

3D PD Imaging of Ovarian Pathology— Advantages and Limitation of the Method: How can We Standardize the Results?

¹Marek Kudla, ²Juan Luis Alcázar

¹Department of Obstetrics and Gynecology, University of Silesia, Katowice, Poland

²Department of Obstetrics and Gynecology, University of Navarra, Pamplona, Spain

Correspondence: Juan Luis Alcázar, MD, Department of Obstetrics and Gynecology, Clinica Universitaria de Navarra, Avenida Pio XII, 36, 31008 Pamplona, Spain

Phone: 34-948-255400, Fax: 34-948-296500, e-mail: jlalcazar@unav.es

Abstract

Three-dimensional Power Doppler ultrasound is a new imaging modality for assessing tissue vascularization, which is being introduced into clinical practice and it is being increasingly used. In the last years a number of papers assessing the role of this method for assessing adnexal masses vascularization have been published. The aim of this work is to address some technical aspects of 3D US, to review critically its current status in clinical practice and to address future perspectives of its use.

Keywords: 3D power Doppler ultrasound, vascularity, standardization.

INTRODUCTION

Three-dimensional power Doppler angiography (3D-PDA) is a relatively new, very promising technique of detecting ovarian pathologies based on measuring blood supply to the areas (tissue volumes) of the pathology. The new 3D/4D technology started establishing its position in Ob/Gyn diagnostics at the end of the last century.

In the last years a number of papers assessing the role of this method for assessing adnexal masses vascularization have been published. However, some methodological issues still remain to be addressed. The aim of this work is to address some technical aspects of 3D-PDA, to review critically its current status in clinical practice and to address future perspectives of its use.

Application of 3D Imaging in Gynecology

Three-dimensional picture in comparison to two-dimensional does not present substantial advantages in interpretation of the ovarian structure. However, the fact that we can analyze the whole volume of the tumor after the patient has left is a

considerable benefit. To make the 3D analysis possible the software had to be developed to integrate a number of 2D pictures taken by a 3D transducer. The pictures are taken by angling and then creating volume of ultrasound reflected signals. The program allows analyzing the whole volume of the tissue (by turning, moving, cutting and measuring volumes and areas).¹

This software is called Virtual Organ Computer-aided AnaLysis (VOCAL) which can also be used separately on a PC computer as a part of an additional program (4D View).

The basic idea behind VOCAL is the combination of 3D-ultrasound tissue representation and the geometric information of surfaces in a 3D dataset.

The software allows the volume to be transmitted to a different location to get a second opinion while still remaining a “live” picture that can be moved, rotated and measured virtually. VOCAL even lets create virtual planes never achievable with 2D (like coronal view of the uterus).

This significantly reduces the scanning time, as analysis of the scan does not require the patient’s presence. However helpful the tool is, rapid improvement in tumor detection should not be expected due to application of 3D alone.²

Application of 3D Power Doppler in Gynecology

The merger of 3D and Power Doppler (PD) created a new tool for tumor vascularity investigation. This new technology called 3D Power Doppler (3D-PDA – 3D Power Doppler Angiography) based on VOCAL software, proved to be a very promising invention to be used in ovarian pathologies. Power Doppler signal reflects energy of flow thus it is dependent on the velocity of the flow and the number of reflectors (blood cells).

This visualization application required a new tool to measure (quantify) blood supply in the volume of the tumor. Based on previous experience with the 2D Power Doppler vessel density evaluation³ the new 3D-vascularization indices were created.

Several papers published on this subject took up efforts aimed at utilizing all possible features of this technology in order to improve sensitivity and specificity of the method.⁴ The problem here is that in contrast to older 2D Doppler techniques, with ranges of normal values of flow indices (Pulsatility index and resistance index) defined, for 3D-Power Doppler Angiography those ranges have not been worked out yet. Even a standardized method of sampling a 3D volume of the tissue has not been established. Lack of standards limits the usefulness of this method.

