66 Umbilical artery doppler sonography for fetal surveillance: Principles and practice

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INTRODUCTION

Antenatal fetal monitoring is an essential component of modern obstetric care in pregnancies at high risk for adverse perinatal outcomes. Technical and clinical advances during the past few decades have resulted in the development of several methods of antepartum fetal surveillance that include fetal heart rate (FHR) monitoring, ultrasound assessment of fetal biophysical status, and Doppler velocimetry of fetal and uteroplacental circulation. This chapter presents a general background of Doppler ultrasound for fetal surveillance with emphasis on an evidence-based approach for its clinical application. The review is focused on the Doppler of the umbilical artery (UA), as it is the only fetal surveillance tool that has shown clinical effectiveness in improving perinatal outcome. Extensively revised since the last edition of the book, this chapter presents the following aspects of Doppler fetal surveillance:

- A brief history of diagnostic Doppler ultrasound
- Principles of Doppler velocimetry
- Doppler velocimetry of the UA
- Other fetal surveillance tests
- Clinical effectiveness of Doppler velocimetry for fetal surveillance
- Guideline for the clinical application of the Doppler fetal surveillance

For a more comprehensive review of the various clinical and basic aspects of Doppler sonography in obstetrics, a dedicated text or reference book is recommended (1).

A BRIEF HISTORY OF DIAGNOSTIC DOPPLER ULTRASOUND

Doppler sonography is based upon the physical phenomenon of Doppler shift first described by Austrian mathematician and physicist Christian Andreas Doppler in 1841. Doppler first reported this phenomenon at a meeting of the Natural Sciences Section of the Royal Bohemian Society in Prague, a meeting with only five members of the society in attendance and a transcriber. His paper, entitled "On the Colored Light of the Double Stars and Certain Other Stars of the Heavens," was published in 1843 in the society's proceedings (2). To Doppler's disappointment, however, the paper was not enthusiastically received by the scientific community of his time, although his principle has been extensively used in science and technology since the beginning of the twentieth century.

The history of diagnostic Doppler ultrasound has been reviewed in greater detail elsewhere (3). The premier medical use of Doppler sonography occurred during the late 1950s. The use of Doppler sonography for the investigation of human fetal circulation was first reported by FitzGerald and Drumm

in 1977 (4). Maulik and coworkers further reported the feasibility of the Doppler ultrasound for fetal circulatory assessment (5). During the following years, many investigators used this technique to characterize most major fetal circulatory systems. In 1986, the National Institute of Child Health and Development organized a workshop that highlighted many issues pertaining to Doppler ultrasound measurement of maternal-fetal hemodynamics (6). These issues were also addressed by many investigators and discussed in several scientific societies around the world including the International Perinatal Doppler Society. For a decade and a half, the latter acted as a unique scientific forum dedicated to the obstetric applications of Doppler ultrasound and critically contributed to its introduction into the clinical practice through research and education. The diagnostic efficacy and clinical effectiveness of the Doppler technique has been extensively investigated. Of the various modalities of fetal surveillance, only the Doppler ultrasound of the UA has been shown to improve the perinatal outcome by randomized clinical trials (RCTs) and meta-analyses, and has now become a standard for fetal surveillance in most parts of the world.

PRINCIPLES OF DOPPLER VELOCIMETRY

Doppler Frequency Shift

When relative motion occurs between a source of wave transmission and an observer, the observed changes in the frequency of energy wave transmission is defined as the Doppler effect. The change in the frequency is called the Doppler frequency shift or just the Doppler shift:

$$f_d = f_t - f_r \quad \text{Equation (1)}$$

where f_d is the Doppler shift frequency, f_t is the transmitted frequency, and f_r is the received frequency. When the source and the observer move closer, the wavelength decreases and the frequency increases. Conversely, when the source and the observer move apart, the wavelength increases and the frequency decreases. The principle applies to all forms of energy wave propagation including sound. The utility of the Doppler effect originates from the fact that the shift in the frequency is proportional to the speed of movement between the source and the receiver and therefore can be used to assess this speed.

The phenomenon of the Doppler effect is observed when an ultrasound beam encounters a scatterer in motion. The scatterer acts first as a moving receiver and then as a moving source. This forms the basis for restating equation (1) as

$$f_d = 2f_t v/c f_r \quad \text{Equation (2)}$$

where f_d represents the Doppler frequency shift, f_t the frequency of the incident beam (transducer frequency),

v the velocity of the scatterer in a given direction, and c the propagation speed of sound in the medium. Note that the transmitted ultrasound undergoes double Doppler shift before returning to the receiving transducer, the scatterer acting first as a receiver and then as a transmitter. This accounts for the factor of 2 in the above equation. In blood circulation, millions of red cells act as moving scatterers of an incident ultrasound, which consequently will undergo frequency shift proportional to the speed of red cell movement and therefore to blood flow velocity.

When the incident beam incurs an angle (θ) to the direction of blood flow, the v in the Doppler equation is replaced by the component of the velocity in the direction of the flow obtained by the cosine of the angle ($\cos \theta$;) (Fig. 1):

$$f_d = 2(f_t \cos \theta v) / c$$

Equation (3)

To determine the velocity of the scatterer, equation (3) can be rewritten as follows:

$$v = f_d c / 2 f_t \cos \theta$$

Equation (4)

Thus, if the angle of beam incidence and the Doppler shift are known, the velocity of blood flow is also known assuming that the transducer frequency and the velocity of sound in tissue remain relatively constant. The above equation forms the basis for the clinical application of the Doppler principle.

Circulatory Information from Doppler Shift

Doppler sonography can yield a variety of clinically useful hemodynamic information. This includes quantification of flow and study of the flow velocity waveform (Table 1). Volumetric flow can be measured by integrating the average velocity across the vascular lumen with the vascular cross-sectional area. In the fetus, the Doppler technique has been used to measure umbilical venous flow (7), descending aortic flow (8), and fetal cardiac output (9). The clinical utility of Doppler flow quantification has remained limited because of its systemic unreliability related to errors in determining the vascular cross-sectional area and the Doppler angle. Consequently, the main perinatal use for Doppler sonography has been the indirect assessment of downstream impedance by Doppler waveform analysis. However, several investigators have now improved the Doppler flow quantification method paving the way for its future potential clinical application (10). Current advances in Doppler and non-Doppler ultrasound methods for volumetric flow measurement have been recently reviewed (11).

Doppler Waveform Analysis

Doppler waveform analysis is usually based on the following characteristics of the maximum frequency shift envelope (Fig. 2): the peak systolic value (S), end-diastolic value (D), and the average value over the cardiac cycle (A). These three parameters have been used to develop indices describing the pulsatility of the Doppler waveform. A Doppler index is calculated as a ratio and is, therefore, virtually independent of the angle of insonation. Of the numerous indices, the pulsatility index (PI) (13), the resistance index (RI) (14), and the S/D ratio (15) are most commonly used in obstetric applications. Maulik and coinvestigators used the receiver

Figure 1 Graphic depiction of the principles of Doppler equation and the proportional relationship between the Doppler shift and the velocity of blood flow. Abbreviations: f_t , Doppler frequency shift; f_r , transmitted frequency; f_d , Doppler frequency shift; v , velocity of blood flow; θ , the angle of insonation between the ultrasound beam and the direction of flow; c , velocity of flow in tissue.

Table 1 Hemodynamic Information from Doppler Sonography

Presence of normal flow in expected location
Presence of flow in unexpected location
Absence of flow in expected location
Speed of blood flow
Direction of flow
Circulatory impedance in the arterial circulation
Volumetric flow
Disturbed hemodynamics, e.g., turbulent flow

Figure 2 Doppler indices estimated from the maximum frequency shift (MFS) envelope. Abbreviations: S, peak systolic frequency shift value of the envelope; D, end-diastolic frequency shift value of the envelope; A, average value of the envelope over one cardiac cycle, $RI = (S - D) / S_6$; $PI = (S - D) / A_5$; S/D ratio 7; D/A ratio 9. Source: From Ref. 12.

operating characteristic (ROC) technique (Fig. 3) to investigate the comparative efficacy of the umbilical arterial Doppler indices for predicting adverse perinatal outcome and showed that the RI had the best discriminatory ability when compared with the S/D ratio ($p < 0.05$), the PI ($p < 0.001$), and the D/A ratio ($p < 0.05$) (16). Although more comprehensive approaches to Doppler waveform analysis have been described (17,18), there is little evidence that these are superior to the traditional Doppler indices. The

hemodynamic, angiomorphologic, and pathophysiologic justifications for Doppler waveform analysis are discussed below.

