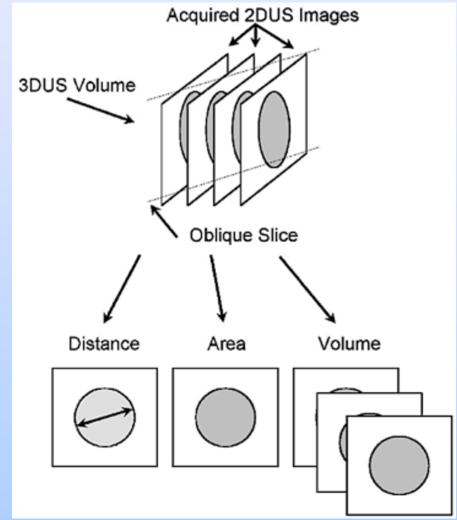
Ultrasound Quantitative Biomarker Planning Meeting

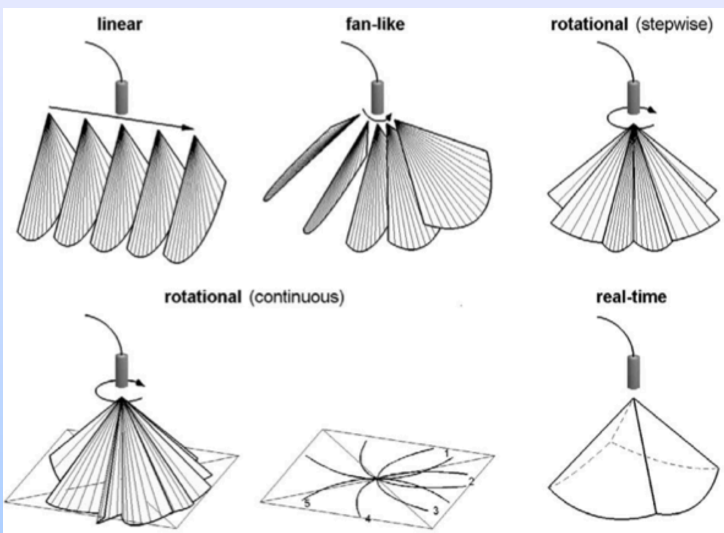
Morphometrics

Brian Garra
Thomas Nelson

Ultrasound Based Measurements



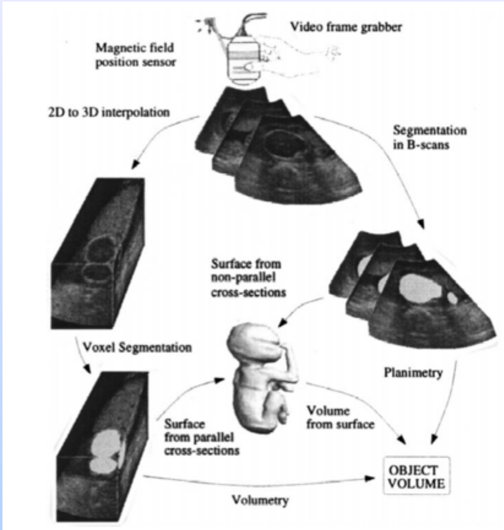
Methods for Acquiring US Volume Data



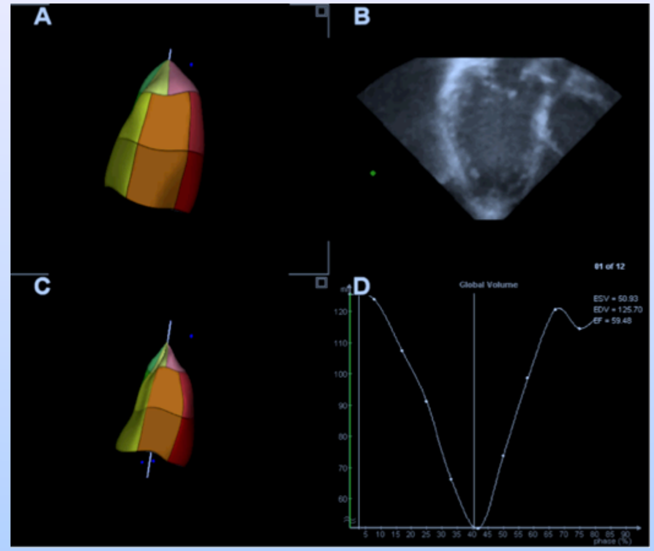
Quantitative Analysis Methods

Comparison of 2DUS and 3DUS volume measurement methods

- 2DUS measurements
  - assume a geometric model
  - uncertainty in key measurements may lead to inaccuracies and variabilities
  - difficult to ensure reproducibility of region being measured for serial studies
- 3DUS measurements
  - measure the geometry of the organ
  - utilize complete organ structure
  - accommodate irregularity in the structure
  - structure can be viewed in optimum orientation.
- 3DUS quantitative measurements can be both accurate and reproducible:
  - Distance optimum plane can be selected for measurement
  - Area optimum cross-section can be selected for area measurement;
