

THE USE OF FETAL DOPPLER IN OBSTETRICS

This guideline has been reviewed by the Diagnostic Imaging Committee and approved by Executive and Council of the Society of Obstetricians and Gynaecologists of Canada.

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Abstract

Objective: To develop national guidelines on the use of fetal Doppler in obstetrics.

Options: Whether umbilical cord artery, umbilical cord venous, ductus venosus, and middle cerebral artery Doppler are useful in assessing fetal health.

Outcome: Prediction of adverse perinatal outcome or prediction of fetal anemia.

Evidence: MEDLINE search and review of bibliographies in identified articles.

Values: The evidence was reviewed by the Diagnostic Imaging Committee and the principal authors. A quality of evidence assessment was undertaken as outlined in the report of the Canadian Task Force on the Periodic Health Examination.

Benefits, harms, and costs: Intrauterine growth restriction complicates 5% to 10% of all pregnancies and up to 30% of multiple pregnancies. In 60% of these pregnancies, the primary cause is placental insufficiency. Improvement in the identification of the fetus at risk of intrauterine demise may lead to more successful management strategies. Management of fetal red blood cell isoimmunization requires a prediction of fetal anemia. If invasive procedures to predict fetal anemia can be replaced with non-invasive tests, fetal morbidity and mortality can be reduced.

Recommendations:

1. Umbilical artery Doppler should be available for assessment of the fetal-placental circulation in pregnant women with suspected severe placental insufficiency. (I-A)

- Depending on other clinical factors, reduced, absent, or reversed umbilical artery end-diastolic flow is an indication for enhanced fetal surveillance or delivery. If delivery is delayed to enhance fetal lung maturity with maternal administration of glucocorticoid, intensive fetal surveillance until delivery is suggested for those fetuses with reversed end-diastolic flow. (II-IB)
- Umbilical artery Doppler should not be used as a screening tool in healthy pregnancies, as it has not been shown to be of value in this group. (I-A)
- Umbilical venous double pulsations, in the presence of abnormal umbilical artery Doppler waveforms, necessitate a detailed assessment of fetal health status. (II-3B)
- Measurement of the fetal middle cerebral artery Doppler peak systolic flow velocity is a predictor of moderate or severe fetal anemia and can be used to avoid unnecessary invasive procedures in pregnancies complicated with red blood cell isoimmunization. (II-1A)
- Since inaccurate information concerning fetal Doppler studies could lead to inappropriate clinical decisions, it is imperative that measurements be undertaken and interpreted by expert operators who are knowledgeable about the significance of Doppler changes and who practise appropriate techniques. Duplex mode with pulsed Doppler and colour Doppler flow mapping is the minimum required ultrasound equipment. (II-1A)

J Obstet Gynaecol Can 2003;25(7):601-7.

Key Words

Fetal Doppler, placental blood flow, placental insufficiency, fetal growth restriction

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PART I: STANDARD ANTENATAL FETAL SURVEILLANCE

INTRODUCTION

Placental insufficiency is the primary cause of intrauterine growth restriction in normally formed fetuses and can be identified using umbilical artery Doppler velocimetry.¹⁻⁴ Umbilical artery Doppler waveforms provide an estimate of downstream placental vascular resistance and placental blood flow.² There is a strong association between reduced end-diastolic umbilical artery blood flow velocity and increased vascular resistance in the umbilical-placental microcirculation.^{5,6} As well, abnormal umbilical artery Doppler waveforms have been associated with an increased risk of fetal acidosis, as measured during cordocentesis,⁷ and may improve the performance of the biophysical profile score in predicting fetal acidemia and hypercarbia.⁸ The use of Doppler during antenatal fetal surveillance has involved assessment of (1) the umbilical arterial and venous flow velocity waveforms, (2) the fetal cerebral circulation, and (3) the fetal venous circulation, in particular the ductus venosus.

