 2008).

Some studies have found that analysis of intraplacental flow by 3-D-PD may constitute a new tool for early detection of the risk of developing certain conditions, such as IUGR, pre-eclampsia and placental insufficiency (Costa et al. 2010; Guimaraes Filho et al. 2010; Guiot et al. 2008; Negrini et al. 2011). Many of these studies, however, were performed during the second and third trimesters of gestation (de Almeida Pimenta et al. 2014; de Paula et al. 2009; Mihu et al. 2012; Odibo et al. 2011;

Tuuli et al. 2010) and revealed the effects of the technical limitations previously mentioned, including discrepancies in the results of reproducibility studies (Guimaraes Filho et al. 2011; Lai et al. 2010; Merce et al. 2004) (Fig. 13).

Unlike at more advanced phases of gestation, 3-D-PD in the late first trimester (11–14 wk) offers the advantage of visualizing the entire placenta, thus enabling the complete vascular tree to be assessed and theoretically providing a more accurate analysis of information on vascularization and flow (Araujo Junior et al. 2011b; Bozkurt et al. 2010; Gonzalez Gonzalez et al. 2014; Odeh et al. 2011; Rizzo et al. 2007, 2009a, 2009b; Yigiter et al. 2011). Moreover, it has been reported that pre-eclampsia prevention strategies should be introduced as early as possible, which further emphasizes the importance of placental 3-D-PD before 16 wk of gestation (Bujold et al. 2010). Some recent studies carried out in the late first trimester have revealed reduced placental 3-D-PD indices (Bozkurt et al. 2010; Odeh et al. 2011; Rizzo et al. 2009b; Yigiter et al. 2011) and more restricted uteroplacental circulation space (Dar et al. 2010; Hafner et al. 2010) in women who later developed pre-eclampsia (Dar et al. 2010; Hafner et al. 2010; Odeh et al. 2011) and/or IUGR (Bozkurt et al. 2010, Rizzo et al. 2009b; Yigiter et al. 2011). In addition, reproducibility studies have validated the technique in the first trimester, with good reproducibility of 3-D-PD at this stage of gestation (Huster et al. 2010; Jones et al. 2010).

There are reports on the use of vascular indices obtained with 3-D-PD for evaluating the fetal brain (Bartha et al. 2009; Chang et al. 2003e; Hata et al. 2012b; Hsu et al. 2013; Nardozza et al. 2009), lungs (Ruano et al. 2006a, 2012), liver (Chang et al. 2003d) and kidneys (Bernardes et al. 2011; Chang et al. 2003f). Few studies have been conducted to assess 3-D-PD in cerebral vascularization. Correlation of 3-D indices with gestational age has yielded conflicting results (Bartha et al. 2009; Chang et al. 2003e; Hata et al. 2012b; Nardozza et al. 2009). Bartha et al. (2009) analyzed fetal cerebral circulation with 3-D-PD in 100 normal pregnant women and 25 women with fetuses with IUGR. The authors observed that the fetuses with IUGR had significantly higher values of these indices compared with normal fetuses. They further found that the central hemodynamics of fetuses with IUGR were more frequently diagnosed using 3-D-PD indices than the pulsatility index of the middle cerebral artery. Further studies are required to better evaluate how 3-D-PD can contribute to investigating circulatory changes in the fetal brain. Ruano et al. (2006a) considered the potential of 3-D-PD for predicting neonatal results and pulmonary hypertension in fetuses with congenital diaphragmatic hernia. They noted that the 3-D indices were statistically lower in cases of congenital diaphragmatic hernia. In such cases, VI and VFI were significantly lower in fetuses that died than in those who survived and were also lower in fetuses with a postnatal diagnosis of pulmonary hypertension. Another study reported that of the several parameters analyzed, VI of the lung contralateral to the hernia was the best predictor of fetal prognosis (Ruano et al. 2012). Further studies are needed to

Table 6. Reference, study population, GA, prenatal US technique and clinical findings from main articles that evaluated placental vascularization in the first trimester by 3-D power Doppler US

