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New Horizons in Doppler Ultrasound Technology: Relevance for Obstetrical Applications

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Abstract: Technologic advances and clinical research have been extending the scope of Doppler sonography and have resulted in the emergence of new diagnostic tools that show significant promise in clinical applications. This article aims to review some of these developments that are relevant for obstetrical practice. One of the major recent technical developments in ultrasound imaging is the ability to assess tissue deformation. This has led to several clinical applications including functional echocardiography that allows evaluation of myocardial function using Doppler and speckle tracking techniques, and sonoelastography, which is ultrasound evaluation of tissue stiffness. Another relevant innovation is power Doppler imaging of regional perfusion. With further critical investigations, these emerging techniques may evolve into useful clinical tools.

Key words: functional fetal echocardiography, tissue Doppler, speckle tracking, Doppler volume flow, power Doppler placental perfusion indices, vascularization index, flow index, vascularization flow index

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Introduction

Since its introduction into the medical field over 50 years ago, the Doppler ultrasound has revolutionized noninvasive investigation of the circulation in almost every branch of medicine. In obstetrical practice, this development has been of special significance as the fetus is relatively inaccessible to external inquiry.[1] The use of a simple Doppler ultrasound device for detecting fetal heart activity was first reported in 1964 and soon its use became ubiquitous in obstetrical practice.[2] Along with the development of diagnostic sonography, Doppler ultrasound has now evolved into a major tool for fetal and maternal hemodynamic surveillance. Doppler-based diagnostic tests have proved efficacious as screening and diagnostic tools and many have shown significant

effectiveness in improving the outcome. Both, basic and clinical researches continue extending the scope of diagnostic sonography in general and Doppler ultrasound in particular, resulting in the emergence of new investigational tools that show significant clinical promise. This review aims to address some of these developments that are pertinent for obstetrical practice.

These aspects of the advances in Doppler and related ultrasound technologies with potential obstetrical applications will be discussed in this update:

(a) Functional Tissue Imaging
(b) Flow quantification;
(c) Doppler perfusion imaging.

FUNCTIONAL TISSUE IMAGING

The main use of diagnostic ultrasound is to assess noninvasively the body's internal anatomy. Ultrasound has also been used for functional evaluation. Doppler sonography for arterial and venous hemodynamic assessment, and the 2D, M-mode, color Doppler, and spectral Doppler modes for cardiac evaluation provide such examples. Significant advances have been made recently in expanding the role of ultrasound for functional imaging. The examples include development of echocardiographic techniques for qualifying and quantifying global or regional myocardial function. Similarly, sonographic characterization of tissue stiffness may aid in diagnosing certain cancers. The underlying principle of both these instances is related to altered tissue deformation. From the clinical perspective, deformation imaging can yield useful information on tissue function in various disease states. This section will briefly review the following relevant aspects of functional tissue imaging:

(a) The concept of tissue deformity and strain, and tissue stiffness
(b) Functional echocardiography of the fetus
(c) Sonoelastography.

Basic Concepts: Tissue Motion, Strain, Strain Rate, and Stiffness

One of the recent technical developments in ultrasound imaging is the ability to assess tissue deformation. This section will briefly review the underlying physical concepts and the parameters for sonographic measurement of deformation. A comprehensive review may be found elsewhere.[3,4]

DEFORMATION

The concept of physical deformation of an object is used extensively in materials science and engineering. When an object or physical body moves with identical displacement of all its constituent particles, it is known as rigid displacement. All the particles in this instance will have the same velocity of movement. However, if the particles differ in their velocity of movement and will be differentially displaced, the body will undergo deformation or strain (Fig. 1). The deformation is elastic when it is temporary so that the constituent particles of the physical body do not show any relative displacement once the stress is removed.

STRAIN AND STRAIN RATE

Strain is relative deformation and therefore, a dimensionless entity. The deformation or strain occurs in the 3-dimensional planes, but the simplest concept deals with 1 dimension. Strain of a 1-dimensional object (whole or a region) is the ratio of the strain-induced change in the length and the original length, and is formulated in the Langragian Equation:

$$e = (L1 - L0)/L0,$$

where e is the symbol for strain in a physical body or object, L0 is the original length of the body before deformation, L1 is the length of the body after deformation (Fig. 1). By convention, lengthening is the