  - Volume structure volume can be measured accurately using: manual planimetry and automated algorithm

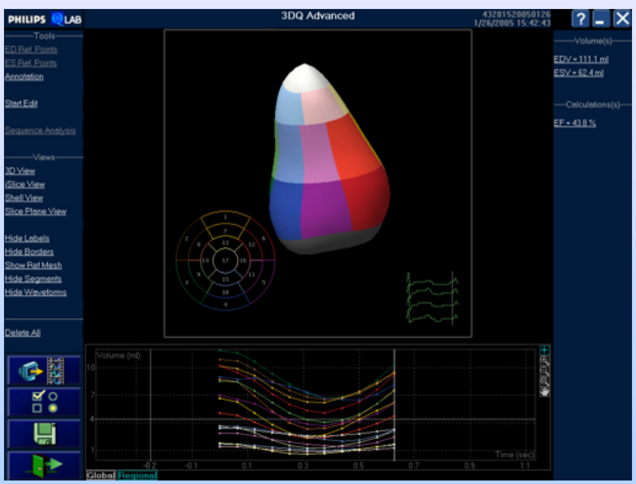


Treece et.al., 3D ultrasound measurement of large organ volume,Medical Image Analysis 5 (2001) 41-54



Krenning et.al, Assessment of left ventricular function by three-dimensional echocardiography, J Cardio US, 2003

Measurement of Cardiac Volume



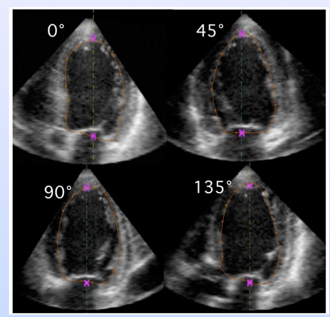


FIGURE 2. LV volume measurement by RT3DE with the average rotation method. The endocardial border of the left ventricle was traced in each cross-sectional image (0°, 45°, 90°, and 135°) at end-diastole and end-systole.

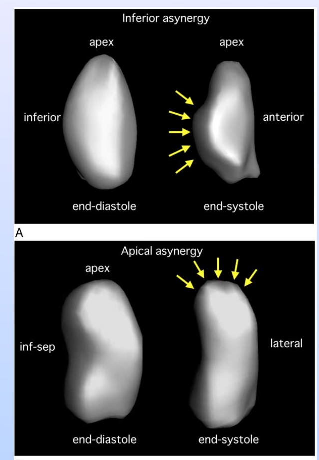
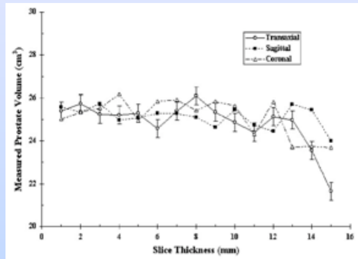
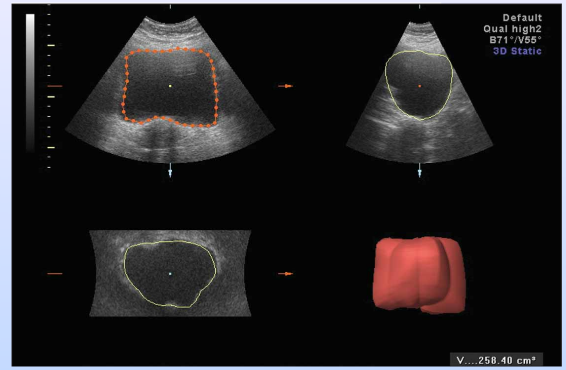


FIGURE 3. Reconstructed LV cavity in patients with wall motion abnormality *(arrows)* in the *(A)* inferior wall and *(B)* apical wall (end-diastole at left, end-systole at right). inf-sep = inferior septum.

