10.5005/jp-journals-10009-1443

REVIEW ARTICLE

Placental Blood Flow by Three-dimensional Doppler Ultrasound

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ABSTRACT

This review aims to provide the reader with an overview of the potential clinical applications in three-dimensional (3D) Doppler ultrasound for the evaluation of vascularity and blood flow within the placenta. Significant innovations have recently occurred, improving the visualization and evaluation of placental vascularity, resulting from enhancements in delineation of tissue detail through electronic compounding and harmonics, as well as enhancements in signal processing of frequency- and/or amplitude-based color Doppler ultrasound. Spatial representation of vascularity can be improved by utilizing 3D processing. Greater sensitivity of 3D Doppler ultrasound to macro- and microvascular flow has provided improved anatomical and physiologic assessment throughout pregnancy. The rapid development of these new sonographic techniques will continue to enlarge the scope of clinical applications in placental studies. Three-dimensional Doppler sonography is a unique ultrasound technique that enables assessment of vascular signals within the whole investigated area. Homodynamic changes included in the process of placentation are one of the most exciting topics in the investigation of early human development.

Keywords: Blood flow, Placenta, Three-dimensional Doppler ultrasound.

How to cite this article: Zalud I. Placental Blood Flow by Three-dimensional Doppler Ultrasound. Donald School J Ultrasound Obstet Gynecol 2016;10(1):55-62.

Source of support: Nil

Conflict of interest: None

INTRODUCTION

Three-dimensional (3D) reconstruction of ultrasound images was first demonstrated nearly 20 years ago, but only now is becoming a clinical reality. Three-dimensional applications in ultrasound have lagged behind computed tomography (CT) and magnetic resonance imaging (MRI) because ultrasound data is much more difficult to render in 3D, for a variety of technical reasons, than either CT or MRI data. Only in recent years has the computing power of ultrasound equipment reached a level adequate enough for the complex signal processing tasks needed to render ultrasound data in 3D. At this point in time, the clinical application of 3D ultrasound is likely to advance rapidly as improved 3D rendering technology becomes more widely available. Three-dimensional ultrasound plays an increasing role in obstetrics predominantly for assessing fetal anatomy. Presenting volume data in a standard anatomic orientation assists both ultrasonographers and pregnant patients to recognize anatomy more readily.

Three-dimensional Doppler ultrasound is advantageous for the study of normal uterine, placental and fetal cardiovascular development. The 3D Doppler reconstruction of ultrasound images has become an available option on ultrasound equipments. Several clinical applications are feasible in all parenchymatous organs (mainly the liver and prostate), peripheral vessels (supra-aortic trunks and limb vessels) and central (the aorta and iliac arteries) or cerebral vessels. Moreover, tumoral vessels in parenchymatous organs can be reconstructed, and the fetal blood flow can be seen with excellent detailing. The introduction of 3D ultrasound has permitted to study normal and abnormal peripheral, central and parenchymatous vessels, with similar patterns to those obtained with digital angiography. The spatial relationships between the vascular structures of the placenta were studied with 3D ultrasound angiograms. The applications of this new technique include the analysis of vascular anatomy and the potential assessment of organ perfusion. Evaluation of fetal status with the purpose of intervening when appropriate in order to avoid fetal morbidity or mortality is a main goal of maternal fetal medicine. Doppler ultrasound waveform analysis of the maternal–fetal circulation has emerged to add useful information in the determination of fetal well-being. One of potential application of 3D Doppler could be in the study of vascular changes in patients with pre-eclampsia. It is a known fact that pre-eclampsia is commonly associated with deficient trophoblastic invasion of the maternal spiral arteries during the first and second trimester.[1] This problem can produce abnormally increased resistance to flow through the uterine circulation, and the resulting placental insufficiency can significantly reduce the delivery of oxygen to the fetus. Abnormal placental development is associated with fetal and neonatal morbidity, growth impairment, incidence

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of major congenital anomalies, increased incidence of preterm birth, fetal non-reassuring status in labor, neonatal intensive care admissions, and overall mortality. Early studies suggested that Doppler ultrasound held great promise as a noninvasive, repeatable, and simple method of predicting hypertension in pregnancy and identifying those hypertensive pregnancies at high risk of maternal and fetal complications.[2,3] However, subsequent studies have emphasized the complexity of factors that may influence the pulsed Doppler waveform analysis.[4] It is hoped that 3D Doppler ultrasound could uphold the original promise.