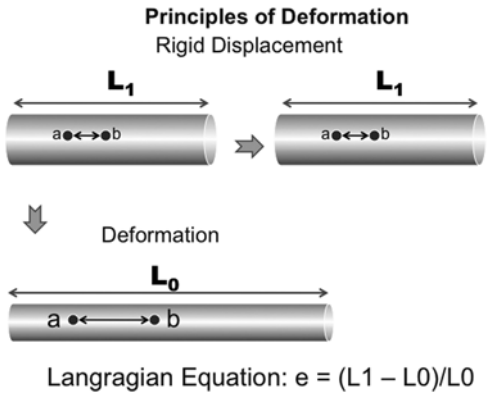

FIGURE 1. Principles of Deformation: Graphic depiction of principles of deformation and rigid displacement of an object is presented. When the object moves with all its constituent particles displaced with the same velocity, it is called rigid displacement. The top panel shows where the object moves to a new position without any changes in its length or constituent particles (a and b). The lower panel shows deformation when the object is displaced with changes in its length and constituent particles (a and b). This illustrates longitudinal strain which is expressed in the Langragian equation. e = longitudinal strain, L0 = original length of the object before deformation, L1 = length of the object after deformation.

positive strain, whereas shortening is the negative strain.

Strain rate is strain or deformational change in an object or a region as a function of time and is formulated as:

$$De/Dt,$$

where De is the change in strain and Dt is the time period during which the strain changed.

STRAIN RATE AND VELOCITY GRADIENT

Strain rate and velocity gradient are interrelated in an object undergoing deformation. Whereas strain rate is deformational change over time, velocity gradient is the change in the velocity over a distance. Measurement of velocity gradient in a region undergoing deformation will reflect the strain rate.

TWO AND 3-DIMENSIONAL STRAIN

In the case of a 2-dimensional object with x and y axes, deformation in 1 axis occurs perpendicular to that axis and parallel to the other axis. The former is called the normal strain and the latter the shear strain. Thus for a 2-dimensional object, there will be 4 strains, 1 normal strain and 1 shear strain for each side, and for a 3-dimensional object there will be 9 strains, 3 normal strains 1 for each XYZ axes and 1 shear strain for each of the 6 sides. These considerations have practical implications in assessing myocardial function or measuring tissue elasticity. In clinical practice, assessment of 3-dimensional strain or strain rate remains experimental.

Clinical applications of functional tissue imaging include functional echocardiography and elastographic measurement of tissue stiffness. These are further discussed below.

Functional Echocardiography

Functional echocardiography evaluates myocardial performance. Traditionally, this is achieved by several approaches including the volumetric measurement of the ejection fraction or Doppler-derived cardiac output. Doppler echocardiography has been used to assess the systolic, diastolic, and combined systolic or diastolic functions. The latter is incorporated in the Tei index which is the ratio of the sum of the isovolumetric contraction and relaxation intervals, and ejection time.[5] More recent developments include tissue Doppler measurements of myocardial velocities, the strain, and the strain rate. These approaches may have several advantages including direct information on the complex mechanics of myocardial activity. More recently, a non-Doppler ultrasound method composed of 2-dimensional speckle tracking has been developed.

Speckle tracking eliminates some of the limitations of the Doppler method. Both the approaches are further discussed.

TISSUE DOPPLER IMAGING

Doppler ultrasound for assessing blood circulation is based on the analysis of Doppler frequency shifts generated by moving blood flow. In contrast, tissue Doppler imaging (TDI) consists of analyzing Doppler frequency shift generated by tissue movement such as the vascular or cardiac wall. The principles of TDI are similar to those of Doppler sonography of blood flow. However, the Doppler signals generated by blood flow are of substantially lower amplitude and higher frequency than those generated by wall movements. In depicting flow-related Doppler shifts, the high pass filter (the wall filter) eliminates the high amplitude and low-frequency Doppler wall signals so that only blood flow-related Doppler signals are displayed. In contrast, TDI filters out the low-amplitude high-frequency flow signals permitting tissue movement-related Doppler signals being displayed (Fig. 2).