Arai etl.al.Accuracy of Measurement of Left Ventricular Volume and Ejection Fraction by New Real-Time Three-Dimensional Echocardiography in Patients With Wall Motion Abnormalities Secondary to Myocardial Infarction, Am J Cardiol 2004;94:552-558

3DUS Prostate Volume

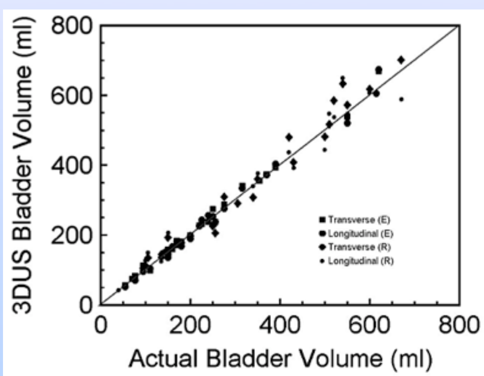




A high degree of reliability was observed between pairs of different rotation angles (ICC, 0.994–0.999). There was good agreement between all pairs of different rotation angles, with percentages of the mean difference ranging from –0.9% to 1.8%. No significant difference was found for bladder volume measurements by the VOCAL technique with varying rotation steps. Intraobserver and interobserver reliabilities were high (ICC, 0.994–0.998). Urinary bladder volume measurement by the VOCAL technique using different rotation steps is highly reliable. A plane rotation of 30° produces the fastest result.

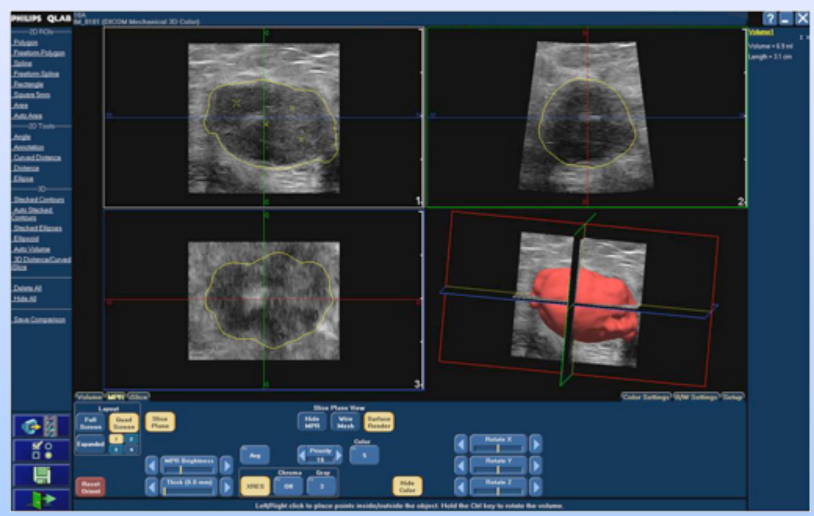
Suwanrath et.al., **Three-Dimensional Ultrasonographic Bladder Volume Measurement,** J Ultrasound Med 2009; 28:847-854