ASSESSMENT OF PLACENTAL FUNCTION USING UMBILICAL ARTERY DOPPLER VELOCIMETRY

From 7 to 16 days postconception, the yolk sac develops and early development of the primary chorionic villi takes place. Thereafter, the chorioallantoic placenta develops in stages consisting of invasion of the spiral arteries by endovascular cytotrophoblast, followed by a second wave of invasion that extends into the myometrium. The basic organization of the human placenta is present by approximately day 20 of pregnancy. Further refinement of this basic structure continues until term, at which time there are approximately 50 to 60 primary fetal stem villi branching into several terminal or tertiary villi. The branching of the stem villi and ensuing development of the non-branching placental microcirculation are responsible for a low vascular resistance, the increase in placental blood flow, and the increase in transplacental gas exchange that characterizes human placentation. This low umbilical-placental vascular resistance is also responsible for the elevated end-diastolic blood flow velocity in the umbilical artery seen during the third trimester in a normal pregnancy.^{5,9} A reduction of the branching of the stem villi and a reduction in the development of the nonbranching placental microcirculation result in fewer small arterioles in the tertiary stem villi, along with a thickened fetal-maternal placental interface. This results in abnormally high umbilical-placental vascular resistance,^{2,10,11} a reduction in umbilical blood flow,¹⁰ and chronic fetal hypoxemia.¹¹

With an increase in downstream placental vascular resistance, velocity of the end-diastolic flow in the umbilical cord artery is reduced, while the peak-systolic component is not significantly affected.¹²⁻¹⁴ As a result, several Doppler indices have been used to quantify abnormalities in umbilical artery Doppler flow waveforms, including the A/B ratio, the resis-

tance index or Pourcelot ratio, and the pulsatility index. These indices closely correlate and they can be used interchangeably with similar predictive values for perinatal outcome.^{15,16}

Placental insufficiency can be quantified based on the reduction of end-diastolic Doppler flow velocity into (1) reduced end-diastolic flow velocity, (2) absent end-diastolic flow velocity, and (3) reversed end-diastolic flow velocity. The risk of perinatal mortality increases up to 60%, with increasing severity from reduced to reversed end-diastolic flow velocity.¹⁷⁻³² Therefore, in the presence of umbilical artery reversed end-diastolic flow velocity, delivery by Caesarean section may be considered if fetal viability is achieved.³² This decision will be influenced by the estimated fetal weight, gestational age, other Doppler parameters, and other assessments of fetal health, such as fetal anatomical and chromosomal anomalies.³³ In cases of prematurity, delivery may be delayed for 48 hours, allowing the maximum fetal benefits of maternal administration of glucocorticoids; under such circumstances, continuous fetal heart rate monitoring until delivery should be considered.³⁴

RECOMMENDATION

1. Umbilical artery Doppler should be available for assessment of the fetal-placental circulation in pregnant women with suspected severe placental insufficiency. (I-A)

At an early gestational age, reduced or absent umbilical artery end-diastolic flow velocity is an indication for increased fetal surveillance, but not necessarily for immediate delivery.^{23,35} However, closer to term, severe placental insufficiency, reflected by absent umbilical artery end-diastolic flow velocity, is an indication for delivery. Fetuses with absent umbilical artery end-diastolic flow velocity are more severely growth restricted,^{2,7} are at higher risk of perinatal morbidity and mortality,¹⁹ and require delivery at an earlier gestational age than those with end-diastolic flow.²¹ However, when fetuses are matched for gestational age and birth weight, no differences in perinatal outcome are found in the groups with and without end-diastolic flow velocity.^{24,36} Although absence of end-diastolic flow velocity may not affect long-term neurological outcome, reversal of end-diastolic flow velocity in the umbilical artery is associated with a wide range of problems at school age,³⁷ suggesting that it represents intrauterine decompensation, which may have adverse effects on the developing brain.²⁴

RECOMMENDATION

2. Depending on other clinical factors, reduced, absent, or reversed umbilical artery end-diastolic flow is an indication for enhanced fetal surveillance or delivery. If delivery is delayed to enhance fetal lung maturity with maternal administration of glucocorticoid, intensive fetal surveillance until delivery is suggested for those fetuses with reversed end-diastolic flow. (II-1B)

Randomized clinical trials have demonstrated that the use of umbilical artery velocimetry in high-risk pregnancy (especially those complicated by hypertension or presumed impaired fetal growth) is associated with a trend to a reduction in perinatal deaths (OR 0.71, 95% CI 0.50–1.01).³⁸ The use of Doppler ultrasound was also associated with fewer inductions of labour (OR 0.83, 95% CI 0.74–0.93) and fewer admissions to hospital (OR 0.56, 95% CI 0.43–0.72), without reports of adverse effects.³⁸ In high-risk pregnancies complicated with maternal hypertension, intrauterine growth restriction, or multiple gestation, evidence supports the use of umbilical artery Doppler studies as part of antenatal assessment.³⁸ As there is no evidence that the use of umbilical artery Doppler has value in low-risk pregnancies,³⁹ it should not be used as a screening tool in healthy pregnancies.