TISSUE DOPPLER ECOCARDIOGRAPHY

Traditionally, cardiac function is assessed by Doppler and M-mode echocardiographic volumetric approach. These, however, are indirect methods of evaluating cardiac function, and can not assess regional myocardial function. Moreover, complexities of cardiac morphology

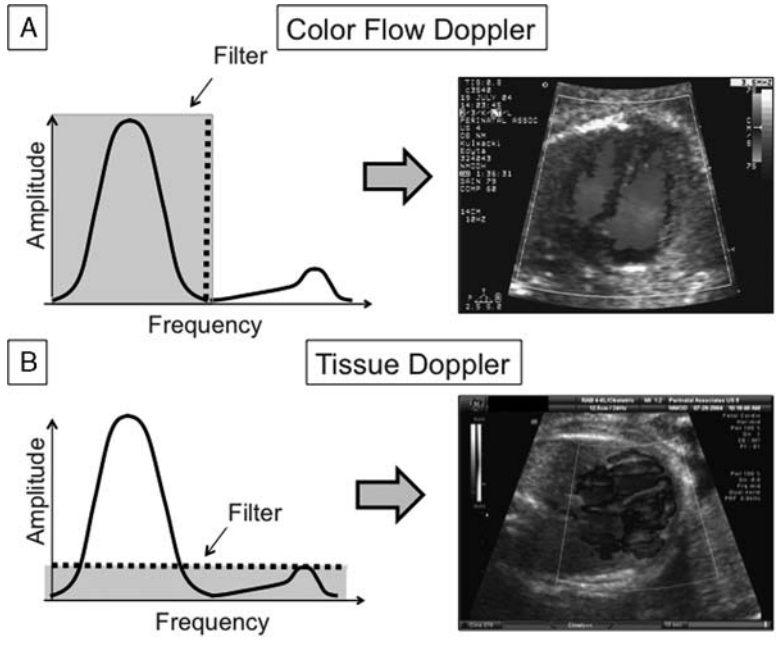

FIGURE 2. Basic Principle of Tissue Doppler: In color flow Doppler, the low-frequency high-amplitude Doppler signals from the wall motion are removed by filter so that high-frequency low-amplitude flow signals can be seen (Panel A). In tissue Doppler, the high-frequency low-amplitude Doppler signals from blood flow are removed by filter allowing the high-amplitude low-frequency Doppler signals from the wall motion can be seen (Panel B).

would affect the underlying assumptions of volumetric approach. In contrast, tissue Doppler echocardiography provides direct appraisal of global and regional myocardial function, and is not limited by the assumptions of cardiac morphology. Tissue Doppler echocardiography can be carried out in spectral pulsed Doppler, color Doppler, and M modes. An example of fetal-pulsed tissue Doppler echocardiogram is presented in Figure 3. The technique has been used for measuring cardiac systolic and diastolic functions including myocardial velocity, myocardial velocity gradient, myocardial strain, and strain rate.[7–9] Use of TDI for functional cardiac assessment has been extensively investigated in adult and pediatric heart diseases.

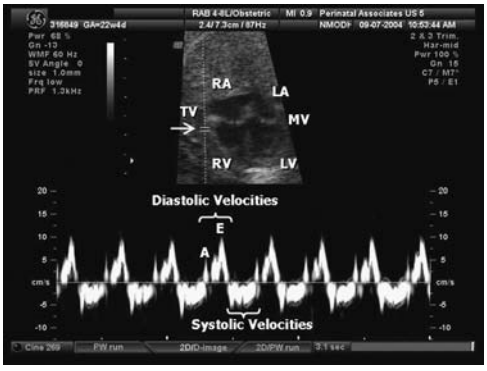

FIGURE 3. Pulsed Tissue Doppler velocity waveforms from the right ventricular wall below the parietal insertion of the tricuspid valve. The sampling site is indicated by the horizontal arrow pointing to the Doppler sample volume (two horizontal lines). The diastolic and systolic velocity waveforms are indicated on the lower panel. A indicates atrial systole; E, end diastole. LA, left atrium; LV, left ventricle; MV, mitral valve; RA, right atrium; RV, right ventricle; TV, tricuspid valve. (With permission from Doppler Ultrasound in Obstetrics and Gynecology. Germany: Springer; 2005:465–483).[6]

MYOCARDIAL STRAIN AND STRAIN RATE

Myocardial strain parameters measure differential velocities in the cardiac wall. Instantaneous Doppler velocity measurements reflect not only the motion of the myocardium but other passive movements of the heart, strain parameters reflect only myocardial deformation during the cardiac cycle and not passive translational motions. The myocardial strain rate can be obtained from the instantanous myocardial velocities at 2 points. In clinical implementation, strain rate is determined from the regression slope of all the velocities between the 2 points. Most current methods measure deformation in the longitudinal plane although in reality the deformation is in 3 dimensions. During systole, as the heart becomes shorter longitudinally, the velocity measurement points come closer. During diastole, the heart becomes longer and the points move apart. Strain rate measured from the velocity gradient between the points represents the longitudinal strain. The strain is derived from temporal integration of the strain rate. Strain rate reflects global and regional myocardial functions better than the myocardial velocity or the velocity gradient.[10] Although these approaches have been studied extensively in adult and pediatric cardiology, few such investigations have been conducted in the fetus.