3D Vascularization Indices and their Meaning

In a 3D volume instead of flat pixels we deal with voxels, the smallest 3D volumes recognized by the system. In power Doppler visualization any voxel reflecting the moving blood is colored by power Doppler software. Intensity of the color depends on energy recorded within the voxel.

3D Power Doppler indices are as follows:^{5,6}

- Vascularization index (VI), presented as percentage;
- Flow index (FI), presented in range from 0 to 100;
- Vascularization-Flow index (VFI), presented in range from 0 to 100.

$$VI = \frac{100}{100} \frac{hc(c)}{hg(g)} = \frac{c}{g}$$

$$VFI = \frac{100}{100} \frac{c - hc(c)}{hg(g)} = \frac{c - hc(c)}{hg(g)}$$

$$FI = \frac{100}{100} \frac{c - hc(c)}{hc(c)} = \frac{c - hc(c)}{hc(c)}$$

Description

- c – color scale value in ultrasound image (value from 1 to 100),
- g – gray scale value in ultrasound image (value from 1 to 100),
- hg(x) frequency of gray value x in ultrasound image,
- hc(x) frequency of color value x in ultrasound image.

VI is the quotient of the number (sum) of color voxels and the total number of voxels (both color and grey) contained in the

analyzed volume. It is important that no information about the weight (color intensity) of single color voxel is used. It means that VI value for the same diameter vessels will be identical in spite of different blood flow in them. Therefore in spite of different intensity of color for two different blood flows (fast and slow) in vessels of identical diameter placed in the same volume of the tissue the result of VI will be the same.

However, VI very well-reflects the density of the vessels which means that if in a defined volume of tissue total number of vessels will double, the value of VI will double as well. This index seems to be an ideal tool to observe and calculate growing density of vessels supplying the tumor volume.

FI is the quotient of the number of weighed color values of the voxels and total number of all color voxels.

By definition FI value changes for a certain net of vessels reflect changes in averaged blood flow in it. Total volume of the tumor is of no importance here. Only values of color and number of color voxels matter.

For example, the result of FI should be identical when analyzing the whole tumor volume that includes a small part containing blood flow, and when analyzing only this small vascularised portion of the tumor. The result of FI will increase/decrease only if intensity of color, reflecting variations in the blood flow changes.

FI result for a chosen tissue volume with a single vessel within it will be influenced by amount of blood going through that vessel. Thus higher blood flow value will result in proportionately higher FI, whereas VI will be identical regardless of the blood flow value.

Hence, FI should be a good tool to differentiate variations in blood volume within the same net of vessels, e.g. for placental vascularisation where the number of the vessels remains unchanged while blood flow value may vary.

In conclusion, FI can differentiate blood supply changes in 3D volume (blood flow, not the number of vessels).

VFI is the quotient of the number of weighed color values of the voxels and total number of voxels (both color and gray) contained in the analyzed volume.

By definition this value increases when either

- The number of vessels within the volume grows while blood flow in each of them remains unchanged or
- The blood flow grows without change in number of vessels or
- Both (a) and (b) occur together.

Practically VFI increase will be influenced by the growth of either VI or FI or both.

VFI is most universal of these three indices. However, if increase in the number of vessels only or in the blood flow alone is expected, VFI is not as representative as VI in the first and FI in the latter case.

VFI value will grow when the volume of the nonvascular part of the tumor diminishes.

Conversely, VFI can stay unchanged if the number of vessels diminishes but the flow increases. Thus this index should be used when comparing structures of highly varied both vascularization and blood flow.

The above explanation of vascularity indices, solely based on physical and mathematical considerations, was aimed at facilitating understanding of how to interpret the indices and which to choose in a specific clinical situation. However, one has to understand that like with all of physical phenomena simple theoretical equation does not reflect nor explain the whole range of other factors influencing results of the calculations.

Physical, Operator Independent Factors Influencing Result of Vascularity Calculations

In clinical reality the measured values of Power Doppler signal and therefore the value of indices are influenced by a variety of other factors. Below we present a few factors that we consider most important.