3DUS Bladder Volume

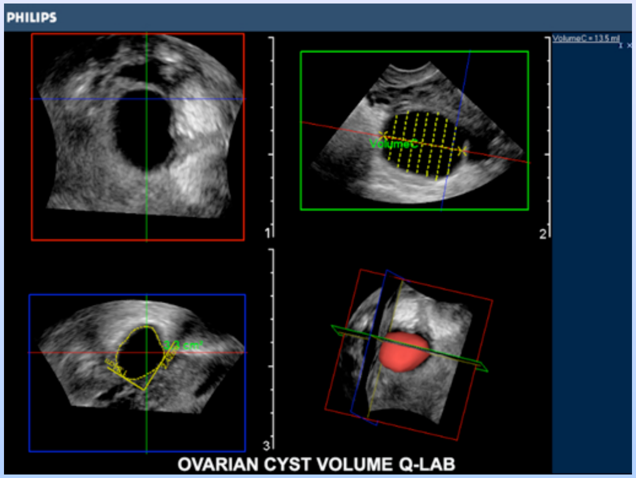


Riccabona M, Nelson TR, Pretorius DH. Three-dimensional ultrasound: accuracy of distance and volume measurements. Ultrasound Obstet Gynecol 1996; 7:429-434.

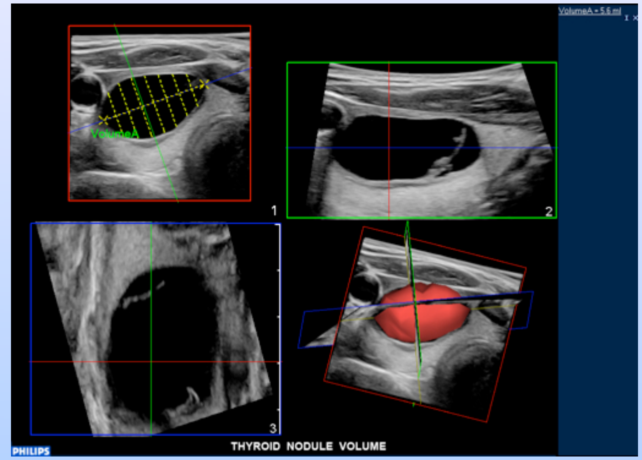
Measurement of Tumor Volume

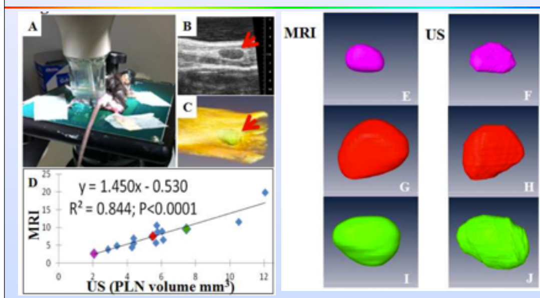


Measurement of Ovarian Cyst Volume



Measurement of Thyroid Nodule Volume





popliteal lymph node volume

Ju et.al., US is comparable to MR imaging for determining relative **popliteal lymph node volume as a biomarker of inflammatory-erosive arthritis**, Arthritis & Rheumatism, 2012

(A) Photograph of an anesthetized mouse positioned on the heating pad with an ECG monitor, and the Scanhead 704 placed above the knee to image the PLN with the US machine.

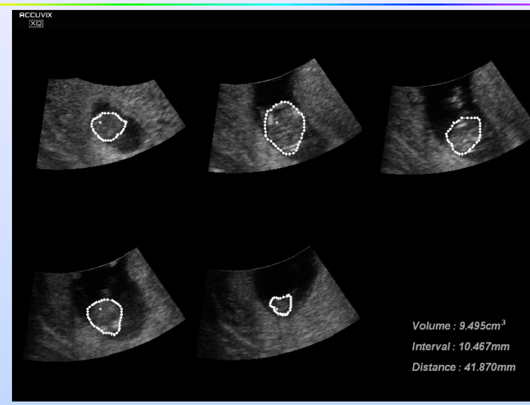
(B) 2D US image of the PLN (red arrow) obtained under B-mode scan. Note the dark PLN surrounded by the triangle fat pad (bright white).

(C) Reconstructed 3D image of the PLN generated with US 3D-mode scan and Amira analysis software. The PLN (green) is indicated by the red arrow, and is embedded in surrounding soft tissue (yellow).

(D) A linear regression analysis was performed by plotting the PLN volume (mm3) measured by MRI (Y-axis) versus US (X-axis). The slope and highly significant R2 value are also presented. The volumes of 16 PLNs were determined by MRI, followed by US.