RECOMMENDATION

3. Umbilical artery Doppler should not be used as a screening tool in healthy pregnancies, as it has not been shown to be of value in this group. (I-A)

FACTORS AFFECTING UMBILICAL ARTERY DOPPLER VELOCIMETRY

Several factors will affect the umbilical artery Doppler waveform, independent of changes in placental vascular resistance (Table 1). Gestational age-dependent normograms are necessary for accurate interpretation of umbilical cord artery velocimetry.¹⁴ No correction is necessary for fetal heart rate within the normal range.^{40,41} In order to reduce methodological variability, it is recommended that umbilical artery Doppler waveforms be measured within 5 cm of the umbilical cord inser-

tion into the fetal abdomen.⁴² This is particularly important for studies obtained in multiple pregnancy, where cord insertion at the umbilicus is relatively easy to obtain to differentiate individual fetuses.⁴³ The angle of the fetal Doppler insonation should be kept to less than 45° for an optimal umbilical artery Doppler recording. Because of the potential for variability and inaccuracy with fetal Doppler, it is imperative that measurements be undertaken by expert operators who are knowledgeable about the significance of Doppler changes and who practise appropriate techniques. Inaccurate information concerning fetal Doppler studies could lead to inappropriate clinical decisions.

PART II: SPECIAL CONSIDERATIONS

INTRODUCTION

Although the greatest impact on perinatal clinical practice from Doppler research has been the use of umbilical artery Doppler assessment of placental function, there have been an increasing number of observational studies that require special considerations. These fetal Doppler studies include assessment of the fetal venous circulation as a marker of severe fetal hypoxia,⁴⁴⁻⁵¹ prediction of fetal hypoxemia using fetal middle cerebral artery,⁵²⁻⁶⁰ and the prediction of severe fetal anemia using fetal middle cerebral artery Doppler.⁶¹⁻⁶⁴

THE USE OF FETAL VENOUS DOPPLER VELOCIMETRY

Blood flow velocity in the fetal systemic venous circulation has a pulsating pattern that reflects changes in central venous pressure, in particular the filling of the atria during ventricular systole and the opening of the atrio-ventricular valves. At the

TABLE 1

FACTORS AFFECTING UMBILICAL ARTERY DOPPLER FLOW VELOCITY WAVEFORMS*

Gestational age	EDFV ratio increases with advancing gestational age ¹⁵
Fetal heart rate	EDFV decreases with decreasing fetal heart rate ^{13,41}
Fetal breathing movements	Increases variability in the measurements ⁶⁶
Site of measurement	EDFV is higher near the umbilical cord insertion into the fetal abdomen than near the placental insertion ⁶⁷
Equipment used: continuous Doppler versus pulsed Doppler	Continuous Doppler is more a "blind technique" compared with pulsed Duplex Doppler, allowing 2D real time ultrasound ⁶⁸
User experience	Reliability increases with increasing experience ⁶⁹
Radius of the umbilical artery	Decreasing radius (vasoconstriction) increases EDFV ⁷⁰
Impedance to pulsatile flow propagation	Increasing vascular impedance increases EDFV ⁷⁰
Downstream vascular resistance within the microcirculation	Increasing vascular resistance decreases EDFV ⁷⁰⁻⁷²
Angle of the fetal Doppler insonation	Best if less than 45° ⁷³ ; <15° for MCA absolute peak systolic flow velocity ^{62,64}

*EDFV = end diastolic flow velocity; MCA = middle cerebral artery.

end of diastole, a reduction in blood velocity occurs due to atrial contraction. Blood velocities in the umbilical vein and portal circulation are normally continuous and without fluctuation.⁴⁴ Umbilical venous pulsations, particularly double pulsations, have been associated with perinatal mortality rates of up to 16% with absent umbilical artery end-diastolic flow velocity, and 60% with reversed umbilical artery end-diastolic flow velocity.^{44,45} However, it is not known if Doppler assessment of the fetal umbilical venous circulation improves perinatal outcome when compared to assessment of umbilical artery Doppler velocimetry alone.⁴⁶⁻⁴⁹

RECOMMENDATION

4. Umbilical venous double pulsations, in the presence of abnormal umbilical artery Doppler waveforms, necessitate a detailed assessment of fetal health status. (II-3B)