Three-dimensional Doppler Technique

Three-dimensional Doppler ultrasound has become a major field of research in obstetrics. The technique of acquiring 3D data involves making a set of consecutive 2D ultrasound slices by moving the transducer and continuously storing the images. These ultrasound data must be converted into a regular cubic representation before presentation in different 3D visualization modes. The creation of new ultrasound sections from the 3D block and also the surface shading of a structure of interest promise improvement in the diagnosis of placental and fetal vascular developments. In addition, the possibility of volume calculation by 3D ultrasound has to be considered as a clear innovation. At present, almost all of the diagnoses illustrated by 3D ultrasound can be made by 2D ultrasound, and this will continue to be so in the foreseeable future. Recently, computer-assisted treatment of ultrasound images has permitted standardized 3D Doppler reconstruction in obstetrics. This is achieved by scanning a given volume containing the organ of interest. Two practical options exist. Some ultrasound probes are equipped with an automatic scanning device while others use manual scanning, electronically normalized or not. Both approaches make possible use of an electronic matrix, i.e. a pile of two-dimensional (2D) ultrasound images. Secondary cuts are possible through the electronic matrix, including plans not normally accessible to ultrasound scanning because of anatomical limitations.

Three-dimensional ultrasound offers several options extending conventional 2D scanning. Various imaging modes are available. Three orthogonal planes displayed simultaneously can be rotated and translated in order to obtain accurate sections and suitable views needed for diagnosis and geometric measurements (Fig. 1). Three-dimensional Doppler ultrasound tomography combines the advantages of ultrasound, e.g. safety, simplicity of application and inexpensiveness, with the advantages of sequentially depictable sections in numerous rotatable and translatable sections. Surface rendering gives detailed plastic images if there are surrounding layers of different echogenicity allowing for the definition of a certain threshold. Transparent modes provide an imaging of structures with a higher echogenicity in the interior of the object (Fig. 2). A combination of the two modes sequentially definable by the sonographer allows for the optimal viewing of structures. These imaging modes are

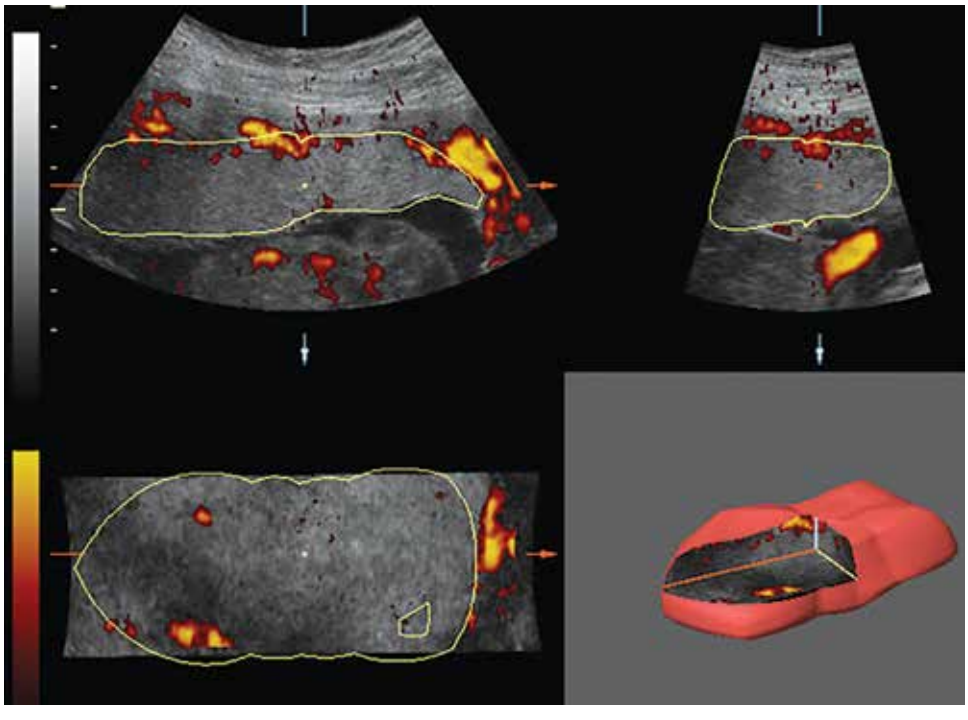

Fig. 1: Three orthogonal planes of the placenta. Three-dimensional power Doppler reconstruction is shown in the right lower quadrant (Niche mode)