Hemodynamic Rationale of Doppler Waveform Analysis

Doppler waveform from an arterial source represents the arterial velocity waveform and is configured by both the upstream and downstream circulatory factors. Analysis of the waveform should, therefore, yield information on downstream impedance to flow. Obviously, this requires verification. Although the term “peripheral vascular resistance” has been traditionally used for describing opposition to flow in an arterial tree, it is applicable only to a steady non-pulsatile flow state. Opposition to flow in a pulsatile circulation is more accurately expressed by the concept of vascular impedance, which also includes the resistance. An integral component of this concept is the phenomenon of wave reflection in a vascular tree. Configuration of pressure and flow waves at a specific location results from the interaction of the forward propagating (orthograde) waves with the reflected backward propagating (retrograde) waves (19). The observed pressure waves, which are produced by the summation of orthograde and retrograde waves, show an “additive” effect; by contrast, the observed flow (or flow velocity) waves demonstrate a “subtractive” effect (Fig. 4). Wave reflections arise whenever there is a significant alteration or mismatching in vascular impedance in a circulation, and the arterial–arteriolar junctions serve as the main source of wave reflections in an arterial tree. Vasodilation leads to a fall and vasoconstriction to a rise in impedance and wave reflection.

The hemodynamic validation studies may be grouped as those relating to the peripheral resistance and those involving the impedance. However, as mentioned above, vascular impedance is the appropriate descriptor of opposition to flow in a pulsatile circulation. This was investigated by Downing and coworkers in a chronic lamb model and it was observed that a significant correlation exists between the PI and the impedance parameters, provided the reflex heart rate changes are suppressed. Evidently, the Doppler indices reflect changes in the downstream impedance (21). The greater the fetoplacental vascular impedance, the lower the end-diastolic flow in the UA and the higher the indices. A more comprehensive review of the hemodynamic interpretation of Doppler waveforms from an arterial system is available elsewhere (22).

Angiomorphologic Validation of the Doppler Indices

Several investigators have demonstrated that abnormal fetal placental angiogenesis is characterized by sparse, elongated, uncoiled, and less ramified terminal capillary loops as the major lesions in growth-restricted pregnancies with abnormal umbilical arterial Doppler (23,24). These observations suggest that aberrant fetoplacental angiogenesis results in an increase in impedance, which is associated with enhanced pressure and flow velocity wave reflections. The reflected flow velocity waves propagate retrogradely and change the shape of arterial flow velocity waves, which show decreased end-diastolic flow and increased pulsatility. Doppler insonation of the appropriate arterial tree identifies this circulatory phenomenon by demonstrating abnormal Doppler waveforms and indices.

Figure 3 Receiver operating characteristic curves of umbilical arterial Doppler indices. Data points are the measured values of indices. Note that the resistance index shows the most and the pulsatility index shows the least diagnostic efficacy. RI, S/D, D/A, PI. Source: From Ref. 12.

Figure 4 The influence of pulse wave reflections on ascending aortic pressure (P) and flow (Q) waveforms. Incident or forward (f) and backward or reflected (r) pressure and flow waves are summed to yield measured (m) pressure and flow waveforms. The forward pressure and flow waves are identical and so are the reflected waves except that the reflected wave form is inverted with impact to the reflected pressure wave. Source: From Ref. 20.

Pathophysiologic Rationale for Doppler Fetal Surveillance

Antepartum challenge to fetal well-being may arise from chronic nutritive and respiratory deprivation. A spectrum of obstetric complications, including fetal growth restriction (FGR) and hypertension, may expose the fetus to such risks. Although an immense amount of information is available on acute and subacute fetal respiratory deficit, the pathophysiologic mechanism of chronic fetal stress has been less clear. However, significant advances have been made recently providing considerable insight into the mechanisms of fetal

Figure 5 Summary of fetal sequential response to progressive stress. Note that the depicted sequence is an approximation and the actual course may vary depending on the characteristics of the chronic deprivation and the individual fetal ability to cope. Source: From Ref. 25.

compensation and decompensation. There is emerging evidence that, encountering sustained stress, the fetus appears to mobilize a spectrum of defensive responses that include preferential preservation of fetal growth over placental growth, changes in fetal movement pattern, and the eventual deceleration of the fetal growth rate (Fig. 5).

In the face of continuing deprivation, compensation gives way to decompensation. For example, growth-restricted human fetuses with abnormal UA waveforms have been shown to develop chronic hypoxia and acidosis. A critical component of fetal homeostatic response involves flow redistribution that favors perfusion of the vital organs (the brain, heart, and adrenals) at the expense of flow to muscle, viscera, skin, and other less critical tissues and organs (26). Underlying this phenomenon are the diverse changes in blood flow impedance in fetal regional circulations. Doppler velocimetry thus elucidates these circulatory changes associated with fetal compromise and allows perinatal prognostication. This constitutes the rationale for using Doppler ultrasound for fetal surveillance in complicated pregnancies.

DOPPLER VELOCIMETRY OF THE UA

Normative Data

The UA was the first fetal vessel to be evaluated by Doppler velocimetry and has since become the most widely investigated fetal circulation. Typically, Doppler interrogation of the umbilical arterial circulation is performed during fetal apnea

(see below). In our experience, the inter- and intra-observer variances of the S:D ratio and the RI, as determined by continuous-wave Doppler, were 9.8% and 11.1%, and 4% and 8%, respectively (27). In normal pregnancy, the umbilical arterial Doppler indices are affected by gestational age, FHR, fetal breathing, and the site of measurement in the cord.

Gestational Age

As pregnancy advances, umbilical arterial Doppler waveforms show a progressive rise in the end-diastolic velocity, which results in a concomitant fall in the pulsatility (Fig. 6). This trend is consistent with a gradual decline in the fetoplacental flow impedance with the advancing gestation (29). The Doppler indices reflect these changes in the waveform (Fig. 7).

FHR

A statistically significant effect of the heart rate on Doppler indices has been reported by a number of investigators (31). It has been shown that changes in the heart rate occur primarily due to alterations in the duration of the diastolic component of the cardiac cycle (32) and that the effect of the FHR may contribute to 15% to 18% of the variance of the Doppler indices (27). However, it is not certain that correcting the Doppler indices for FHR changes would improve the diagnostic efficacy of the indices and may not be clinically significant so long as the heart rate remains within the normal range.

Figure 6 Gestational age effect on the umbilical arterial Doppler frequency shift waveforms. Panels are organized from the top to the bottom according to advancing gestation. Abbreviations: A, waveforms at 16 weeks; B, at 20 weeks; C, at 24 weeks; D, at 28 weeks; E, at 32 weeks; F, at 36 weeks; G, at 40 weeks. Note the progressive increase in the end-diastolic velocity and the concomitant fall in the pulsatility as gestation advances. Source: From Ref. 28.

Figure 7 Variation in the umbilical arterial resistance index (RI) at different stages of gestation. Source: From Ref. 30.

Fetal Breathing

Substantial changes in the intrathoracic pressure and central hemodynamics occur during fetal breathing, which produce dynamic variability in the umbilical arterial Doppler waveform and, therefore, in the Doppler indices. This severely compromises the utility of the Doppler indices during fetal breathing and provides the rationale for measuring the indices only during fetal apnea. However, the indices do not appear to be affected by fetal behavioral states (33).

Site of Doppler Interrogation

The location of the Doppler sampling site in the umbilical cord affects the Doppler waveform and therefore the Doppler indices, which are higher at the fetal than at the placental end of the cord (27).