The ductus venosus may play a role in the regulation of venous blood flow between the inferior vena cava and the umbilical vein. Under normoxic conditions, approximately 40% of the umbilical venous blood flow passes through the ductus venosus.⁵⁰ During fetal hypoxemia, the proportion of umbilical venous flow passing through the ductus venosus increases.⁵² It is not clear if this increase is the result of an increase in central venous pressure or due to vasodilatation.⁴⁴ It is reported that a reduction in vascular resistance through the ductus venosus is responsible for retrograde umbilical venous flow velocity leading to umbilical venous pulsations during atrial contraction in the presence of fetal hypoxemia.⁵¹ If umbilical venous pulsations are detected in the absence of fetal breathing movements, careful assessment of fetal health should be considered. Although available in many tertiary centres, further research is needed on the benefit of umbilical venous and ductus venosus Doppler velocimetry before it can be recommended as a standard of care to evaluate high-risk pregnancies.

USE OF MIDDLE CEREBRAL ARTERY VELOCIMETRY TO DETECT FETAL HYPOXIA

The same factors that affect umbilical artery Doppler waveforms can also affect fetal cerebral artery Doppler waveforms.⁵² Fetal behavioural states can also alter cerebral artery waveforms.⁵³⁻⁵⁶ Of interest, an increase in pCO₂ or a reduction in pO₂ will cause an increase in fetal cerebral arterial Doppler end-diastolic flow velocity, likely related to cerebral vasodilatation.⁵⁷⁻⁵⁹ This phenomenon has been described as the “brain sparing” effect.⁶⁰ Although an increase in fetal cerebral end-diastolic Doppler flow velocity may reflect chronic fetal hypoxemia, there is no evidence that this measurement will provide any additional benefit to perinatal outcome beyond the assessment of the umbilical circulation alone.²³

USE OF DOPPLER TO DETECT FETAL ANEMIA

Several noninvasive methods have been suggested to detect fetal anemia. Umbilical vein maximum velocity and middle cerebral artery peak-systolic flow velocity (MCA-PSV) are the most promising methods.^{61,62} A recent systematic review indicated that studies evaluating noninvasive techniques to detect fetal anemia were methodologically poor and lacked a standard approach to evaluate the techniques for fetal hemoglobin prediction.⁶³ However, since then, it has been shown that the MCA-PSV is an accurate predictor of severe fetal anemia in pregnancies complicated by red cell alloimmunization.⁶⁴ Although the correlation between the fetal hemoglobin value and MCA-PSV becomes more accurate as the severity of anemia increases, almost 70% of the cordocentesis needed, using current standard criteria for assessment of fetal hemoglobin, can be avoided.⁶² This approach is likely to decrease the need for cordocentesis and its potential risks.

RECOMMENDATION

5. Measurement of the fetal middle cerebral artery Doppler peak systolic flow velocity is a predictor of severe fetal anemia and can be used to avoid unnecessary invasive procedures in pregnancies complicated with red blood cell isoimmunization. (II-1A)

In order to accurately measure the MCA Doppler waveforms, pulsed Doppler with colour Doppler flow mapping is recommended to visualize the direction of MCA blood flow. Since the MCA-PSV is a measurement of absolute instead of relative velocity, the angle of the fetal Doppler insonation should be kept as close as possible to 0° for accurate estimate of the absolute peak systolic flow velocity. Software-based angle correction cannot be used instead of proper positioning of the transducer since it could lead to erroneous value and interpretation.

RECOMMENDATION

6. Since inaccurate information concerning fetal Doppler studies could lead to inappropriate clinical decisions, it is imperative that measurements be undertaken and interpreted by expert operators who are knowledgeable about the significance of Doppler changes and who practise appropriate techniques. Duplex mode with pulsed Doppler and colour Doppler flow mapping is the minimum required ultrasound equipment. (II-1A)

EVALUATION OF EVIDENCE

The quality of evidence and classification of recommendations reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam (Table 2).⁷⁴