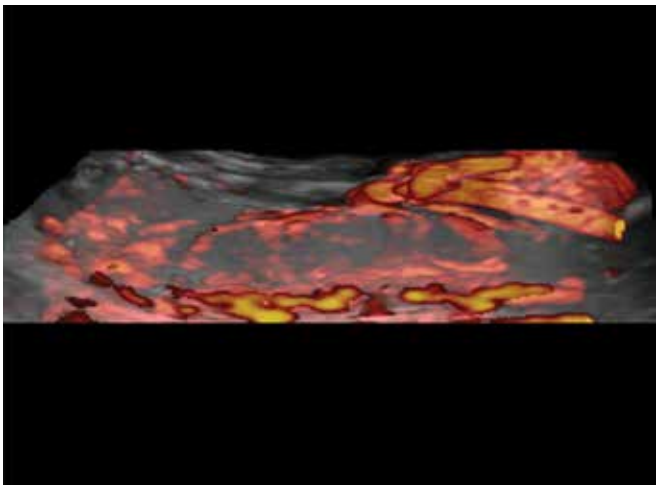

Fig. 2: Three-dimensional power Doppler of the normal placental vasculature and umbilical cord insertion in the second trimester of pregnancy shown in transparent mode

Fig. 3: Ultrasound 'angiogram' of the placental blood flow assessed by 3D Doppler

innovative features that have to be evaluated for clinical applicability and usefulness. Digital documentation of whole volumes enables full evaluation without loss of information at a later point. Three-dimensional Doppler technology provides an enormous number of technical options that have to be evaluated for their diagnostic significance and limitations in obstetrics (Figs 3 and 4).

Doppler methods are routinely used to study the vascular system. Flow and tissue motion information can be obtained by frequency and time domain processing. Instruments range in complexity from simple continuous wave devices without imaging capability through to advanced real-time 2D color flow scanners. Three-dimensional display is now available. The properties of the tissue impose an envelope on achievable ultrasonic imaging. Doppler studies can provide information about flow velocity profile, vessel compliance, wall shear rate, pressure gradient, perfusion, tumor blood flow and the presence of emboli. These capabilities can be integrated in a holistic picture of ultrasonic vascular studies.

Three-dimensional Doppler ultrasound has the potential to study placental blood flow and process of neovascularization. Traditionally, we defined blood flow information as:

Quantitative: Volume flow measurements (cm^3/min), and *Semiquantitative*: Pulsed Doppler waveform analysis (RI, PI, S/D index).

Three-dimensional power Doppler (3DPD) introduces a new way to look at blood flow detection and analysis. Using a computer generated the virtual organ computer-aided analysis (VOCAL) imaging program (GE, Milwaukee, USA), different patterns of blood flow can be described:

- Vascularization index (VI)
- Flow index (FI)
- Vascularization flow index (VFI).

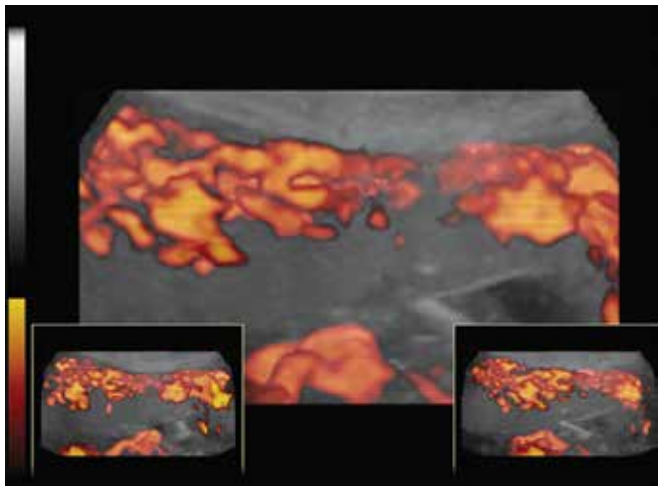

Fig. 4: Another example of 3D power Doppler reconstruction of the normal placental blood flow