Umbilical Arterial Doppler in FGR

FGR is associated with defective development of placental vascular systems. FGR and pre-eclampsia are associated with aberrant angiogenesis of fetoplacental arterial system. The efficacy of UA Doppler indices for detecting suboptimal fetal growth has shown to be variable and has been reviewed (Table 2) (34). This may be partly explained by the considerable amount of ambiguity that surrounds the use of the terms "FGR" and "small for gestational age (SGA)." It is well recognized that neither all growth-restricted fetuses are SGA, nor are all SGA infants growth compromised. Furthermore, being SGA does not necessarily mean a compromised outcome. It is apparent that not all FGR or SGA fetuses may suffer from in utero compromise in terms of asphyxia, which correlates better with absent end-diastolic velocity (AEDV) in the UA than with subnormal fetal abdominal circumference (<5th percentile) as measured by ultrasound (35). This issue, however, is apparently controversial and is further discussed in the next section. With regard to the various sonographic modalities for diagnosing FGR, the majority of studies have demonstrated that conventional fetal ultrasound biometry is more sensitive than umbilical arterial Doppler velocimetry (36). This should not be surprising as fetal size is expected to be better expressed by sonographic measurement of fetal dimensions than by Doppler velocimetry, which assesses the hemodynamic state; unless the latter is compromised, the Doppler indices will not change.

Umbilical Arterial Doppler Velocimetry and Antepartum Fetal Hypoxia-Asphyxia

The purpose of fetal surveillance is to detect fetal compromise from intrauterine hypoxia and asphyxia. Fetal homeostatic response to hypoxic and asphyxial challenge has been well described in animals (37). A central manifestation of this response is the flow redistribution that favors perfusion of the vital organs (the brain, the heart, and the adrenals) at the expense of less critical organs and tissues. This compensatory phenomenon provided the justification for investigating the efficacy of the Doppler velocimetry in identifying fetal hypoxia and asphyxia. Both clinical and animal experimental studies have been reported to address this issue.

Further insight may be obtained from experimental studies conducted in animal models. Many of the relevant findings in this area have been reviewed (38). It has been noted that in the

aorta of the fetal lamb, significant changes in the Doppler waveform occur only when the oxygen saturation declines to 10% to 15% or the fetal pH drops to <7.15 (39). Apparently, in an ovine fetus, hypoxia and acidosis may significantly affect umbilical and aortic velocity waveforms but only as a late phenomenon.

The association between the Doppler findings and fetal blood gases has been clinically investigated (35,40–47). These have been reviewed and are summarized in Table 3. Some investigators performed umbilical cord blood sampling at the time of elective cesarean section. Obviously, these studies are limited because blood gases measured in this manner may not reflect fetal acid–base status in utero. Others determined fetal blood gases by cordocentesis. Most studies used Doppler assessment of the UA, whereas one used aortic mean velocity and another added aortic and carotid Doppler assessment. All studies measured pH, most performed PO₂, and some also measured PCO₂ and lactate. Most investigators found a significant association between Doppler assessment of fetal circulation and fetal acid–base compromise. The response of fetal cerebral Doppler waveform presents another perspective on fetal hypoxia and acidosis. This is discussed later in the section dealing with fetal cerebral circulation.

Umbilical Arterial Doppler Velocimetry and Adverse Perinatal Outcome

The discriminatory efficacy of Doppler velocimetry for predicting perinatal outcome is briefly discussed in this

section. A fetal surveillance test may be used either as a diagnostic test for identifying the fetal compromise in high-risk pregnancies or as a screening test in a general obstetric population at low risk for fetal compromise. Both are presented below. In evaluating this information, we need to recognize the imprecision inherent in the available criteria for defining adverse perinatal outcome.

High-Risk Pregnancies

Several preliminary studies indicated that the Doppler indices might be powerful predictors of adverse perinatal outcome in complicated pregnancies. The diagnostic efficacy of umbilical arterial A/B (systolic, diastolic) ratio was investigated by Trudinger and coworkers in 170 high-risk patients (48). The parameters of fetal compromise included birth weight below the 10th percentile or an Apgar score of <7 at 5 minutes. The FHR was assessed in terms of reactivity and a modified Fischer score. The Doppler results revealed a sensitivity of 60%, a specificity of 85%, and a positive predictive value of 64%. For the FHR reactivity, the corresponding results were 17%, 97%, and 69%, respectively. The values for the Fischer score results were 36%, 88%, and 58%, respectively. In this study, the umbilical arterial S/D ratio appeared to be more sensitive but less specific than the electronic FHR monitoring techniques. Farmakides and others investigated the diagnostic efficacy of the nonstress test (NST) and of the umbilical arterial S/D ratio in 140 pregnancies (49). The measures of outcome included FGR, fetal distress, cesarean section for fetal distress, and

Table 2 Diagnostic Efficacy of Umbilical Arterial Doppler in Intrauterine Growth Retardation

Investigators	Doppler index	Prevalence rate (%)	Sensitivity (%)	Specificity (%)	Positive predictive value (%)
Fleischer et al. (1985)	S:D >3.0	16.8	78	83	49
Arduini et al. (1987)	PI >1SD	30.7	60.8	73	50
Berkowitz et al. (1988)	S:D >3.0	25	55	92	73
Divon et al. (1988)	S:D >3.0	35.4	49	94	81
Gaziano et al. (1988)	S:D >4.0	9.4	79	66	79
Ott (1990)	S:D >3.0	10.4	59	84	29
Maulik et al. (1990)	S:D >2.9	12.3	75	71	27
Lowery et al. (1990)	S:D >4.0	22.6	65	66	24

Abbreviations: S:D ratio, systolic/diastolic ratio; PI, pulsatility index. Source: From Ref. 34.

Table 3 Association Between Fetal Doppler Results and Fetal Blood Gases

Author (reference)	Patient population	Patient risk category	Cord blood sampling	Doppler assessment	Acid–base parameters	Association correlation
Soothill (39)	29	SGA	Cordocentesis	Aortic MV	pH, PO ₂ , PCO ₂	Present
Nicolaides (40)	59	SGA	Cordocentesis	Umbilical arterial AEDV	pH, PO ₂	Present
Ferrazzi (41)	14	High risk	Cesarean section	Umbilical arterial PI	pH, PCO ₂ lactate	Present
Tyrell (42)	112	Unselected	Cesarean section	Umbilical arterial AEDV	pH, PO ₂	Present
Bilardo (43)	51	SGA, AGA	Cordocentesis	Umbilical arterial, aortic, carotid PI, RI, MV	pH, PO ₂	Present
Vintzileos (44)	62	High risk	Cesarean section	Umbilical arterial S:D	pH	Absent
Yoon (45)	105	Unselected	Cesarean section	Umbilical arterial PI	pH, PO ₂ , PCO ₂	Present
Pardi (46)	21	SGA	Cordocentesis	Umbilical arterial PI lactate	pH, PO ₂ , PCO ₂	Present
Yoon (47)	24	High risk	Cordocentesis	Umbilical arterial PI	pH, PO ₂ , PCO ₂	Present

Abbreviations: SGA, small for gestational age; AGA, appropriate for gestational age; AEDV, absent end-diastolic velocity; MV, mean velocity; PI, pulsatility index; RI, resistance index; S:D, systolic diastolic ratio. Source: From Ref. 1.

admission to the neonatal intensive care unit. Fetuses with a normal NST but abnormal S/D ratio had an outcome worse than those with an abnormal NST and a normal S/D ratio; however, those with both tests abnormal experienced the worst outcome.

Maulik and coworkers studied the diagnostic efficacy of the umbilical arterial S/D ratio for predicting adverse perinatal outcome in 350 high-risk pregnant patients utilizing the ROC technique and other traditional parameters of testing a test (50). The latter included sensitivity, specificity, and the predictive values. The kappa index was used to investigate the degree of agreement between the test and the outcome. The abnormal outcome parameters included SGA (<10th percentile), Apgar score at 5 minutes >7, fetal distress (late and severe variable decelerations, absent variability, fetal scalp pH <7.20), umbilical cord arterial pH <7.20, presence of thick meconium, and admission to neonatal intensive care unit for more than 48 hours. The study indicated that the ratio predicted the general adverse perinatal outcomes well; however, the diagnostic efficacy was better when the SGA infants were excluded (Table 4).

Low-Risk Pregnancies

Although the above findings are very encouraging, there are a few recent reports that demonstrate the inadequate efficacy of Doppler velocimetry of the UA as a screening test in a general obstetric population at a low risk for adverse perinatal outcome. In a large prospective study involving 2097 singleton pregnancies, Beattie and Dornan evaluated the capability of umbilical arterial Doppler indices (PI, A/B ratio, RI) to detect FGR and perinatal compromise (52). It was noted that the indices did not adequately predict any of the parameters of adverse perinatal outcome. The suboptimal efficacy of umbilical Doppler insonation in a low-risk population has been corroborated by others (53). Beattie and associates (54) performed Bayesian analysis of the above four studies to determine the posttest probability of an abnormal outcome for an individual patient. The posttest probabilities of an adverse

outcome was determined for an individual in terms of positive and negative likelihood ratios and are summarized in Table 5. It is evident that umbilical arterial Doppler velocimetry is of limited utility in a low-risk obstetric population. Clinical effectiveness of UA Doppler as a screening test in low-risk pregnancies is discussed later.