Distance

One of the most essential factors is the distance between transducer and the region of interest.

The longer the distance, the less of reflected ultrasound signal reaches the transducer as attenuation in surrounding tissue weakens the signal. Attenuation also depends on other factors, for example amount of water in the tissue. To maintain maximum sensitivity, Doppler signal should be received from the shortest distance possible.

Based on the authors' own experience the closest and most typical achievable distance between the transvaginal probe and the ovary surface is 5-10 mm. To make the VI, FI and VFI results comparable, this distance should not be significantly exceeded. Therefore, for example, an ovary located behind the uterus is usually not very useful for histogram calculation.

Blood Viscosity

Blood viscosity is another often forgotten factor, which is independent from the operator. In most of blood vessels the blood flow is laminar (so-called streamline flow). It is like this as the blood flows in parallel layers. Due to its viscosity blood flows fastest in the middle of vessels whereas the blood layers closest to the wall of the vessel are slowest. Therefore, when measuring an increasing volume of blood in a vessel, at first we will not see the whole vessel. Color will start filling up the vessel along its centerline first, as the central layers of blood will be the first to exceed flow detection threshold. Therefore initially VI will be artificially low and FI will be higher than expected.

VI will be growing logarithmically following the flow increase until the whole vessel is filled with color.

Hematocrit

Third important factor is hematocrit and its impact not only on viscosity but most of all on concentration of blood cells acting

as reflectors for Doppler signal. This phenomenon is indirectly confirmed *in vivo* by the influence of contrast media injected to vessels on strengthening the ultrasound Power Doppler signal. Up until today this issue has not been a subject of a profound study. In 3D, only Raine-Fenning et al. discussed the issue of concentration in relation to PD signal.⁷ During their *in vitro* study they found a relationship between different concentrations of the blood mimicking artificial medium and 3D Power Doppler signal represented by vascularity indices.

Operator Dependent Factors Influencing Result of Vascularity Calculations.

Power Doppler factors that can be set by operator are presented here. PD power signal is set to maximum level by assumption. We focus on 3D PD settings only, omitting those related to 2D and 3D grey picture.

Pulse Repetition Frequency (PRF)

Pulse Repetition Frequency is an important factor, clearly dependent on the operator's decision. PRF is the frequency with which Doppler signal portions are sent. This frequency (from 0.1 to 5.5 kHz) limits the range of blood velocities recognizable by the system. The higher the velocity to be measured, the higher PRF has to be set by the operator. On the other hand, the higher PRF is set the less signal (color) from the vessels with low blood flow is visible. Hence if two different PRF values are used with no change to the region of interest (ROI), for the higher PRF the values of indices will be lower. To make two examinations and their corresponding values of indices comparable, Power Doppler PRF must be set to the same frequency in both cases.

PRF has to be set individually for every human organ, depending on characteristic energy of blood flow in its vessels. The lower the PRF, the more color signals are displayed. However, if PRF is set too low, color signal intensity values will be artificially high. For higher blood flow they will stop representing flow differences. Above a certain flow value all color voxels will reach the highest score of color. Increased amount of color artifacts is an additional inconvenient side effect of using too low PRF because then the device is so sensitive that it detects even small blood or tissue movements. Based on clinical experience for the ovary the authors chose PRF of 0.6 kHz as the most suitable for ovarian blood measurements (Figs 1 to 4.).