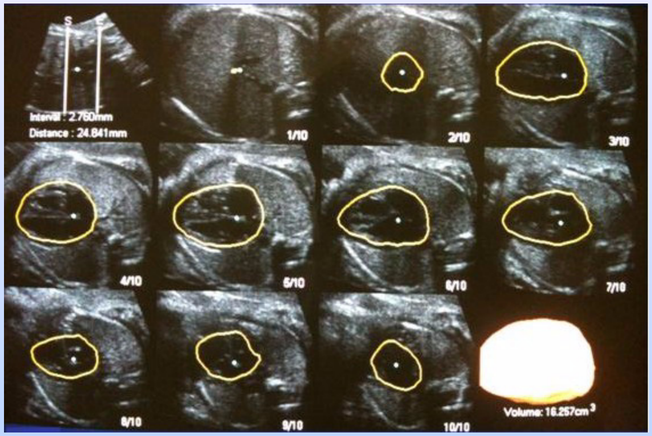
The 3D images of representative PLN by MRI (E, G, I) were similar to the 3D image by US (F, H, J). The colors for each PLN correspond to the color dots in D.

Fetal Volumetry



The 3D volume datasets from 30 fetuses at 11–14 weeks of gestation using a commercially available ultrasound system showed that XI VOCAL (with 10, 15 and 20 slices) can be used interchangeably with the multiplanar techniques (1-mm interval) for the measurement of fetal volume. XI VOCAL (10 slices) and VOCAL (18°) can be used interchangeably, as can XI VOCAL (15 slices) and VOCAL (12°), for the measurement of fetal volume.

Cheong et.al., Comparison of inter- and intra-observer agreement between three types of fetal volume measurement technique (XI VOCAL, VOCAL and multiplanar), Ultrasound Obstet Gynecol 2009; 33: 287–294



Excellent intra- and inter-observer reliability for fetal cardiac volumes assessed by XI VOCAL demonstrating highly reproducible performance for 19-34 weeks.

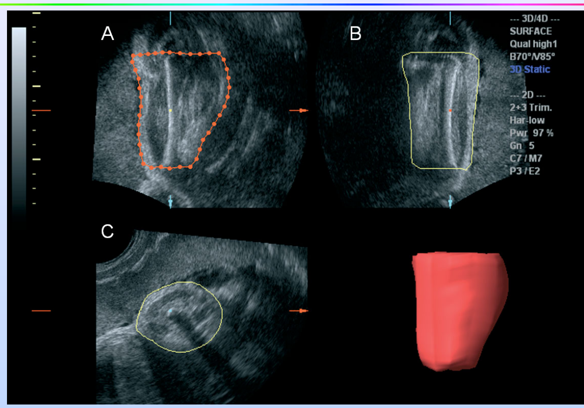
Barreto et al. Reproducibility of fetal heart volume by 3D-sonography using the XI VOCAL method, Cardiovascular Ultrasound 2010, **8**:178

Table 1: Volume and function measurement by reconstruction 3DE in comparison with magnetic resonance imaging

Author/ref.	Object	N	r.	SEE	Mean Diff. ± SD
Gopal et al.[12,14]	LV-EDV	15	0.92	7 ml	
	LV-ESV	--	0.81	4 ml	
Iwase et al.[15]	LV-EDV	30	0.93		-17 ± 23 ml
	LV-ESV	--	0.96		-4 ± 18 ml
	LV-EF	--	0.85		-2 ± 6%
Buck et al.[16]	LV-EDV	23	0.97	14.7 ml	-10.7 ± 14.5 ml
	LV-ESV	--	0.97	12.4 ml	-3.4 ± 12.9 ml
	LV-EF	--	0.74	5.6%	-2.5 ± 6.7%
Altmann et al.[18]	LV-EDV	12	0.98	8.7 ml	-14.2 ± 8.3 ml
	LV-ESV	--	0.98	5.6 ml	-3.4 ± 5.5 ml
	LV-EF	--	0.85	5.3%	-4.4 ± 5.3 %
Nosir et al.[19]	LV-EDV	46	0.98		-1.4 ± 13.5 ml
	LV-ESV	--	0.98		-1.5 ± 10.5 ml
	LV-EF	--	0.98		0.2 ± 2.5%
Kim et al.[20] (patients)	LV-EDV	18			6.4 ± 20 ml
	LV-ESV	--			0.0 ± 13.3 ml
	LV-EF	--			1.4 ± 3.5 %
Kim et al.[20] (volunteers)	LV-EDV	10			-3.1 ± 4.9 ml
	LV-ESV	--			-1.4 ± 2.2 ml
	LV-EF	--			0.5 ± 1.8 %
Poutanen et al. [21] (children)	LV-EDV	0.80			4.0 ± 19.6 ml
	LV-ESV	0.88			0.4 ± 13.0 ml
	LV-EF	0.20			1.7 ± 15.1%
Mannaerts et al. [22]	LV-EDV	17	0.74		-13.5 ± 13.5 %
	LV-ESV	--	0.88		-17.7 ± 23.9 %
	LV-EF	--	0.89		-1.8 ± 5.8 %
Krenning et al. (submitted)	LV-EDV	15	0.98	13.4 ml	-22.7 ± 13.6 ml
	LV-ESV	--	0.99	8.7 ml	-12.6 ± 9.9 ml
	LV-EF	--	0.97		