Significance of AEDV in the UA

Absence or reversal of end-diastolic flow velocity (Fig. 8) is associated with markedly adverse perinatal outcome including a high perinatal mortality rate with a higher prevalence of chromosomal abnormalities (especially trisomy 13, 18, and 21) and congenital anomalies. In the European multicenter study involving 245 cases with absent or reversed end-diastolic flow, the perinatal mortality was 28% and 96% to 98% of the infants required intensive care (55). In a review of 1126 cases of absent and reverse end-diastolic flow in the UA reported in the literature, it was observed that 170 per 1000 were stillborn and 280 per 1000 died during the neonatal period (Table 6) (56). Most deaths were due to obstetric complications such as growth restriction, prematurity, fetal anomalies, and aneuploidy. The perinatal mortality corrected for congenital malformations and chromosomal abnormalities was approximately 340 per 1000 births. This group demonstrates a high risk of chromosomal abnormalities with a predominance of trisomy 13, 18, and 21. There is also a high association between absent end-diastolic flow and a variety of congenital anomalies (Table 7). The frequency of absent end-diastolic flow is approximately 2% in well-defined high-risk pregnancies and may be as low as 0.3% in a general obstetric population.

In a prospective study involving pregnancies with FGR, Baschat and associates (58) investigated the relationship between fetal Doppler (UA, middle cerebral artery, and ductus venosus), biophysical profile score (BPP), and neurodevelopmental outcome at 2 years of age. Of the various fetal tests, only the UA reverse end-diastolic flow independently predicted poor neurodevelopment.

Table 4 Diagnostic Efficacy of Systolic/Diastolic Ratio Cutoff Point of 3.0 to Predict the Various Abnormal Outcomes

Category	Sensitivity	Specificity	Positive predictive value	Negative predictive value	Kappa index
General abnormal outcome	0.79	0.93	0.83	0.91	0.73
SGA only	0.75	0.77	0.32	0.95	0.33
Fetal distress, Apgar, pH, NICU	0.86	0.88	0.68	0.96	0.69
Fetal distress, Apgar, pH, NICU, and meconium	0.82	0.92	0.81	0.92	0.74

Abbreviations: NICU, neonatal intensive care unit admission; SGA, small for gestational age. Source: From Ref. 51.

Table 5 Posttest Probability of an Adverse Outcome and Umbilical Arterial Doppler in Low-Risk Pregnancies: a Summary of Four Studies

Outcome	Positive likelihood ratio	Negative likelihood ratio
Small for gestational age (birth weight <10th centile)	+1.1 to +4.2	-0.8 to -1.0
Adverse perinatal outcome (Apgar <7 at 1 min, umbilical arterial pH <7.2, operative delivery for fetal distress, abnormal fetal heart rate)	+1.0 to +3.1	-0.9 to -1.0

Source: From Ref. 54.

Figure 8 Doppler sonography depicting reverse end-diastolic flow in the umbilical artery (vertical arrows). The upper panel shows the two-dimensional image of the umbilical artery and the directed placement of the Doppler sample volume. Color flow in the cord is shown in gray scale.

Table 6 Absent and Reverse End-Diastolic Frequency in the Umbilical Artery and Adverse Perinatal Outcome		
Perinatal outcome	Mean	Range
Perinatal mortality	45%	17–100%
Gestational age	31.6 weeks	29–33 weeks
Birth weight	1056 g	910–1481 g
Small for gestational age	68%	53–100%
Cesarean section for fetal distress	73%	24–100%
Apgar score at 5 min <7	26%	7–69%
Admission to neonatal intensive care unit	84%	77–97%
Congenital anomalies	10%	0–24%
Aneuploidy	6.4%	0–18%

Source: From Ref. 34.

It has been observed that absent end-diastolic flow may improve, although often only transiently, and that weeks or more may elapse before the fetus may show additional evidence of compromise especially in preterm pregnancies. Thus, this finding is not necessarily an immediate indication for delivery in pregnancies before 34 weeks if fetal surveillance tests, such as the NST or biophysical profile, are reassuring (see “Guidelines for clinical practice” below).

OTHER FETAL SURVEILLANCE TESTS

Doppler sonography of ductus venosus, middle cerebral artery, and uterine artery has shown significant screening or diagnostic efficacy in high-risk pregnancies. However, their clinical effectiveness has not been adequately demonstrated by randomized trials. Ductus venosus Doppler does provide an additional tool for assessing serious fetal compromise (59).

Table 7 Absent End-Diastolic Velocity and Congenital Malformations	
Cardiovascular system	
Ventricular septal defects	
Hypoplastic left heart syndrome	
Double-outlet right ventricle	
Ebstein anomaly	
Arrhythmia—congenital heart block	
Central nervous system	
Hydrocephaly	
Holoprosencephaly	
Agenesis of corpus callosum	
Urogenital system	
Renal agenesis	
Hydronephrosis	
Gastrointestinal system/abdominal wall	
Esophageal atresia	
Omphalocele	
Gastroschisis	
Skeletal system	
Polydactyly	
Dysplasia	

Source: From Ref. 57.

The effectiveness of ductus venosus Doppler is under investigation at present in a multicenter randomized trial known as “Trial of Umbilical and Fetal Flow in Europe” (TRUFFLE), which is in the process of completion (60).

Current standard of practice for fetal monitoring includes antepartum FHR monitoring and fetal biophysical profile (BPP) or its modifications. The most common FHR monitoring technique is NST. The five-parameter BPP remains the main approach; however, modifications of this test have been proposed. Although diagnostic efficacy of NST and BPP has been demonstrated over the decades, there is insufficient evidence for their effectiveness in improving the outcome (61,62). Their usefulness has been shown in clinical experience and they remain an essential part of the standard of practice in fetal surveillance.

It may be more prudent to use multiple tests of fetal well-being in high-risk pregnancies. Fetal response to chronic stress progresses from compensation to decompensation and involves multiple systems. However, there is no consensus in clinical practice at present regarding the optimal choice or sequence of fetal testing.

CLINICAL EFFECTIVENESS OF DOPPLER VELOCIMETRY FOR FETAL SURVEILLANCE
Randomized Trials

Introduction of a new diagnostic test involves sequential and often parallel developmental processes that transform the potential of a new technique into an effective diagnostic tool making a measurable improvement in the outcome. The steps include the demonstration of feasibility, association with disease processes, and diagnostic efficacy of the technique, but in the end it must be shown without bias that the technique improves the clinical outcome. This level of effectiveness can be demonstrated only by RCTs.

It is encouraging that at the time of the writing of this revised chapter, 20 RCTs on fetal Doppler ultrasound have

Table 8 Published Randomized Trials of Umbilical Artery Doppler Ultrasound in High-Risk, Low-Risk, and Unselected Populations