Reference	Study population	GA (wk)	Prenatal US technique	Clinical findings
Rizzo et al. (2007)	100 healthy pregnancies	$11\text{–}13^{+6}$	Placental indices (VI, FI, VFI) calculated by VOCAL histogram (whole placenta)	Provide normal ranges of placental vascular indices between 11 + 0 and 13 + 6wk of gestation, which may be useful in future research on placental vascularity
Rizzo et al. (2009a)	84 pregnancies with ↓PAPP-A	$11\text{–}13^{+6}$	Placental indices (VI, FI, VFI) calculated by VOCAL histogram (whole placenta)	Low serum maternal PAPP-A levels <0.4 multiple of the median are associated with altered 3-D-PD indices; these changes related to subsequent development of IUGR and adverse pregnancy outcomes
Dar et al. (2010)	277 healthy pregnancies	$10^{+4}\text{–}13^{+6}$	Placental indices (VI, FI, VFI) calculated by VOCAL histogram (sphere biopsy)	Patients who develop pre-eclampsia have lower 3-D-PD indices of their uteroplacental circulation space during first trimester; prediction of pre-eclampsia was 78.9%, 77.6%, and 79.6% for VI, FI, and VFI, respectively
Odeh et al. (2011)	308 healthy pregnancies	$10^{+6}\text{–}13^{+6}$	Placental indices (VI, FI, VFI) calculated by VOCAL histogram (whole placenta)	VI significantly lower when pregnancy-induced hypertension developed (7.86 ± 3.92 vs. 12.02 ± 7.09) in normal group, $p = 0.035$; VI may be of some potential in detection of pregnancy-induced hypertension

3-D-PD = 3-D power Doppler ultrasound; FI = flow index; IUGR = intra-uterine growth restriction; PAPP-A = pregnancy-associated plasma protein A; VFI = vascularization flow index; VI = vascularization index; VOCAL = virtual organ-computer-aided analysis.

establish the validity and applicability of 3-D-PD for investigating alterations in fetal pulmonary vascularization. With respect to evaluation of fetal hepatic and renal vascularization by 3-D-PD, a positive linear correlation has been observed between the three indices (VI, FI and VFI) and gestational age in both organs (Chang et al. 2003d, 2003f). A study of fetuses suspected of having urinary tract obstruction indicated that renal vascularization (VI and VFI) was significantly lower in fetuses that developed renal failure (Bernardes et al. 2011).

Table 6 summarizes the most important articles on 3-D -PD in the first trimester of pregnancy.

CONCLUSIONS

After an extended review of articles from the medical literature on 3-DUS and 4-DUS in obstetrics, and after determining whether 3-DUS may contribute additional diagnostic information to the data currently provided by 2-DUS, Gonçalves et al. (2005a) and Kurjak et al. (2007) concluded that "three-dimensional ultrasound provides additional diagnostic information for the diagnosis of facial anomalies, evaluation of neural tube defects, and skeletal malformations. Additional research is needed to determine the clinical role of 3-DUS/4-DUS for the diagnosis of congenital heart disease and central nervous system anomalies."

It is increasingly observed that 3-DUS may enhance parental–fetal bonding compared with 2-DUS, and that 3-DUS is less time consuming, allows accurate reconstruction of the fetal anatomy and permits simultaneous rendering in the sagittal, axial and coronal planes compared with 2-DUS. In addition, 3-DUS/4-DUS offers the ability to construct planes that may be difficult to obtain by 2-DUS, thus offering greater flexibility to sonographers in their attempts to determine the severity, location and extent of anomalies. Furthermore, 3-DUS/4-DUS provides important new technical capabilities that can be employed in clinical training programs for sonographers, who can freely "navigate" within the volume, and the volume can be sectioned in all three orthogonal planes on demand. Recently developed software also allows operators intelligent navigation and exploration of diagnostic planes of interest ("virtual" sonographer).

Finally, a stored volume and video clip can be compressed and shared on a dedicated website over the Internet or sent to a remote site for off-line analysis by expert consultation through telemedicine.

For these reasons, it is our belief that technologic advancements in 3-DUS/4-DUS have greatly contributed to the widespread use and availability of such techniques. They have also established 3-DUS/4-DUS as a diagnostic procedure that can be used in everyday obstetric practice.

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