Krenning et.al, Assessment of left ventricular function by three-dimensional echocardiography, J Cardio US, 2003

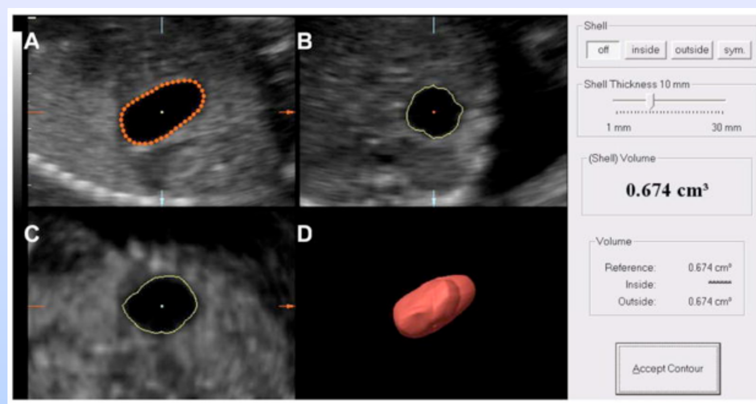
Fetal thigh volumetry



The mean percentage difference between measurements performed using the VOCAL technique and the multiplanar technique was +/−0.04 and the 95% limits of agreement were +/−8.17 and 8.09.There is good agreement between the VOCAL and multiplanar techniques for assessment of total fetal thigh volume. Measurements performed using both methods are repeatable and reproducible. For prediction of birth weight, the formulas generated in this study can be used interchangeably.

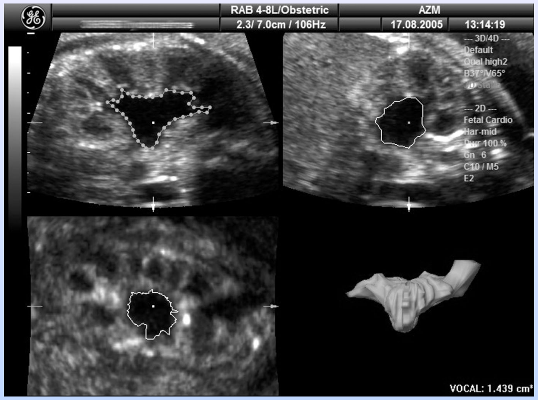
Beninni et. al., **Fetal thigh volumetry by three-dimensional ultrasound: comparison between multiplanar and VOCAL techniques,** Ultrasound Obstet Gynecol 2010; **35:** 417–425

Measurement of Fetal Stomach Volume



Ultrasound images of the fetal stomach at 20 weeks' gestation showing volume measurement by Virtual Organ Computer-aided AnaLysis (VOCAL). A 30° rotational angle was used and the organ contours were manually traced (Panel A). Panels B and C show the trace in the transverse and coronal sections. Panel D displays a three-dimensional image of the fetal stomach. The volume is expressed in cubic centimeters. Ultrasound Obstet Gynecol. 2008 February; 31(2): 177–186.