Reference	Population (risk category)	Doppler index	Doppler in controls	Better outcome
Trudinger et al. (1987). Lancet 1:188	300 (High risk)	UA S/D	Concealed	Yes
Tyrrell et al. (1990). Br J Obstet Gynaecol 97:909	500 (High risk)	UA S/D Ut S/D	Selective	Yes
Hofmeyr et al. (1991). Obstet Gynecol 78:359	897 (High risk)	UA S/D	Selective	No
Newnham et al. (1991). Br J Obstet Gynaecol 98:956	505 (High risk)	UA S/D Ut S/D	Concealed	No
Alstrom et al. (1992). Lancet 340:936	426 (High risk)	UA BFC	No Doppler	Yes
Davies et al. (1992). Lancet 340:1299	2475 (Unselected)	UA S/D Ut S/D	No Doppler	No
Mason et al. (1993). Br J Obstet Gynaecol 100:130	2025 (Unselected)	UA S/D	No Doppler	No
Johnstone et al. (1993). Br J Obstet Gynaecol 100:733	2289 (High risk)	UA RI	No Doppler	No
Newnham et al. (1993). Lancet 342–887	2834 (Unselected)	UA S/D Ut S/D	Selective	No
Omtzigt et al. (1994). Am J Obstet Gynecol 170:625	1598 (Unselected)	UA S/D	No Doppler	Yes
Pattinson et al. (1994). Br J Obstet Gynaecol 101:114	212 (High risk)	UA S/D	Concealed	Yes
Whittle et al. (1994). Am J Obstet Gynecol 170:555	2986 (Unselected)	UA S/D	Concealed	Yes
Nienhuis et al. (1997). Ultrasound Obstet Gynecol 9:6	150 (High risk)	UA PI	Concealed	No
Doppler French Study Group (1997). Br J Obstet Gynaecol 104:419	4187 (Low risk)	UA RI	No Doppler	No
Haley et al. (1997). Br J Obstet Gynaecol 104:431	150 (High risk)	UA S/D	No Doppler	No
Ott et al. G (1998). Am J Obstet Gynecol 178:1346	665 (High risk)	UA S/D / MCA S/D	11% UA S/D	Yes
McCowan et al. (2000). Am J Obstet Gynecol 182:81	167 (High risk)	UA RI	MCA RI Ut A RI	No
Williams et al. (2003). Am J Obstet Gynecol 188:1366	1340 (High risk)	UA S/D	No	Yes
The GRIT Study Group. (2003). Br J Obstet Gynaecol 110:27	547 (High risk)	UA EDV	Posttest randomization	No
Giles et al. (2003). Br J Obstet Gynaecol 110:593	526 (Twins)	UA S/D	No Doppler	No

Abbreviations: BFC, blood flow classes; EDV, end-diastolic flow velocity; MCA, middle cerebral artery; PI, pulsatility index; RI, resistance index; S/D, systolic/diastolic ratio; UA, umbilical artery; Ut, uterine artery. *Source:* From Ref. 64.

been published involving a total population of almost 25,000 women. A detailed review of these studies is available elsewhere (63) and summarized in Table 8. Additional trials were reported only in the abstract form or as presentations. As noted before, the multicenter randomized trial TRUFFLE study has completed the enrollment and is awaiting further analysis and eventual publication.

It is noteworthy that most trials performed in high-risk populations showed improved outcome. As observed previously, fetal Doppler ultrasound is the only fetal surveillance modality that is supported by this level of evidence of effectiveness. All the RCT studies evaluated umbilical arterial velocimetry; a few also used uterine arterial velocimetry. While most were conducted in high-risk patients, many were used in low-risk mothers. Considerable heterogeneity exists among the trials regarding the selection criteria, the study design, and the measures of pregnancy outcome. Most studies did not have any protocol of management based on the test results. Finally, none of the studies had adequate sample size and therefore lacked sufficient power. Depending on the choice of the outcome parameter and the effect size, it will probably require thousands of patients involving multiple centers to conduct such a study. It would be a tremendous

challenge to organize and obtain sufficient resources for a trial of this magnitude.

Several meta-analyses or systemic reviews of the Doppler trials have been conducted and are briefly summarized below.

Meta-analysis of Doppler Trials

Alfirevic and Neilson conducted a systematic review of 12 studies selected out of 20 identified studies and observed a 38% decline in the odds of perinatal mortality, which was significant (95% CI 15–55%) (65). Additional benefits of the Doppler usage included significant reductions in antenatal admissions, inductions of labor, and cesarean sections for fetal distress. Maulik briefly reported a meta-analysis that looked only at trials involving high-risk pregnancies where there were guidelines for the use of Doppler data in the clinical management (66). Only three studies were identified with a total of 1575 patients. An average of 80% reduction in fetal deaths without malformations was noted (odds ratio 0.19, 95% CI 0.06–0.63).

Westergaard and associates reported a meta-analysis that included only well-defined high-risk pregnancies complicated with FGR or hypertension. Of the 13 trials of Doppler in high-risk pregnancies, only six had defined FGR and/pregnancy hypertension as indications for surveillance. The analysis

showed that in the well-defined trials, there were significantly higher preventable perinatal deaths in the study than that in the control group (50% and 20% respectively) (67).

The most recent Cochrane review (68) included 18 completed trials encompassing over 10,000 patients. The review demonstrated a 29% decrease in perinatal mortality, which was significant with a risk ratio (RR) of 0.71 and a 95% CI of 0.53 to 0.98. This meant that 203 women needed to be treated for preventing one perinatal death. There were also less impressive but significant decreases in inductions of labor (RR 0.89, 95% CI 0.80–0.99) and cesarean deliveries (RR 0.90, 95% CI 0.84–0.97). No significant effects were noted in operative vaginal deliveries or Apgar scores <7 at 5 minutes.

In conclusion, most randomized trials of UA Doppler in high-risk pregnancies and their meta-analysis demonstrated a clinically and statistically significant improvement in the perinatal mortality. This constituted a level I evidence of effectiveness and that makes it unique among the other fetal surveillance tests.

Low-Risk Pregnancies

In contrast to high-risk pregnancies, trials of UA Doppler as a screening test in low-risk pregnancies did not show any improvement in pregnancy outcome. For example, a multicenter French randomized trial involving 4187 low-risk pregnant mothers failed to observe any improvements in the outcome with routine UA Doppler sonography between 28 and 34 weeks of gestation (69). Goffinet and coworkers conducted a systematic review of four trials selected out of seven studies and found no impact of UA Doppler on perinatal mortality in 11,451 low-risk pregnant mothers (odds ratio 0.51, 95% CI 0.20–1.29) (70). The Cochrane review of the topic in 2007 that included five trials with a total population of 14,338 women found no benefits of routine Doppler sonography in pregnancy (71). Moreover, the possibility of adverse outcome as suggested in two studies needs further investigation. In conclusion, routine Doppler ultrasound in low-risk pregnancies should be discouraged in clinical practice unless it is conducted under an approved experimental protocol.

Fetal Doppler in Multiple Pregnancy

The efficacy of Doppler velocimetry for identifying twin growth restriction has been variable with the sensitivity ranging from 29% to 82% (72). Fetal biometry remains the standard for the diagnosis of discordant twins. However, significant efficacy in predicting adverse perinatal outcome has been reported. Gaziano and associates (73) observed, in 94 twin pairs and 7 sets of triplets, that an abnormal pulsed Doppler velocimetry showed high correlation with adverse pregnancy events and that those with abnormal Doppler findings tended to be born 3 to 4 weeks earlier and to exhibit a greater number of stillbirths, malformations, and greater morbidity. Giles and coworkers (74) have suggested that the incorporation of the Doppler technique in the clinical management of twins may improve the perinatal outcome. A decline in corrected perinatal deaths from 42.1 in 1000 to 8.9 in 1000 was noted in their study. However, this was not a randomized trial.

A prospective randomized controlled multicenter trial of women with twin pregnancies was conducted that demonstrated

no improvement in the perinatal mortality with the addition of UA Doppler to the standard management (75). The perinatal mortality was 9/1000 live births in the Doppler group and 11/1000 live births in the control group. The study however was underpowered with a total of 526 women. The study did demonstrate that close monitoring in twin gestation is associated with a lower-than-expected fetal mortality in both the control and the Doppler groups.

Quintero and coworkers showed the prognostic value of Doppler of the UA, umbilical vein, and ductus venosus along with other ultrasound findings that constitute the staging of twin transfusion syndrome (76). The staging was proposed for individualizing the treatment options, especially the laser ablation procedure, and has become widely accepted in managing this complication.

In conclusion, fetal Doppler may be beneficial in managing multifetal gestations complicated with twin growth discordancy and those with twin transfusion syndrome. A comprehensive and relatively current review of the Doppler in multiple gestation is available elsewhere (72).

GUIDELINE FOR THE CLINICAL APPLICATION OF THE DOPPLER FETAL SURVEILLANCE

Based upon the above evidence of clinical efficacy of umbilical arterial Doppler indices, the following practical recommendations for its usage in managing high-risk pregnancy are suggested. These guidelines incorporate the existing modalities of fetal surveillance although some investigators advise the use of Doppler as the exclusive primary tool for fetal surveillance. Such a recommendation may not be pragmatic and patho-physiologic evidence suggests a more comprehensive approach for fetal surveillance.

Indications for Doppler Fetal Surveillance

Common indications for performing Doppler surveillance of the fetus at risk for chronic nutritive and respiratory stress are listed in Table 9 and are discussed below.