Power Doppler Gain Control

The value of PRF has to be coordinated with value of the PD gain. Theoretically value of the gain should be set as high as possible without displaying random color speckle (Figs 1 and 3) Gain control set too low results in lack of color from vessels with small energy of flow.⁸ On the other hand, the gain settings for a certain organ (e.g. ovary) should be kept unchanged along



Fig. 1: 3D PD picture of an example ovary A.
Settings: PRF = 0.6 kHz, gain = 0.8. Calculated values of indices for the ovary at the rotation step of 9 degrees: VI = 7.02%, FI = 40.290, VFI = 2.830

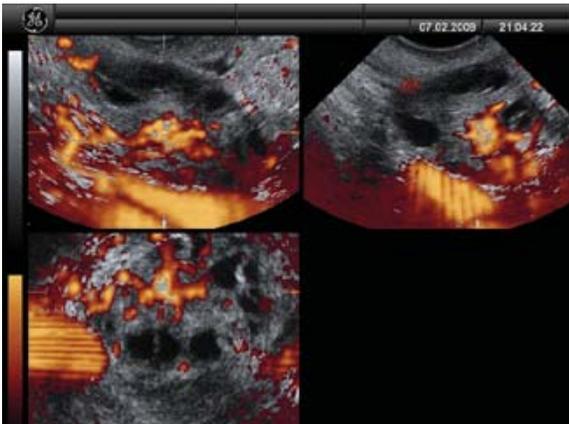


Fig. 2: 3D PD picture of an example ovary A.
Settings: PRF = 0.1 kHz, gain = 0.8. Note the amount of color and compare with Figure 1. Calculated values of indices for the ovary at the rotation step of 9 degrees: VI = 33.32%, FI = 41.690, VFI = 13.890

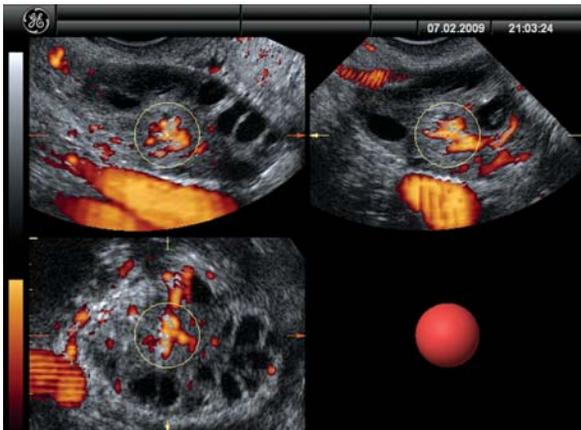


Fig. 3: 3D PD picture of an example ovary A.
Settings: PRF = 0.6 kHz, gain = 4.0. Note the amount of color and compare with Figure 1. Calculated values of indices for ovary at the rotation step of 9 degrees: VI = 29.75%, FI = 34.430, VFI = 10.240

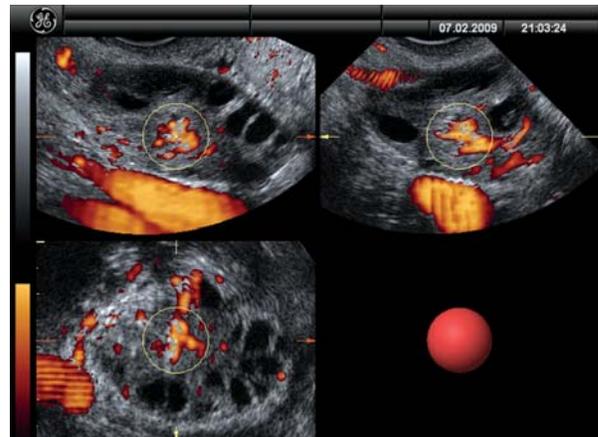


Fig. 4: 3D PD picture of an example ovary A.
Settings: PRF = 0.6 kHz; gain = 0.8. Sphere sampling. Calculated values for the sphere of 1cc: VI = 26.13%, FI = 47.240, VFI = 12.350

with PRF although for various systems, transducers and/or software versions optimum settings may differ.

For example, the settings, suggested by the authors for ovarian examination with the use of Voluson 730 Expert (Beta 05 version, RIC 5-9H transvaginal transducer), are as follows: PRF = 0.6 kHz and gain 0.8.