LIMITATIONS OF TISSUE DOPPLER ECOCARDIOGRAPHY

There are several limitations to this technique. Being a Doppler-based approach, TDI measurements are angle dependent, which may compromise the accuracy of measuring myocardial velocities. As of the angle dependency, Doppler methods can measure the components of velocity or deformation only along the beam axis. Moreover, as noted before, Doppler methods cannot distinguish between the Doppler echoes from the actual cardiac

activity, and those owing to the translational movements of the heart within the thorax or the tethering of the cardiac base. These difficulties are more accentuated in the fetus than in the adults and children. Not surprisingly, replicability of the tissue Doppler measurements of cardiac motion or deformation has been suboptimal.

SPECKLE ECOCARDIOGRAPHY

Ultrasound speckles are the manifestation of the amplitude variations in the backscattered ultrasound signals from randomly distributed subresolution scatterers. An ultrasound pulse travelling through a tissue medium encounters multiple scatterers and simultaneously produces multiple subresolution echoes that reinforce or eliminate one another. The former is known as the positive or constructive interference and the latter as the destructive or negative interference. Constructive interference produces the dots that represent scatter distribution in the insonated tissue. Speckles literally mean small spots, represent ultrasound noise and produce the mottled appearance of the B-mode images. Myocardial deformation parameters can be measured from tracking the frame to frame displacement of the speckles.[11] Such measurements are angle independent allowing multidirectional assessment of the deformation. Two dimensional speckle echocardiography derived values are replicable and the measurements have been validated in animals and patients. Furthermore, this approach is less prone to interference by artefacts than the tissue Doppler approach.

LIMITATIONS OF SPECKLE ECOCARDIOGRAPHY

Significant limitations of this method include the need for optimal image quality for accurate tracking. Echo drop out, reverberations, and high fetal heart rate may contribute to tracking error. In addition, the results from different ultrasound devices may not be comparable because of proprietary algorithms for tracking speckles.

FETAL TISSUE DOPPLER ECOCARDIOGRAPHY

The feasibility and usefulness of TDI for the functional assessment of the fetal heart have been reported by several investigators. The population included normal fetuses, and those with growth restriction or heart failure. More recently, the 2-dimensional speckle tracking echocardiography has also been reported in the fetus. These investigations are selectively summarized here.

The feasibility of using TDI for studying regional myocardial velocities was investigated by Harada et al[12] in 30 normal fetuses. The regions interrogated were the left ventricular (LV) posterior wall, right ventricular (RV) anterior wall, interventricular septum along the long axis. Peak myocardial velocities during early diastole of both the ventricles and atrial contraction showed significant increments with advancing gestation indicating progressive maturation. Gardiner et al used pulsed Doppler and M-mode ultrasound to measure myocardial tissue velocities in 159 normal fetuses.[13] The study was cross sectional. Myocardial velocities increased progressively with advancing gestation, except in the left basal area. Left and right ventricular myocardial velocities showed similar maturational increases in systole (LV 0.14 vs. RV 0.10 cm/s/wk) and early diastole (LV 0.16 vs. RV 0.14 cm/s/w).

Aoki et al[14] used Doppler echocardiography and TDI to assess right ventricular function in 7 fetuses with heart failure. The control group consisted of 36 normal fetuses. The cardiac parameters included RV peak myocardial velocity during early diastole (Ea), tricuspid peak velocity during early diastole (E), E/Ea as an index of filling pressure, and TDI-derived Tei index. The latter combines systolic and diastolic functions and has been used to assess

global cardiac function in various diseases including congestive heart failure and cardiomyopathy. In the fetuses with heart failure, the TDI Tei index and E/Ea ratio were significantly higher (0.79 ± 0.11 vs. 0.55 ± 0.05, $P < 0.0001$; 9.71 ± 0.91 vs. 6.20 ± 0.97, $P < 0.0001$; respectively).