Vascularization index gives information in % about the amount of color values (vessels) in the observed organ or area (e.g. uterus, ovary or mass). Flow index is a dimensionless index (0–100) with information about intensity of blood flow. It is calculated as a ratio of weighted color values (amplitudes) to the number of color values. Vascularization flow index is combined information of vascularization and mean blood flow intensity. It is also a dimensionless index (1–100) that is calculated by dividing weighted color values (amplitudes) by the total voxels minus background voxels. Three-dimensional Doppler is used to acquire volumes. VOCAL is then used to delineate the 3D areas of interest and the 'histogram facility' employed to generate three described indices of vascularity. Ultrasonographers should be aware that 3D Doppler is prone to the same artifacts and pitfalls as 2D Doppler. This information should be taken into account when any assessment of placental blood flow is made.

Placental Blood Flow

In pregnancy, the spiral arteries are transformed into distended low-resistance channels capable of increasing the blood supply to the fetal–placental unit until the third trimester to 10 times that of the nonpregnant uterus.[1] This uteroplacental vascular adaptation is dependent on invasion of the spiral arteries by the trophoblast which becomes incorporated into the vessel wall. This invasion occurs in a stepwise fashion starting with plugging of the distal ends of the arteries followed by migration into the decidual segments and, after several weeks' delay, into the myometrial segments. The first phase of this process starts from at least 8 weeks of gestation and continues to the 10th week, and the second phase is at 14 to 24 weeks.

Doppler ultrasound has been demonstrated to be a valuable, noninvasive method of examining utero–placental perfusion, especially in patients with pre-eclampsia and intrauterine growth restriction (IUGR).[5] Although several screening studies have been carried out at 16 to 24 weeks of gestation, they varied widely in populations examined, Doppler methodology, cut-off for abnormal values and definitions of the disease, producing wide differences in sensitivity.[6,7] A recent multicenter study examined 8335 singleton pregnancies at 23 weeks of gestation and the pulsatility index (PI) in each uterine artery was measured by color Doppler.[8] The sensitivity of increased mean PI (4 the 95th percentile) for subsequent development of pre-eclampsia (with or without IUGR) was 40.7% and for IUGR alone was 13.2%. For pregnancies with these complications requiring delivery before 32 weeks, the sensitivity was 90.0 and 56.3%, respectively.

Establishment of the uteroplacental circulation in the second trimester is not a random phenomenon, but rather a consequence of events in the first trimester. This is supported by the findings of a Doppler study in 55 pregnancies, which reported a significant association between measurements of the uterine artery PI at 10 to 14 weeks and those at 19 to 22 weeks.[9] There are also two previous uterine artery Doppler studies which reported an association between abnormal results in early pregnancy and the subsequent development of pre-eclampsia and IUGR. Examining 302 women at 12 to 13 weeks of gestation, van den Elzen et al found that in the group with PI in the highest quartile, compared to those with PI in the lowest quartile, the risk for subsequent development of hypertensive disorders and IUGR was higher by a factor of four and two, respectively.[10] Harrington et al examined 652 pregnancies at 12 to 16 weeks and reported that a seven-parameter model, including vessel diameter, PI, resistance index, time averaged mean velocity, peak systolic velocity, volume flow and the presence or absence of a diastolic notch, identified 93% of those developing pre-eclampsia with a specificity of 85%.[11] In this study there was no breakdown of the number of women scanned at each gestational age and it is therefore not possible to evaluate the efficiency of the test in the first trimester.

Our study was aimed to define normal placental and spiral arteries volume and blood flow as assessed by 3D Doppler in the second trimester of pregnancy.[12] We have been studying uncomplicated singleton pregnancies with normal pregnancy out-comes. As we expected, spiral arteries and placental volumes steadily increased as pregnancy advanced. Placental vascular indices slowly increased, indicating progressive development of vascular network and increase in the volume blood flow. These changes were not rapid in nature but rather slow progressing. The same was true for spiral arteries blood flow. These findings could serve as a basis for future studies of abnormal vascular development as known in pre-eclampsia and intrauterine growth restriction. Most likely changes in 3D Doppler indices could reflect profound changes in the hemodynamics of the placenta and especially spiral arteries in patients suffering from pre-eclampsia and/or IUGR. Further investigations are needed to address the exact extent of vascular changes that could be detected *in vivo* by 3D Doppler ultrasound modalities.