Defining the Region of Interest (ROI), Rotation Step

The way in which ROI is determined using VOCAL software is another crucial operator dependent postprocessing factor affecting VI, FI, and VFI values. The process of defining ROI is usually done manually along one of three axes X, Y or Z. After choosing the axis a certain rotation step has to be picked. Then the operator has to draw a series of 2D contour line around the region of interest (e.g. tumor). Manual drawing of the contour is the most precise. However a less exact, faster, semi automatic option can be useful in some cases.

The choice of rotation step determines how many contours have to be drawn. The angle step has to be selected based on the shape of the structure being evaluated. The simplest rotation step of 30 degrees should be used only for symmetrical rounded structures. For other structures, step of 6, 9 or 15 degrees should be chosen. Smaller angle results in a higher precision of surface evaluation, however needs more 2D drawings to be done in order to cover full 180 degrees. For example, for the step of 30 degrees we need to draw six 2D traces while for 6 degrees rotation angle 30 traces are needed. For the ovary and for ovarian pathologies the authors, like most other researchers, decided to use a step of 9 degrees. This is the best compromise between precision and time to determine the volume of interest. To explain why it is important one has to understand that bigger rotation step can result in creating imprecise shape representing the ovary. In such case the evaluated volume may incidentally include iliac vessels located next to the ovary. Resulting VI, FI and VFI evaluations will be based on too high values and will

not reflect real vascularization of the ovarian structure alone (Figs 5 to 7).

The most important for clinical research is to create reproducible results. There are not many research papers on 3D-PDA and even fewer have been published on its application for ovarian cancer evaluation. Lack of standardization is the main problem here.

Above, we have discussed technical standardization issues in relation to human body and examined tissue.

Ovarian pathology evaluation with tissue sampling and use of 3D-PDA indices.

Now we present current trends in application of 3D-PDA for ovarian pathology studies with its advantages and limitations, focusing mainly on methodology rather than statistical results. We also present the direction in which presumably the 3D PD technology might develop in the future.

The first papers on the subject of 3D PD technology with the use of three-dimensional tissue sampling in ovarian pathologies were published by Alcazar et al. and Testa et al. in 2005.^{9,10} The potential usefulness of this technology was confirmed in further publications in 2006.^{11,12}

Research done by Alcazar proved that 3D-PDA technology was a useful tool in differentiating advanced, metastatic, and early stage ovarian tumors.¹³ The study assumed neoangiogenesis as a prognostic factor in ovarian malignancy.¹⁴

The region of interest was defined in various ways depending on the tumor structure and its appearance: as a solid volume of the tumor, papillary projections, solid areas, and in cases of solid tumors the whole volume of the tumor.^{9,14}

At that early stage standardization of volume samples was not the subject of consideration. The study done later proved good reproducibility of the power Doppler indices results for tumor evaluation.¹⁵ However, analyzing this methodology we came up to conclusion that, a possible risk existed that in certain circumstances two researchers with a different background, independently applying “the whole volume” method for evaluation of the same tissue might come to different results. The differences can be a result of imprecisely excluding cystic areas from calculation or inaccurately including solid areas in the histogram calculation (Figs 5 to 9).

This technique is apparent in simpler cases with clearly visible contours of the pathology, however, seems to be more difficult in cases with more irregular and blurred contours (Figs 8 and 9). Additionally even within clearly compact, very well visible tumor volumes there are usually regions better or worse vascularized. From oncological point of view the most representatives are regions with the highest vascularization and presumably with the highest oncological potential (like papillary projections e.g.).