Watanabe et al[15] used TDI to assess left and right ventricular global performance in 38 normal, 6 hydrops, and 12 FGR fetuses during 16 to 37 completed weeks of gestation. Pulsed wave Doppler was used to measure peak flow velocity in early diastole (E). TDI was used to measure the peak annular velocities in systole (Sa) and early diastole (Ea), and the ratio between flow velocity and annular velocity in early diastole (E/Ea) and the ratio of the Sa of right ventricle to that of the left ventricle (RVSa/LVSa). Hydropic fetuses showed decreased LV global performance. The RVSa/LVSa ratio may reflect ventricular afterload changes and cardiovascular response in fetal compromise associated with placental insufficiency and fetal heart failure.

FETAL SPECKLE TRACKING ECOCARDIOGRAPHY

Fetal myocardial functional assessment with 2-dimensional speckle tracking has also been reported recently. As discussed above, this approach is not based on Doppler technology and therefore, does not suffer from the latter's limitations such as angle dependence. An example of fetal speckle tracking echocardiography for myocardial functional evaluation in a normal fetus at 21 weeks gestation is shown in Figure 4. Di Salvo et al used this approach to measure fetal myocardial strain and strain-rate measurement for evaluating regional myocardial performance in 100 consecutive normal fetuses with no evidence of structural cardiovascular disease.[16] The gestation age was 20 to 32 weeks. The cardiac regions included the interventricular septum, left ventricular lateral wall, and right ventricular free wall. The peak longitudinal strain did not differ between the regions, but was dependent on the gestational age. The interobserver and intraobserver variability for strain was < 3 and $< 6\%$, respectively.

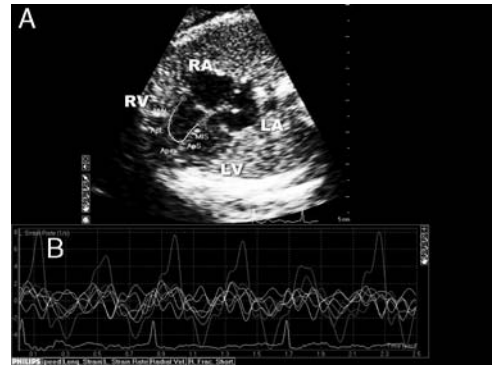

FIGURE 4. Speckle Tracking Strain Echocardiography of The Fetus: Panel A shows 2-dimensional echocardiographic image of the fetal heart. The image also shows the speckle tracking points in the lateral wall and the septal wall of the RV. Panel B shows strain rate tracings for the lateral and septal wall of RV. Corresponding data are stored and can be further analyzed. LA indicates left atrium; LV, left ventricle; RA, right atrium; RV, right ventricle.

These preliminary reports show not only the feasibility of using these approaches in the fetus, but also show their potential use for evaluating fetal cardiac performance in high-risk pregnancies.

Sonoelastography

The basic concept of tissue deformation and its echocardiographic applications have been discussed above. Sonoelastography uses the same principles to measure tissue stiffness or elasticity. Essentially, it is composed of ultrasound imaging of tissue deformation in response to external stress. The importance of palpation for assessing tissue softness or hardness has been well recognized in clinical practice since ancient times. Sonoelastography extends this

important aspect of physical examination of a patient. Ophir et al[17] described a sonographic tool for measuring tissue strain and elastic modulus using a phantom system and animal tissue samples. Recent advances in this field have led to the development of several real-time approaches to sonoelastography. Its diagnostic efficacy has been shown in diverse clinical conditions including breast tumors,[18] hepatic malignancy,[19] and cirrhosis of liver.[20] Sonoelastography has also been used to assess the elasticity of normal and abnormal cervix in perimenopausal women.[21] The potential usefulness of this technique for obstetric applications needs further exploration.

Flow Quantification

Doppler ultrasound velocimetry has been used widely for in vivo flow volume estimation. Volumetric flow in a given instant is the product of the Doppler-derived mean velocity across the vascular lumen at that instant multiplied by the vascular cross sectional area at that instant. The feasibility and potential use of Doppler volumetric flow measurements in the umbilical vein,[22] and the fetal heart[23] were shown decades ago. However, prenatal use of this technique has been limited because of the inaccuracies and assumptions in measuring the Doppler mean frequency shifts, the angle dependency of the Doppler measurement, and the errors in measuring the vascular luminal cross sectional area. A more detailed discussion on this topic can be found elsewhere.[24]

Several innovations have been reported in improving the reliability and accuracy of volumetric flow estimation by using Doppler and non-Doppler ultrasound techniques. A selection of these approaches is summarized below.