A variety of pregnancy complications such as FGR and pre-eclampsia can cause fetal stress. As discussed above, randomized trials have shown significant improvement in the rate of perinatal mortality in pregnancies complicated with clearly

Table 9 Indications for Umbilical Arterial Doppler Velocimetry
Primary indications
Fetal growth restriction by ultrasound fetal biometry (estimated fetal weight <10th centile)
Pre-eclampsia
Primary
Superimposed
Multiple gestation
Discordancy
Fetal growth restriction
Twin transfusion syndrome
Extended indications
Autoimmune vascular disease: SLE, APL syndrome
Pregestational diabetes: ≥ class C or vasculopathy
Sickle cell disease
Abbreviations: SLE, systemic lupus erythematosus; APL, antiphospholipid.
Source: From Ref. 77.

defined FGR and hypertension. Although umbilical arterial Doppler has been recommended in the past for prenatal diagnosis of FGR, sonographic biometry is a better predictor of fetal size. Although the indices may be helpful in distinguishing a growth-restricted fetus from a constitutionally SGA fetus, there is a dearth of evidence guiding how this should be translated into a clinical management policy.

UA Doppler is helpful in recognizing fetal compromise in multiple pregnancies, particularly in those with discordant growth and twin transfusion syndrome. Current recommendations include the use of UA and ductus venosus Doppler for classifying the severity of fetal compromise in twin transfusion syndrome, known as the Quintero staging system, which assists in guiding the management options. Doppler velocimetry may also be useful in managing pregnancies affected by autoimmune disorders including systemic lupus erythematosus and antiphospholipid syndrome; however, its effectiveness is uncertain in the absence of fetal growth compromise. Finally, the utility of umbilical arterial Doppler in managing postdated pregnancies remains unproven.

Technique of Umbilical Arterial Doppler Interrogation

Before Doppler examination, the mother is appropriately counseled regarding the reason for the test, the nature of the information generated by the device, its reliability and safety, and other relevant issues. Similar to the procedure in FHR monitoring, the mother lies in a semirecumbent position with a slight lateral tilt to minimize the risk of significant caval compression. Examination should be conducted only during fetal apnea and in the absence of fetal hiccup or excessive movement. Doppler insonation can be performed by either a

continuous-wave Doppler device or a pulsed Doppler duplex system; the latter is preferred for the UA.

With a pulsed-wave duplex Doppler system, an obstetric scan is initially performed to identify the loops of the cord (Fig. 9). Unlike the continuous-wave mode, the pulsed-wave Doppler insonation permits selection of the location in the umbilical cord for interrogation. Usually a free-floating loop of the cord is insonated. The cursor line representing the beam path is aligned to intersect the umbilical vessels at the selected location and the Doppler sample volume is placed in that location. The Doppler mode is then activated and the Doppler waveforms are recorded and analyzed.

Management of High-Risk Pregnancy Using Doppler Sonography

Principles of managing a high-risk pregnancy utilizing UA Doppler velocimetry in conjunction with other fetal surveillance test findings are described in this section. Management of high-risk pregnancies where fetal Doppler is indicated depends on several factors including the severity of fetal compromise as indicated by the Doppler and other fetal tests, and the underlying obstetric conditions such as pre-eclampsia, the gestational age, and the presence of fetal aneuploidy and malformations. These are further discussed below.

(i) Initial fetal assessment should rule out malformations. Such screening ultrasound is now in common practice and is typically performed at mid-pregnancy. If indicated, fetal karyotype should be determined especially in early-onset growth restriction with absent end-diastolic flow in the UA or with the presence of positive ultrasound or screening indicators. For those with FGR, appropriate follow-up growth

Figure 9 Duplex Doppler interrogation of the umbilical arterial flow. The upper panel shows gray scale and color (gray scale in the figure) depiction of the umbilical flow. The Doppler sample volume is placed in a free loop of the umbilical cord. The lower panel shows spectral Doppler waveforms from the umbilical artery. Cursors demonstrate the peak systolic and the end-diastolic velocity points in the wave. The inset shows the corresponding values and the Doppler indices.

scan should be performed according to the prevailing standard of practice (usually 3–4 weeks interval).

(ii) Fetal surveillance should be multimodal including UA Doppler and full or modified biophysical profile. FHR pattern should also be used using the traditional NST or the computerized cardiotocography (cCTG). The frequency of these should be usually once a week. Daily fetal movement assessment by the mother may be added to this list. Many would also advise the incorporation of the ductus venosus Doppler.

(iii) As abnormal elevation of the umbilical arterial Doppler indices usually precedes ominous changes in other tests, a high or increasing UA Doppler index (S/D, RI, or PI) warrants more intense fetal surveillance, which consists of biweekly umbilical Doppler, and FHR monitoring (NST or cCTG) or the BPP. There is considerable variability in the choice, frequency, and sequence of these tests. As the fetal compromise involves multiple systems, it is more prudent to use a combination of tests rather than sequence of single tests.

If these tests are assuring, fetal surveillance should continue unless intervention is indicated because of other complications. On the other hand, if these tests are ominous, delivery should be planned.

(iv) The development of AEDV in the UA indicates more urgent action as it is associated with an unusually adverse perinatal outcome.

Preterm pregnancies: In preterm pregnancies greater than 28 weeks but less than 34 weeks of gestation, when the risk of fetal lung immaturity is high, the management is conservative and further assurance of fetal well-being should be sought from daily surveillance by the UA Doppler and other fetal tests. Steroids should be administered for enhancing fetal lung maturity.

Delivery is recommended in the presence of ominous signs that include the reversal of UA end-diastolic flow by Doppler, non-reassuring FHR patterns (nonreactive NST, poor FHR baseline variability by NST or cCTG, persistent late decelerations), oligohydramnios, BPP score <4, and reversal or absence of the “a” wave of the ductus venosus Doppler. In many tertiary perinatal centers with the availability of advanced neonatal care, the threshold may be lowered to 32 weeks. A more conservative approach is advised in pregnancies less than 32 weeks.

There is controversy regarding conservative management versus immediate delivery in very preterm pregnancies. The growth restriction intervention trial project attempted to address this issue in a multicenter trial but failed to demonstrate any difference between immediate and delayed delivery groups (78). A follow-up study investigating the long-term outcome at 2 years showed a trend toward a higher rate of disability with immediate intervention but no differences in the median Griffiths test (79).

If the gestational age is less than 28 weeks, the management remains challenging. The validity of NST and BPP at this stage of gestation is not well established. Doppler of ductus may provide additional useful information, but there is no evidence of its effectiveness in this gestational group.

Term and near-term pregnancy: The development of AEDV should prompt consideration of delivery when fetal lung maturity is anticipated or proven. Although the prudence of

emergency delivery for this complication has been questioned, RCTs and their meta-analyses have shown improved outcome from obstetric interventions based on UA Doppler. It is recommended therefore that the mother should be delivered when this complication develops in a pregnancy at or near term (>34 weeks) when continuation of the pregnancy presents a greater threat to fetal safety and well-being.

Management of delivery: Standard guideline for intrapartum maternal and fetal monitoring in high-risk pregnancies should be followed. There is a higher risk of developing intrauterine asphyxia in fetuses with FGR or other associated complications arising from placental insufficiency. Close fetal surveillance during labor and delivery is therefore mandatory. The mode of delivery is determined by assessing relevant obstetric factors including cervical status, fetal presentation, and the severity of fetal compromise. If reversed end-diastolic velocity develops in the UA, the probability of impending fetal death is very high; therefore, it may be more prudent to deliver the infant promptly by cesarean section rather than to test its tolerance to the rigors of labor induction.