Doppler studies are not new in obstetrics. In addition to anatomical information, Doppler measurements give us the opportunity to study hemodynamics of the uterus, placenta and fetus *in vivo*. Steady and sometimes abrupt changes in the uterine artery, umbilical artery or middle cerebral artery can be observed by pulsed Doppler waveform analysis. One of the major weaknesses of more traditional 2D Doppler studies is the reproducibility of obtained results that at the end makes obtained results less clinically useful. Thorough knowledge of Doppler physics and understanding of instrumentation is essential. Even in an expert hand there are limits. Three-dimensional Doppler is aimed to minimize operator influence on obtained results and allows assessment of the blood flow in real volume and remotely. It is the hope that future investigation protocols would prove this true and clinically useful. Merce et al wanted to study the reproducibility of 3DPD study of placental vascularization in order to establish its methodological base for its further application in normal and pathological pregnancies.[13] A prospective study was carried on 30 normal singleton pregnancies from 14 to 40 weeks. Placental volume and mean gray presented an intra-class correlation coefficient of 0.98 and 0.94, respectively, with differences approaching

zero. All 3DPD vascular indices (VI, FI and VFI) showed a correlation greater than 0.85, with a better intra-observer agreement for the flow indices (FI and VFI). Their results provide validation of the technique, demonstrating a good reproducibility of the 3DPD parameters when applied to study of the placental vascular tree in normal pregnancies. Jarvela et al in their study also confirmed excellent 3D Doppler reproducibility.[14] Their results suggested that measurement of gray-scale and color Doppler flow indices were reproducible thus allowing them to be used in clinical practice and research.

Recent Studies

If proven clinically useful in large-scale prospective studies, 3D Doppler evaluation of placenta could establish a foundation for earlier *in vivo* recognition of homodynamic changes in pre-eclampsia and possibly in IUGR. Pre-eclampsia and IUGR are among the leading causes of perinatal and maternal morbidity and mortality.[15,16] Additionally, long-term implications for health include growing evidence of fetal origin of adult diseases (e.g. surviving IUGR infants could be predisposed to chronic hypertension later in life).[17] Intrauterine growth restriction and pre-eclampsia start developing in the first 12 weeks of gestation yet currently there is no available clinical method to detect these events *in vivo*. Three- dimensional power Doppler sonography has the potential to study the process of placentation and evaluate the development of the embryonic and fetal cardiovascular system.[18,19] Rapid technological development will allow real-time 3D ultrasound to provide improved and expanded patient care on the one hand, and increased knowledge of developmental anatomy on the other. Three-dimensional power Doppler sonography is a unique instrument that enables assessment of vascular signals within the whole investigated area. Homodynamic changes included in the process of placentation are one of the most exciting topics in the investigation of early human development.

Matijevic and Kurjak compared the performance of 2D and 3DPD ultrasound in the visualization of the placental vascular network during ongoing pregnancy.[20] They intended to follow the branching of the main stem vessel as far as possible distally in the placenta. In addition, they assessed the visualization rate of terminal parts of uteroplacental circulation, radial and spiral arteries. In that study, there was no difference in the visualization of primary placental stem vessels by 2D and 3DPD. However, 3DPD performed better distally, with statistically significant differences at the level of secondary stem, and even more prominent differences at the level of tertiary stem vessels. There was no difference in the visualization rate of radial and spiral arteries. The authors concluded that 3D Doppler was superior to 2D Doppler in the determination of the distal vascular branches of the fetal placental blood vessels.

The relationship of large and vascularized chorio-angiomas and adverse pregnancy outcome is well recognized. Shih et al studied a patient with a large placental tumor and signs of impending fetal cardiac failure.[21] The angioarchitecture of the tumor depicted by 3DPD ultrasound enabled them to accurately diagnose a placental chorioangioma. During the follow-up period, quantitative flow data obtained using 3DPD indicated altered hemodynamics in the tumor and concomitant improvement in the condition of the fetus, enabling them to manage the mother conservatively. Spontaneous delivery occurred at 38 weeks without any complications. This report demonstrates the potential value of 3DPD in prenatal diagnosis and monitoring of pregnancies complicated by large, vascularized chorioangioma.