The whole volume approach may result in diminishing the mathematical value of 3D-PDA indices for highly vascularized focal regions of the tumor. In addition, not omitting the cystic,

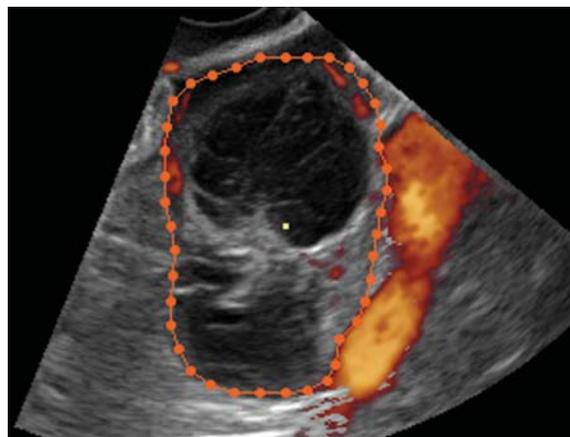


Fig. 5: Power Doppler picture of an example ovary B. Shown in red is contours of the ovary. Note iliac vessels on the right next to the ovary

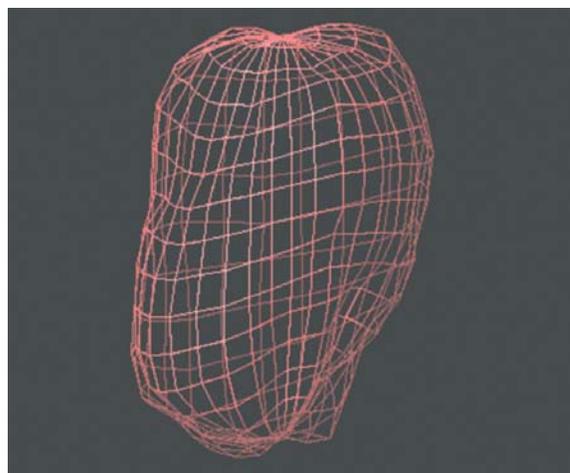


Fig. 6: Wire model representing virtual shape of the surface of ovary B. Rotation step of 9 degrees. The values of indices for this volume: VI = 2.31%, FI = 60.580, VFI = 1.330

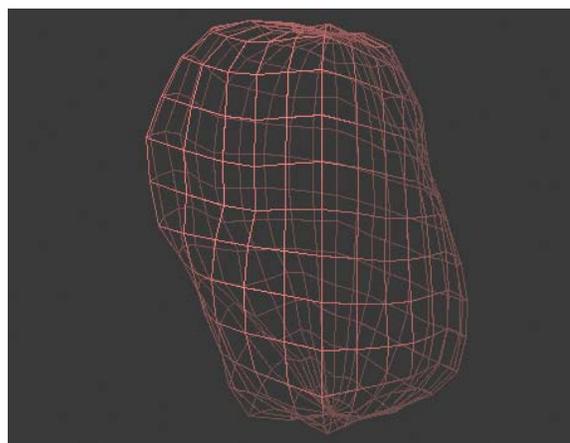


Fig. 7: Wire model representing virtual shape of the surface of ovary B. Rotation step of 30 degrees. In comparison to the previous picture one can see that the net is less dense than one presented in Figure 6 and the shape of the ovary is not as precisely visible. The values of indices for this volume were VI = 10.65%, FI = 34.550, VFI = 3.680

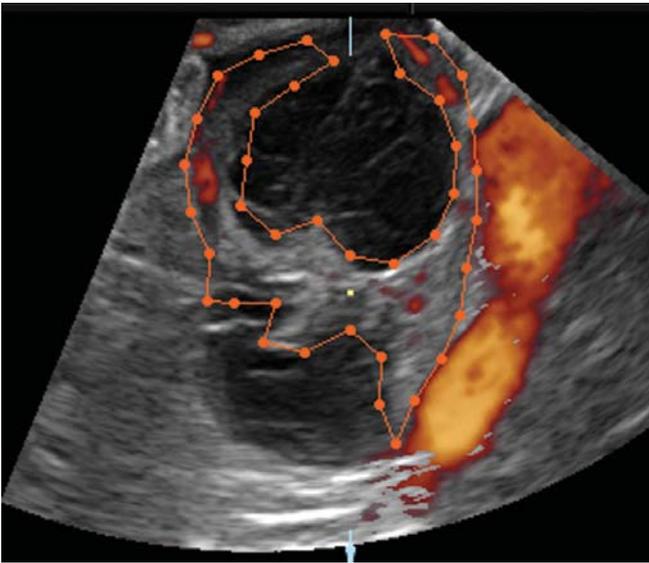


Fig. 8: Ovary B: Shown in red are contours of the compact part of ovary with excluding the cystic parts