fetal renal pelvis volume



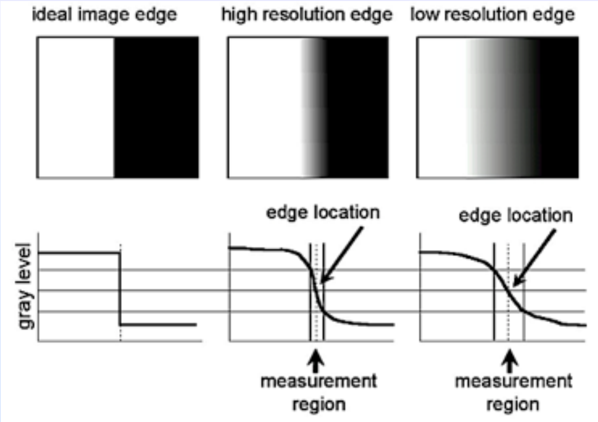
Intra- and inter-observer reliability of the fetal renal pelvis volume measurements were considered to be very good. For intra-observer reliability, the ICC was 0.996 and the CV was 10.8%. For the overall inter-observer reliability, the ICC was 0.998 and the CV was 15.7%; the inter-observer reliability between pairs of observers had ICCs between 0.994 and 0.999, and CVs between 19.5% and 7.6% for inexperienced and experienced observers, respectively. 3D ultrasound using the VOCAL imaging program makes it technically feasible to reproduce fetal renal pelvis volume measurements.

Duin et.al., Reproducibility of fetal renal pelvis volume measurement using three-dimensional ultrasound, Ultrasound Obstet Gynecol 2008; 31: 657-661

Quantitative Analysis Methods Summary

- Measurement accuracy and precision depends on slice spacing, resolution and organ complexity
  - In Vitro approximately 2% to 5%
  - In Vivo approximately 5%-10% depending on segmentation
  - Inter- and intra-observer variability for 3DUS smaller than 2DUS by factor of 2 to 3
- Sources of measurement error primarily due to resolution, slice spacing and improper calibration
  - Mechanical Scanning
    - Measurement accuracy depends on image slice distance and angle spacing
  - Free Hand Scanning with position sensing:
    - Measurement accuracy depends on calibration
  - Free Hand Scanning without position sensing
    - Measurements not reliable or accurate

Reproducibility



- Schematic diagram showing: an idealized image of a high contrast edge; the image of the idealized edge obtained with a high resolution imaging system; and the image of the idealized edge obtained with a low resolution imaging system. The gray scale profiles are shown below with the location of the edge as well as the region over which the measurement location often is.

Boundary Contour Image Segmentation Algorithm

- The operator identifies the structure to be segmented.
- The operator provides an initial boundary contour or seed point(s).
- The algorithm filters the image to reduce noise and speckle.
- The algorithm filters the image to enhance edges.
- The algorithm identifies the edge contour either as disconnected segments or as a continuous contour.
- The algorithm connects the contour segments (if necessary) and optimizes the fit of the contour to the structure.
- The operator inspects the contour and corrects errors for final result.

Ultrasound Image Artifacts Affecting Boundary Contour Detection

- Shadowing, e.g. by calcifications in organs, arterial plaques, bony structures or gas which cause distal structures to be obscured;
- Speckle, which causes the boundary or surface of an object to be discontinuous and not smooth;
- Attenuation of the sound that causes signal drop-off in deep structures, which causes distal boundaries to become less distinct, or invisible at times.

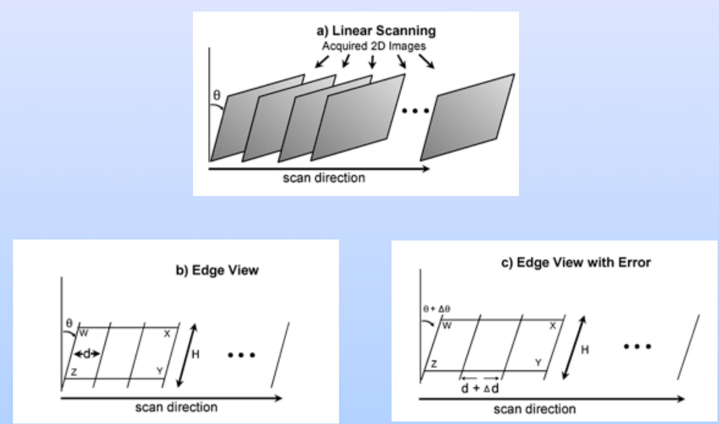
Deficiencies of Organ Volume Measurement Strategies