Three-dimensional Doppler ultrasound is a new method which allows the spatial presentation of fetal vessels *in utero*. In the presented study, Hartung et al have examined the feasibility of this technique in prenatal diagnosis.[22] The aim of their pilot study with normal human fetuses was to determine the adjustment of the system presets, the optimal insonation planes and the regions of interest. Seven regions of interest were examined in three different planes. Best examinations were achieved in the vessels of the umbilical cord (successful rate 100%), followed by the placental and abdominal (84% each), cerebral (80%), pulmonary (64%), and renal vessels (51%). The most difficult conditions for examination and the most unreliable results were found for the fetal heart with a success rate of only 31% of the cases. Similar to the experience in 2D power Doppler, a plane with blood flow toward the transducer was the best insonation plane. In this study the authors were able to show that 3D Doppler of fetal vessels is possible. The feasibility is limited by fetal movements and unfavorable fetal positioning. The possible benefit of the method is to diagnose complex fetal vascular malformations in the future. In order to visualize the vascular anatomy of parenchymal organs, Ritchie et al have developed a system for producing 3D angiograms from a series of 2D power-mode Doppler ultrasound scans.[23] Two-dimensional Doppler scans were acquired using a commercial scanner and image-registration hardware. Two-dimensional images were then digitized, and specially designed software reconstructed 3D volumes and displayed volume-rendered images. The geometric accuracy of their system was assessed by scanning a flow phantom constructed from tubing. The system was tested

on patients by scanning native and transplanted kidneys, and placentas. Three-dimensional images of the phantoms depicted the spatial relationships between blood flows within the tubing segments and contained less than 1 mm of geometric distortion. Three-dimensional images of the kidney and placenta demonstrated that spatial relationships between vasculature structures could be visualized with 3D Doppler ultrasound. Applications of this new technique include analysis of vascular anatomy and the potential assessment of organ perfusion.

Chaoui et al wanted to assess the fetal cardiovascular system using 3DPD in normal and abnormal conditions during the second half of pregnancy.[24] The following regions of interest were assessed: placental, umbilical, abdominal, renal, pulmonary and intracranial vessels together with the heart and great arteries. Satisfactory visualization of the fetal vascular system using 3D Doppler could be achieved in normal pregnancies. The main difficulty during the learning curve was the optimization of the power Doppler image prior to 3D data acquisition. Despite good visualization conditions, the reconstruction of satisfactory images was only possible in 56 out of the 87 (64%) pregnancies with abnormal vascular anatomy. These were abnormalities of placenta and umbilical vessels, intra-abdominal and intrathoracic anomalies, renal malformations, central nervous system and cardiac defects. The main reasons for the lack of information were fetal position and movements, overlapping with signals from neighboring vessels as well as technical limitations of the online system.

Merce et al most recently described the evolution of placental vascularization during a normal course of gestation.[25] The FI increased linearly with gestation, whereas the VI showed a dispersion of values with a plateau from the 30th week onwards and a decrease from the 37th week to the end of pregnancy. The VFI behaved as a combination of both VI and FI indices from which it was derived. All 3D Doppler indices were significantly related to fetal biometric parameters, except VI and fetal weight. The authors concluded that 3D Doppler indices change as pregnancy progresses and were significantly related to fetal biometry and umbilical artery Doppler velocimetry. It is obvious now that 3D ultrasound has greatly improved evaluation of organ circulation. Dubiel et al aimed the study to explore the possible use of this new technique in normal and high-risk pregnancies.[26] Fetal brain, lung and placental 3D Doppler ultrasound were recorded in singleton pregnancies at 24 to 42 weeks gestation. In normal pregnancy, placental and lung signal intensity increased until 33, with a rapid decrease after 38, weeks of gestation. Fetal cerebral signal intensity increased with gestational age. Placental and fetal lung signal intensity was significantly lower in high-risk pregnancies than in the control group, with increased fetal brain and brainlung ratios. The present results suggest a reduction of placental perfusion after 38 weeks of gestation in normal pregnancy, with redistribution of fetal circulation. Lung signal intensity increased abruptly at 32 weeks of gestation, which might reflect lung maturity. The new method showed signs of centralization of fetal circulation at the end of gestation. These results might suggest a possible clinical use of fetal surveillance in high-risk pregnancies.