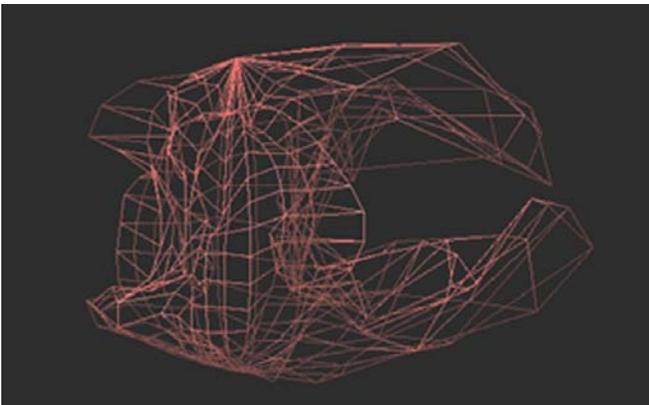


Fig. 9: Ovary B: The 3D net representing volume of the compact part of ovary B. The complicated shape of the net is due to omitted non-vascular, cystic areas of the tumor. Rotation steps 9 degrees. The values of indices: VI = 9.51%, FI = 29.580, VFI = 2.810

nonvascularized parts of the pathology volumes could reduce vascularity results even to those representing normal, physiological values.

Moreover the whole tumor volume approach would not support creating an appropriate control group because healthy ovaries are usually smaller than pathological ones.

To solve the problem we came up with a new idea of gathering vascularity information by using a standardized, always identical in size, tissue volume sample from the most vascularized region, rather than analyzing the whole solid part of the tumor.

In the first pilot studies,^{16,17} we decided to use spherical sampling as it provided the best control of sampled tissue, made

sampling angle independent, and was readily available in 4D view software. Several attempts with different sample sizes proved that the 1cc spherical sample was the most universal one. Easier to apply and less time consuming, it permitted to cover the highest vascularization area without the inclusion of less vascularized or cystic parts of examined structure. Not only can the sample be representative of any size of tumor due to its small dimensions, but it can also be applied to normal ovaries to create a control group (Fig. 4).

Our results showed that spherical virtual sampling of vessels supplying ovarian tissue can be a new, more universal, representative and easier to implement an approach compared to other 3D-PD based methods.

CONCLUSIONS

Limited size of this paper did not allow us to present a variety of other approaches including vascular network architecture.^{18,19}

Without defining the size, volume, and/or shape of the examined sample; results might neither be comparable nor repeatable.

Future effective clinical use of 3D-PDA method requires an adoption of internationally agreed upon conditions of the examination and ultrasound equipment settings.

REFERENCES

1. Maymon R, Herman A, Shlomo A, Dreazen E, Buckovsky I, Weinraub Z. Three-dimensional vaginal sonography in obstetrics and gynaecology. *Hum Reprod Update* 2000; 6:475-84.
2. Alcázar JL, Castillo G. Comparison of 2-dimensional and 3-dimensional power-Doppler imaging in complex adnexal masses for the prediction of ovarian cancer. *Am J Obstet Gynecol* 2005; 192:807-12.
3. Marret H, Sauget S, Giraudeau B, Body G, Tranquart F. Power Doppler vascularity index for predicting malignancy of adnexal masses. *Ultrasound Obstet Gynecol* 2005;25:508-13.
4. Kurjak A, Kupesic S, Sparac V, Kosuta D. Three dimensional ultrasonographic and power Doppler characterization of ovarian lesions. *Ultrasound Obstet Gynecol* 2000;16:365-71.
5. Raine-Fenning NJ, Campbell BK, Clewes JS, Kendall NR, Johnson IR. The reliability of virtual organ computer-aided analysis (VOCAL) for the semi-quantification of ovarian, endometrial and subendometrial perfusion. *Ultrasound Obstet Gynecol* 2003;22:633-39.
6. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A, Johnson IR. Evaluation of the effect of machine settings on quantitative three-dimensional power Doppler angiography: An in vitro flow phantom experiment. *Ultrasound in Obstet Gynecol* 2008;32:551-59.
7. Raine-Fenning NJ, Nordin NM, Ramnarine KV, Campbell BK, Clewes JS, Perkins A., Johnson IR. Determining the relationship between three-dimensional power Doppler data and true blood flow characteristics: An in-vitro flow phantom experiment. *Ultrasound in Obstet Gynecol* 2008;32:540-50.