- Some normal geometric model of the organ that only approximates the organ shape, must be assumed, so that an estimate of the organ volume may be calculated from its "key dimensions in a few 2D cross-sections
- The measured estimate of a key dimension may be inaccurate because of the difficulty in orienting the ultrasound probe so that the 2D image plane is correctly located within the organ
- The optimal location of the 2D image plane is sometimes inaccessible, due to the restrictions imposed on the orientation of the ultrasound probe by the patient's anatomy
- It is difficult to orient the ultrasound probe so that the 2D image plane is placed at exactly the same location as in an earlier exam, in serial monitoring of organ volume, resulting in the inability to follow small changes

Deficiencies in Geometric Methods for Estimating Volume

- Many organs (e.g. prostate) are generally non-ellipsoidal, so that the choice of which three chords in the 2D images are to be selected to measure H, W, and L is not obvious, and subject to observer preference, resulting in high inter-observer variability.
- Even for a single observer, the choice of chords is still arbitrary, leading to high intra-observer variability.
- The placement of the thin 2D image planes within the organ is variable and arbitrary, increasing further the variability of the selected chord locations, and hence the intra- and inter-observer variabilities.

Sources of Error in Geometric Methods for Estimating Volume



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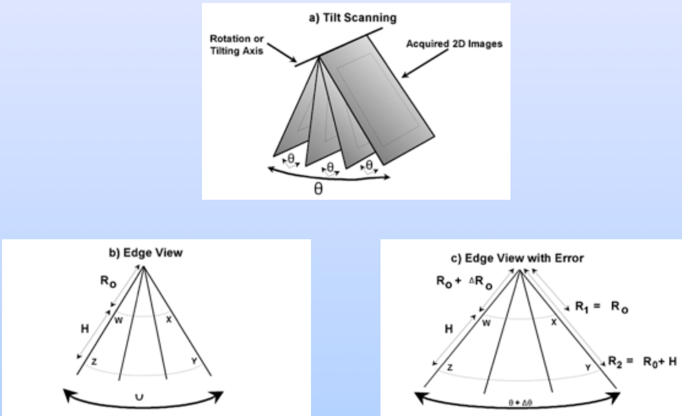

Recommendations for Implementation

- Make sure that the 3DUS system is properly calibrated
- Make sure that there are no motion artifacts
- Make sure that the resolution is optimized in all 3DUS data directions
  - DISTANCE: Place measurement cursor at the midpoint of contrast transition (not the bottom or top).
  - AREA: For planimetric tracing of the boundary, make sure that the steps along the boundary are sufficiently small to follow the contour accurately.
  - AREA: For automated techniques, make sure to verify and edit the contour if it is not correct to accommodate shadowing artifacts.
  - VOLUME: For measurements using areas from multiple parallel slices, make sure that the interslice distance is sufficiently small.
  - AREA & VOLUME: In manual planimetry, verify that the edge has been outlined by viewing it also from orthogonal planes.

3D ultrasound measures - detection, classification, or monitoring over time.

- Absolutely quantitative or relative - quantitative
- accuracy should be achieved when the profile is followed - better than 5%
- Techniques and potential biomarkers measured - length, area and volume
  - manual, semi-automated, automated
  - further algorithm improvements needed
- Degree of fit with QIBA biomarker selection criteria:
  - Transformative - not so much
  - Translational - perhaps
  - Feasible - in clinical use today
  - Practical (basic techniques already in clinical use) - yes
  - Collaborative - ??
- Numbers of exams that might be involved in the US and worldwide by use of the biomarker:
  - routine 2DUS and 3DUS in Ob/Gyn, Pediatrics, Adult imaging
- Implementations by the various manufacturers - most have some capability
- QUALY's saved, or most important impact estimates that can be made

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