TRIPLEX DOPPLER FLOWMETRY

This method uses color Doppler, spectral Doppler, and 2D gray scale ultrasound imaging modes to improve the accuracy of the traditional Doppler flowmetry and has been reviewed by Ferrazzi and Rigano.[25] Color Doppler imaging used to identify an appropriate segment of the target vessel parallel to the beam axis. Spectral pulsed Doppler sample volume is placed covering the vascular lumen with the angle of insonation maintained below 300, and the temporal mean velocity is measured from Doppler frequency shift waveforms. The vascular cross sectional area is calculated from the averaged luminal diameter measured from the magnified 2D ultrasound images. Flow is quantified from the integration of the mean velocity and the vascular cross sectional area. This modified approach has been used for volumetric flow estimation in the umbilical vein in normal and growth restricted pregnancy, and in the uterine artery.[26]

MULTIGATED DOPPLER FLOWMETRY

Unlike the spectral pulsed Doppler that measures only the velocity vector parallel to the ultrasound beam, multigated pulse wave Doppler measures multiple individual velocity vector components across the vascular lumen. Being a Doppler technique, it is necessary to measure the angle of insonation for transforming the Doppler frequency shifts into velocity information. The volumetric flow is obtained from the summation of these velocity components. An implementation of this approach has been reported in which 2 ultrasound beams are used and numerous small (< 200 mm length) sample volumes at successive depths are collected and analyzed by Fast Fourier Transform in real time.[27] The beams are set at a fixed known angle which allows computation of the angle of insonation. The system is capable of measuring volumetric flow in real time. This technique is at present limited to assessing superficial vessels such as the

carotid arteries and is not available for maternal or fetal applications.

REAL-TIME 3-DIMENSIONAL DOPPLER FLOWMETRY

In this novel approach, a 2-dimensional matrix array transducer with 2 to 3 thousand elements are used to obtain in real time 3D Doppler mode. The live 3D Doppler volume dataset is then post-processed with proprietary software. The color flow is visualized in the region of interest which is the vessel cross-sectional area. The program samples the region, determines the actual velocity profile over the cardiac cycle, and calculates the flow rate. The technique has been validated in animal models and in patients.[28] With continuing advances, this technique has significant potential for reliable flow quantification in real time.

Doppler Perfusion Imaging

Doppler signals from blood flow originate from the moving red cells and the power or the amplitude of the Doppler spectrum depends on the number of scattering red cells. Several approaches have been described for assessing tissue perfusion using the color or power Doppler image analysis. Regional or tissue perfusion measurement may be clinically important in several areas. For example, reliable assessment of the increased vascularity of malignant tumors may assist in imaging diagnosis. Potential applications also exist in obstetrics in which an efficacious replicable tool for perfusion assessment may be helpful in managing pregnancy complications such as fetal growth restriction or preelcampsia. Relatively recently, 3-dimensional (3D) power Doppler-derived perfusion indices have been described[29]:

(a) Vascularization index (VI), which is the ratio of color voxels normalized by all the voxels in the target volume.
(b) Flow index (FI), which is the color voxels weighted by the Doppler signal amplitude divided by the total color voxels in the target volume.
(c) Vascularization flow index which is the combination of the vascularization and the flow indices (VFI).

With advancing pregnancy, progressive increases in the perfusion indices of the placenta and spiral arteries have been reported in a study involving almost 200 normal pregnancies.[30] A preliminary study showed that after 32 weeks, the placental perfusion indices were significantly lower ($P < 0.01$) in 10 FGR pregnancies than in 79 normal pregnancies.[31]

Despite the potential clinical benefits, the indices suffer from several limitations including the dependence of the power Doppler signals on ultrasound instrument settings, the depth of the target region, and signal attenuation. A normalization process, named "fractional moving blood volume estimation," has been described by Rubin et al, which compensates for the depth and attenuation.[32] The instrument settings that may seriously affect the results include the gain setting, acoustic power output level, and the pulse repetition frequency.[33] Addressing these challenges will facilitate clinical utilization of this approach. Despite these limitations, Morel et al found significant interobserver and intraobserver reproducibility of this technique (0.92 and 0.94, respectively).[34]

Conclusions

Technical innovation and clinical research will continue to offer new opportunities for extending the scope of diagnostic ultrasound. This review presents selected examples of such development encompassing Doppler and non-Doppler ultrasound methods relevant for obstetric practice. Clinical application of these developments will depend upon the demonstration of their diagnostic efficacy and clinical effectiveness in improving the outcome.

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