CONCLUSION

Development of Doppler ultrasound has allowed noninvasive assessment of the fetal circulatory state. Hemodynamic, angiomorphologic, and pathophysiologic evidence affirms the rationale for using the method for fetal surveillance. Numerous studies, as reviewed in this chapter, have established the efficacy of abnormal Doppler indices for identifying adverse perinatal outcome in various pregnancy disorders, especially FGR. More importantly, the majority of clinical trials have demonstrated the effectiveness of UA Doppler in improving the perinatal outcome in high-risk pregnancies. The most promising benefit is a significant reduction in preventable perinatal deaths. Current evidence clearly indicates that Doppler velocimetry should be an essential component of antepartum fetal surveillance in high-risk pregnancies especially those with FGR. Clearly, no single testing modality should be regarded as the exclusive method for fetal monitoring as the various fetal monitoring tests reveal different aspects of fetal compromise, often in a complementary manner. The recommendations in this chapter do not provide a solution for every contingency that may develop in the course of a high-risk pregnancy. The physician must individualize the care in light of the myriad of variations in the clinical situation. The information presented in this chapter should be used as a pragmatic guideline that integrates the new modality with the existing standards of fetal surveillance. As new evidence accumulates and experience grows, evidence-based integration of the various modalities of fetal monitoring in appropriate sequence and frequency will add further refinement to this plan of management.

REFERENCES

1. Maulik D. Doppler Ultrasound in Obstetrics and Gynecology, 2nd edn. Springer, 2005.
2. Doppler C. Über das farbige Licht der Dopplesterne und einiger anderer Gestirne des Himmels. Abhandl Konigl Bohm Ges Ser 1843; 2: 465–82.

3. Maulik D. Doppler sonography: a brief history. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*, 2nd edn. Springer, 2005: 1–7.
4. FitzGerald DE, Drumm JE. Noninvasive measurement of the fetal circulation using ultrasound: a new method. *BMJ* 1977; 2: 1450–1.
5. Maulik D, Saini VD, Nanda NC, Rosenzweig MS. Doppler evaluation of fetal hemodynamics. *Ultrasound Med Biol* 1982; 8: 705.
6. Maulik D, McNellis D, eds. *Doppler Ultrasound Measurement of Maternal-Fetal Hemodynamics*. Ithaca, NY: Perinatology Press, 1987.
7. Gill RW. Pulsed Doppler with B-mode imaging for quantitative blood flow measurements. *Ultrasound Med Biol* 1979; 5: 223–7.
8. Eik Nes SH, Brubakk AO, Ulstein MK. Measurement of human fetal blood flow. *Br Med J* 1980; 28: 283–4.
9. Maulik D, Nanda NC, Saini VD. Fetal Doppler echocardiography: methods and characterization of normal and abnormal hemodynamics. *Am J Cardiol* 1984; 53: 572–8.
10. Ferrazzi E, Rigano S. Doppler interrogation of umbilical venous flow. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. Springer, 2005: 443–9.
11. Maulik D, Heitmann E, Maulik D. New horizons in Doppler ultrasound technology: relevance for obstetrical applications. *Clin Obstet Gynecol* 2010; In press.
12. Maulik D, Yarlalagadda P, Youngblood JP, Ciston P. Comparative efficacy of umbilical arterial Doppler indices for predicting adverse perinatal outcome. *Am J Obstet Gynecol* 1991; 164: 1434.
13. Gosling RG, King DH. Ultrasound angiology. In: Marcus AW, Adamson J, eds. *Arteries and Veins*. Edinburgh: Churchill Livingstone, 1975: 61.
14. Pourcelot L. Applications cliniques de l'examen Dopple transcutane: velocimetrie ultrasonore Doppler. In: Pourcelot L, ed. *Velocimetrie Ultrasonore Doppler*. Semin INSERM 1974; 34: 213–40.
15. Stuart B, Drumm J, FitzGerald DE, Duigan NM. Fetal blood velocity waveform in normal and complicated pregnancy. *Br J Obstet Gynaecol* 1980; 87: 780–5.
16. Maulik D, Yarlalagadda P, Youngblood JP, Ciston P. Comparative efficacy of the umbilical arterial Doppler indices for predicting adverse perinatal outcome. *Am J Obstet Gynecol* 1991; 164: 1434–40.
17. Maulik D, Saini VD, Nanda NC, Rosenzweig MS. Doppler evaluation of fetal hemodynamics. *Ultrasound Med Biol* 1982; 8: 705–10.
18. Thompson RS, Trudinger JB, Cook CM. Doppler ultrasound waveforms in the fetal umbilical artery: quantitative analysis technique. *Ultrasound Med Biol* 1985; 11: 707–14.
19. Westerhof N, Sipkema P, Van den Bos GC, Elzinga G. Forward and backward waves in the arterial system. *Cardiovasc Res* 1972; 6: 648–56.
20. Nichols WW, O'Rourke MF, Avolio AP. Age related changes in left ventricular/arterial coupling. In Yin FCP, ed. *Ventricular/Vascular Coupling*. New York: Springer Verlag, 1987: 79.
21. Downing GJ, Yarlalagadda AP, Maulik D. Comparison of the pulsatility index and input impedance parameters in a model of altered hemodynamics. *J Ultrasound Med* 1991; 10: 317–21.
22. Maulik D. Hemodynamic interpretation of the arterial Doppler waveform. *Ultrasound Obstet Gynecol* 1993; 3: 219.
23. Krebs C, Macara LM, Leiser R, et al. Intrauterine growth restriction with absent end-diastolic flow velocity in the umbilical artery is associated with maldevelopment of the placental terminal villous tree. *Am J Obstet Gynecol* 1996; 175: 1534.
24. Todros T, Sciarra A, Piccoli E, et al. Umbilical Doppler waveforms and placental villous angiogenesis in pregnancies complicated by fetal growth restriction. *Obstet Gynecol* 1999; 93: 499–16, 17.
25. Maulik D. Doppler velocimetry for fetal surveillance: adverse perinatal outcome and fetal hypoxia. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Springer Verlag, 1997: 349.
26. Peeters LLH, Sheldon RE, Jones MD, et al. Blood flow to fetal organs as a function of arterial oxygen content. *Am J Obstet Gynecol* 1979; 135: 637–46.
27. Maulik D, Yarlalagadda AP, Youngblood JP, Willoughby L. Components of variability of umbilical arterial Doppler velocimetry – a prospective analysis. *Am J Obstet Gynecol* 1989; 160: 1406–12.
28. Maulik D. Umbilical arterial Doppler velocimetry: normative data and diagnostic efficacy. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Springer Verlag, 1997: 129.
29. Dawes GS. *Fetal and Neonatal Physiology*. Chicago, IL: Yearbook Medical Publishers, 1968: 66.
30. Maulik D. Basic principles of Doppler ultrasound as applied to obstetrics. *Clin Obstet Gynecol* 1989; 32: 641.
31. Yarlalagadda AP, Willoughby L, Maulik D. Effect of fetal heart rate on umbilical arterial Doppler indices. *J Ultrasound Med* 1989; 8: 215–18.
32. Maulik D, Downing GJ, Yarlalagadda AP. Umbilical arterial Doppler indices in acute uteroplacental flow occlusion. *Echocardiography* 1990; 7: 619–27.
33. van Eyck J, Wladimiroff JW, van den Wijngaard JA, et al. The blood flow velocity waveform in the fetal internal carotid and umbilical artery; its relationship to fetal behavioral states in normal pregnancy at 37–38 weeks of gestation. *Br J Obstet Gynaecol* 1987; 94: 736–41.
34. Maulik D. Doppler in ultrasound in Obstetrics. In: Cunningham FG, et al., eds. *Williams' Obstetrics*, 19th edn. Stamford CT: Appleton & Lange, 1995.
35. Nicolaides KH, Bilardo CM, Soothill PW, et al. Absence of end diastolic frequencies in umbilical artery: a sign of fetal hypoxia and acidosis. *Br Med J* 1988; 297: 1026–7.
36. Chambers SE, Hoskins PR, Haddad NG, et al. A comparison of fetal abdominal circumference measurements and Doppler ultrasound in the prediction of small-for-dates babies and fetal compromise. *Br J Obstet Gynaecol* 1989; 96: 803–8.
37. Cohn H, Sachs E, Heymann M, Rudolph A. Cardiovascular responses to hypoxemia and acidemia in fetal lambs. *Am J Obstet Gynecol* 1974; 120: 817–24.
38. Hasaart THM, Maulik D, Morrow RJ. Validation of fetal flow velocimetry: a review of in vitro and in vivo modeling. *J Matern Fetal Invest* 1993; 3: 95–104.
39. Malcus P, Hokegard KH, Kjellmer I, et al. The relationship between arterial blood velocity waveforms and acid–base status in fetal lamb during acute experimental asphyxia. *J Matern Fetal Invest* 1991; 1: 29–34.
40. Soothill PW, Nicolaides KH, Bilardo CM, Campbell S. Relation of fetal hypoxia in growth retardation to mean blood velocity in the fetal aorta. *Lancet* 1986; 2: 1118–20.
41. Ferrazzi E, Pardi G, Bauscaglia M. The correlation of biochemical monitoring versus umbilical flow velocity measurements of the human fetus. *Am J Obstet Gynecol* 1988; 159: 1081–7.
42. Tyrrell S, Obaid AH, Lilford RJ. Umbilical artery Doppler velocimetry as a predictor of fetal hypoxia and acidosis at birth. *Obstet Gynecol* 1989; 74: 332–7.
43. Bilardo CM, Nicolaides KH, Campbell S. Doppler measurements of fetal and uteroplacental circulations: relationship with umbilical venous blood gases measured at cordocentesis. *Am J Obstet Gynecol* 1990; 162: 115–20.
44. Vintzileos AM, Campbell W, Rodis J, et al. The relationship between fetal biophysical assessment, umbilical artery velocimetry, and fetal acidosis. *Obstet Gynecol* 1991; 77: 622–6.
45. Yoon BH, Syn HC, Kim SW. The efficacy of Doppler umbilical velocimetry in identifying fetal acidosis. A comparison with fetal biophysical profile. *J Ultrasound Med* 1992; 11: 1–6.
46. Pardi G, Cetin I, Marconi AM, et al. Diagnostic value of blood sampling in fetuses with growth retardation. *N Engl J Med* 1993; 328: 692–6.
47. Yoon BH, Romero R, Roh CR, et al. Relationship between the fetal biophysical profile score, umbilical artery Doppler velocimetry, and fetal blood acid–base status determined by cordocentesis. *Am J Obstet Gynecol* 1993; 169: 1586.
48. Trudinger BJ, Cook CM, Jones L, Giles WB. A comparison of fetal heart rate monitoring and umbilical artery waveforms in the recognition of fetal compromise. *Br J Obstet Gynaecol* 1986; 93: 171.
49. Farmakides G, Schulman H, Winter D, et al. Prenatal surveillance using non-stress testing and Doppler velocimetry. *Obstet Gynecol* 1988; 71: 184.
50. Maulik D, Yarlalagadda AP, Youngblood JP, Ciston P. Efficacy of umbilical arterial Doppler velocimetry in predicting adverse perinatal outcome: a prospective study. *Am J Obstet Gynecol* 1990; 162: 1518.
51. Maulik D, Yarlalagadda P, Youngblood JP, Ciston P. The diagnostic efficacy of the umbilical arterial systolic/diastolic ratio as a screening tool: a prospective blinded study. *Am J Obstet Gynecol* 1990; 162: 1518.
52. Beattie RB, Dornan JC. Antenatal screening for intrauterine growth retardation with umbilical artery Doppler ultrasonography. *Br Med J* 1989; 298: 631.