8. Basic User Manual, Voluson 730 Expert, GE Medical Systems, Kretz Ultrasound 2004;9-15.
9. Alcázar JL, Mercé LT, García-Manero M. Three-dimensional power Doppler vascular sampling: A new method for predicting ovarian cancer in vascularized complex adnexal masses. *J Ultrasound Med* 2005;24:689-96.
10. Testa AC, Ajossa S, Ferrandina G, Fruscella E, Ludovisi M, Malaggesse M, Scambia G, Melis GB, Guerriero S. Does quantitative analysis of three-dimensional power Doppler angiography have a role in the diagnosis of malignant pelvic solid tumors? A preliminary study. *Ultrasound Obstet Gynecol*. 2005;26:67-72.
11. Geomini PM, Kluivers KB, Moret E, Bremer GL, Kruitwagen RF, Mol BW. Evaluation of adnexal masses with three dimensional ultrasonography. *Obstet Gynecol* 2006;108:1167-75.
12. Czekierdowski A, Smolen A, Danilos J, Kotarski J. Applications of three-dimensional ultrasound "vascular tumor biopsy" for the discrimination of ovarian tumors. *Ultrasound Obstet Gynecol* 2006;28 (suppl 1):404.
13. Alcázar JL. Tumor angiogenesis assessed by three-dimensional power Doppler ultrasound in early, advanced and metastatic ovarian cancer: A preliminary study. *Ultrasound Obstet Gynecol* 2006;28:325-29.
14. Fleischer AC, Rodgers WH, Rao BK, et al. Assessment of ovarian tumor vascularity with transvaginal color Doppler sonography. *J Ultrasound Med* 1991;10:563-68.
15. Alcazar JL, Rodriguez D, Royo P, Galvan R, Ajossa S, Guerriero S. Intraobserver and Interobserver Reproducibility of 3-dimensional Power Doppler Vascular Indices in Assessment of Solid and Cystic –Solid Adnexal Masses. *J Ultrasound Med* 2008;27:1-6.
16. Kudla MJ, Timor-Tritsch IE, Hope JM, Monteagudo A, Popiolek D, Monda S, Lee CJ, Arslan AA. Spherical tissue sampling in 3-dimensional power Doppler angiography: a new approach for evaluation of ovarian tumors. *J Ultrasound Med* 2008; 27: 425-33.
17. Kudla MJ, Timor-Tritsch IE, Alcazar JL, et al. Spherical virtual tissue sampling with different size samples in 3D power Doppler angiography for evaluation of ovarian cancers. *Ultrasound Obstet Gynecol* 2008;3:369.
18. Jokubkiene L, Sladkevicius P, Valentin L. Does three-dimensional power Doppler ultrasound help in discrimination between benign and malignant ovarian masses? *Ultrasound Obstet Gynecol* 2007;29:215-25.
19. Alcázar JL, Cabrera C, Galván R, Guerriero S. Three-dimensional power Doppler vascular network assessment of adnexal masses: Intra- and inter-observer agreement analysis. *J Ultrasound Med* 2008;27:997-1001.