Some authors have speculated that the placental fractional moving blood volume is different with advancing gestational age. Yu et al assessed the VI, FI, and VFI of the placenta in normal pregnancy.[27] Their results showed the linear regression equations for VI, FI and VFI by using gestational age as the independent variable. In addition, the VI, FI and VFI values of the placental flow were also positively correlated with the fetal growth indices biparietal diameter, occipitofrontal diameter, head circumference, abdominal circumference and estimated fetal weight. Presented data may be used as a reference in the assessment of the placental fractional moving blood volume using quantitative 3D Doppler ultrasound measurements.

Rosner's at al study was conducted to compare the 3DPD of the uteroplacental circulation space in the first trimester between women who subsequently deliver growth-restricted *vs* normally grown neonates.[28] Five hundred seventy-seven women were enrolled. Five hundred twenty-six were eligible for analysis using population centiles, and 497 were available for evaluation using customized centiles. There was no difference in the first-trimester 3DPD indices between patients with growth-restricted and normally grown neonates using either curve. The authors concluded that 3DPD indices of the uteroplacental circulation space in the first trimester are similar between neonates who develop growth restriction and those who will grow normally.

Hafner et al evaluated the performance of placental bed vascularization in a low-risk population to predict severe pregnancy risks.[29] Vascularization was measured in the first trimester, using 3DPD VI. Power Doppler VI of the placental bed (PBVI) was measured in 4325 women and correlated to 7 outcome groups: (1) normal, (2) IUGR $\leq$ 3rd centile, (3) delivery $\leq$ 34 weeks, (4) pregnancy induced hypertension (PIH), (5) all pre-eclampsia (PE), (6) severe PE, (7) severe pregnancy problems (SPP, i.e. PIH or PE plus IUGR $\leq$ 3rd centile and/or delivery $\leq$ 34 weeks). In addition, measurements of mean uterine artery Doppler at 12 and 22 weeks, placental volume and PAPP-A were also performed on all women and their

predictive strength for pregnancy risks was compared with the PBVI. Severe PE and SPP occurred in 0.6 *vs* 1.5% of all pregnancies. First trimester PBVI below the 10th centile detected 60% of severe PE and 66.2% of SPP, the odds ratio being 4.48 (95th CI 1.98–11.82) for severe PE and 9.92 (95th CI 5.55–17.71) for SPP. Second trimester uterine artery Doppler detected 72% of PE and 50.8% of SPP, the odds ratio being 14.58 (95th CI 5.78–36.79) and 5.46 (95th CI 3.18–9.36) respectively. All other measured parameters performed much worse compared to PBVI and 22 weeks uterine artery Doppler. The authors concluded that placental bed VI could be used for a quick and reliable first trimester assessment of severe pregnancy risks.

Another most recent study was aimed to improve ultrasonic diagnosis of retained placental tissue by measuring the volume of the uterine body and cavity using 3D ultrasound.[30] Twenty-five women who were to undergo surgical curettage due to suspected retained placental tissue were included. The volume of the uterine body and cavity was measured using the VOCAL imaging program. Twenty-one women had retained placental tissue histologically verified. Three of these had uterine volumes exceeding the largest volume observed in the normal puerperium. Seventeen of the 21 women had a uterine cavity volume exceeding the largest volume observed in the normal puerperium. In all 14 cases examined 28 days or more after delivery the cavity volume exceeded the largest volume observed in the normal puerperium. A large cavity volume estimated with 3D ultrasound was indicative of retained placental tissue. However, 3D ultrasound adds little or no diagnostic power compared to 2D ultrasound.

CONCLUSION

This review aims to provide the reader with an overview of the present and future clinical applications of 3D Doppler ultrasound for the evaluation of vascularity and blood flow within the placenta. Significant innovations have recently occurred, improving the visualization and evaluation of placental vascularity, resulting from enhancements in delineation of tissue detail through electronic compounding and harmonics, as well as enhancements in signal processing of frequency- and/or amplitude-based color Doppler ultrasound. Spatial representation of vascularity can be improved by utilizing 3D processing. Greater sensitivity of 3D Doppler ultrasound to macro- and microvascular flow has provided improved anatomic and physiologic assessment throughout pregnancy. The rapid development of these new ultrasound techniques will continue to enlarge the scope of clinical applications in placental studies.

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