53. Hanretty KP, Primrose MH, Neilson JP, Whittle MJ. Pregnancy screening by Doppler uteroplacental and umbilical waveforms. *Br J Obstet Gynaecol* 1989; 96: 1163–7.
54. Beattie RB, Hannah ME, Dornan JC. Compound analysis of umbilical artery velocimetry in low-risk pregnancy. *J Matern Fetal Invest* 1992; 2: 269.
55. Karsdorp VH, van Vugt JM, van Geijn HP, et al. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet* 1994; 344: 1664–9.
56. Maulik D, Figueroa R. Absent end diastolic velocity in the umbilical artery and its clinical significance. In: Maulik D, Zalud I, eds. *Doppler Ultrasound in Obstetrics and Gynecology*. Springer, 2005: 375–86.
57. Maulik D. *Doppler Ultrasound in Obstetrics and Gynecology*. New York: Springer-Verlag, 1997.
58. Baschat AA, Viscardi RM, Hussey-Gardner B, Hashmi N, Harman C. Infant neurodevelopment following fetal growth restriction: relationship with antepartum surveillance parameters. *Ultrasound Obstet Gynecol* 2009; 33: 44–50.
59. Turan S, Turan OM, Berg C, et al. Computerized fetal heart rate analysis, Doppler ultrasound and biophysical profile score in the prediction of acid-base status of growth-restricted fetuses. *Ultrasound Obstet Gynecol* 2007; 30: 750–6.
60. Current Controlled Trials. ISRCTN56204499, Lancet protocol 02PRT/34, revised 2007: Trial of umbilical and foetal flow in Europe.
61. Grivell RM, Alfirevic Z, Gyte GM, Devane D. Antenatal cardiotocography for fetal assessment. *Cochrane Database Syst Rev* 2010: CD007863.
62. Lalor JG, Fawole B, Alfirevic Z, Devane D. Biophysical profile for fetal assessment in high risk pregnancies. *Cochrane Database Syst Rev* 2008: CD000038.
63. Maulik D, Figueroa R. Doppler velocimetry for fetal surveillance. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. Springer, 2005: 161–76.
64. Maulik D, Figueroa R. Doppler velocimetry for fetal surveillance: randomized clinical trials and implications for practice. In: Maulik D, ed. *Doppler Ultrasound in Obstetrics and Gynecology*. Springer, 2005: 387–402.
65. Alfirevic Z, Nielson JP. Doppler ultrasonography in high risk pregnancies: systematic reviews with meta-analysis. *Am J Obstet Gynecol* 1995; 172: 1379–87.
66. Maulik D, Figueroa R, Sicuranza G, Garry D. Doppler fetal surveillance in clinical practice: evidence based guidelines. *J Fertil Reprod* 1998; SE 2: 5–6.
67. Westergaard HB, Langhoff-Roos J, Lingman G, Marsal K, Kreiner S. A critical appraisal of the use of umbilical artery Doppler ultrasound in high risk pregnancies: use of meta-analyses in evidence-based obstetrics. *Ultrasound Obstet Gynecol* 2001; 17: 466–76.
68. Alfirevic Z, Stampalija T, Gyte GM. Fetal and umbilical Doppler ultrasound in high risk pregnancies. *Cochrane Database Syst Rev* 2010: CD007529.
69. Doppler French Study Group. A randomised controlled trial of Doppler ultrasound velocimetry of the umbilical artery in low risk pregnancies. *Br J Obstet Gynaecol* 1997; 104: 419–22.
70. Goffinet F, Paris-Llado J, Nisand I, Breart G. Umbilical artery Doppler velocimetry in unselected and low risk pregnancies: a review of randomised controlled trials. *Br J Obstet Gynaecol* 1997; 104: 425–30.
71. Bricker L, Neilson JP. Routine Doppler ultrasound in pregnancy. *Cochrane Database Syst Rev* 2007: CD001450.
72. Gaziano E, Harkness EF. Doppler velocimetry and multiple gestation. In: Maulik D, ed. *Doppler ultrasound in obstetrics and gynecology*, 2nd edn. Springer, 2005.
73. Gaziano EP, Knox H, Ferrera B, et al. Is it time to reassess the risk for the growth-retarded fetus with normal Doppler velocimetry of the umbilical artery? *Am J Obstet Gynecol* 1994; 170: 1734–41.
74. Giles WB, Trudinger BJ, Cook CM, et al. Umbilical artery flow velocity waveforms and twin pregnancy outcome. *Obstet Gynecol* 1988; 72: 894–7.
75. Giles W, Bisits A, O'Callaghan S, Gill A, DAMP Study Group. The Doppler assessment in multiple pregnancy randomised controlled trial of ultrasound biometry versus umbilical artery Doppler ultrasound and biometry in twin pregnancy. *BJOG* 2003; 110: 593–7.
76. Quintero RA, Morales WJ, Allen MH, et al. Staging of twin-twin transfusion syndrome. *J Perinatol* 1999; 19(8 Pt 1): 550–5.
77. Maulik D, Mundy D, Heitmann E, Maulik D. Evidence based approach to umbilical artery Doppler fetal surveillance in high risk pregnancies: an update. *Clin Obstet Gynecol* (In press).
78. GRIT Study Group. A randomized trial of timed delivery for the compromised preterm fetus: short term outcomes and Bayesian interpretation. *BJOG* 2003; 110: 27–32.
79. GRIT study group. Infant wellbeing at 2 years of age in the Growth Restriction Intervention Trial (GRIT): multicentred randomised controlled trial. *Lancet* 2004; 364: 513–20.