TABLE 2 QUALITY OF EVIDENCE ASSESSMENT ⁷⁴	CLASSIFICATION OF RECOMMENDATIONS ⁷⁴
<p>The quality of evidence reported in these guidelines has been described using the Evaluation of Evidence criteria outlined in the Report of the Canadian Task Force on the Periodic Health Exam.</p> <p>I: Evidence obtained from at least one properly randomized controlled trial.</p> <p>II-1: Evidence from well-designed controlled trials without randomization.</p> <p>II-2: Evidence from well-designed cohort (prospective or retrospective) or case-control studies, preferably from more than one centre or research group.</p> <p>II-3: Evidence obtained from comparisons between times or places with or without the intervention. Dramatic results in uncontrolled experiments (such as the results of treatment with penicillin in the 1940s) could also be included in this category.</p> <p>III: Opinions of respected authorities, based on clinical experience, descriptive studies, or reports of expert committees.</p>	<p>Recommendations included in these guidelines have been adapted from the ranking method described in the Classification of Recommendations found in the Canadian Task Force on the Periodic Health Exam.</p> <p>A. There is good evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>B. There is fair evidence to support the recommendation that the condition be specifically considered in a periodic health examination.</p> <p>C. There is poor evidence regarding the inclusion or exclusion of the condition in a periodic health examination, but recommendations may be made on other grounds.</p> <p>D. There is fair evidence to support the recommendation that the condition not be considered in a periodic health examination.</p> <p>E. There is good evidence to support the recommendation that the condition be excluded from consideration in a periodic health examination.</p>

REFERENCES

- Giles WB, Trudinger BJ, Cook CM. Fetal umbilical artery flow velocity-time waveforms in twin pregnancies. *Br J Obstet Gynaecol* 1985;92:490-7.
- Giles WB, Trudinger BJ, Baird PJ. Fetal umbilical artery flow velocity waveforms and placental resistance: pathological correlation. *Br J Obstet Gynaecol* 1985;92:31-8.
- Lackman F, Capewell V, Gagnon R, Richardson B. Fetal umbilical cord oxygen values and birth to placental weight ratio in relation to size at birth. *Am J Obstet Gynecol* 2001;185:674-82.
- Lackman F, Capewell V, Richardson B, daSilva O, Gagnon R. The risks of spontaneous preterm delivery and perinatal mortality in relation to size at birth according to fetal versus neonatal growth standards. *Am J Obstet Gynecol* 2001;184:946-53.
- Adamson SL. Arterial pressure, vascular input impedance, and resistance as determinants of pulsatile blood flow in the umbilical artery. *Eur J Obstet Gynecol Reprod Biol* 1999;84:119-25.
- Thompson RS, Trudinger BJ. Doppler waveform pulsatility index and resistance, pressure and flow in the umbilical placental circulation: an investigation using a mathematical model. *Ultrasound Med Biol* 1990;16:449-58.
- Yoon BH, Syn HC, Kim SW. The efficacy of Doppler umbilical artery velocimetry in identifying fetal acidosis. A comparison with fetal biophysical profile. *J Ultrasound Med* 1992;11:1-6.
- Yoon BH, Romero R, Roh CR, Kim SH, Ager JW, Syn HC, 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;169:1586-94.
- Trudinger BJ, Giles WB, Cook CM. Flow velocity waveforms in the maternal uteroplacental and fetal umbilical placental circulations. *Am J Obstet Gynecol* 1985;152:155-63.
- Hitschold TP. Doppler flow velocity waveforms of the umbilical arteries correlate with intravillous blood volume. *Am J Obstet Gynecol* 1998;179:540-3.
- Kingdom JC, Burrell SJ, Kaufmann P. Pathology and clinical implications of abnormal umbilical artery Doppler waveforms. *Ultrasound Obstet Gynecol* 1997;9:271-86.
- Gagnon R, Challis J, Johnston L, Fraher L. Fetal endocrine responses to chronic placental embolization in the late-gestation ovine fetus. *Am J Obstet Gynecol* 1994;170:929-38.
- Mansouri H, Gagnon R, Hunse C. Relationship between fetal heart rate and umbilical blood flow velocity in term human fetuses during labor. *Am J Obstet Gynecol* 1989;160:1007-12.
- Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveforms in the fetal umbilical artery: quantitative analysis technique. *Ultrasound Med Biol* 1985;11:707-18.
- Thompson RS, Trudinger BJ, Cook CM. A comparison of Doppler ultrasound waveform indices in the umbilical artery - I. Indices derived from the maximum velocity waveform. *Ultrasound Med Biol* 1986;12:835-44.
- Thompson RS, Trudinger BJ, Cook CM. Doppler ultrasound waveform indices: A/B ratio, pulsatility index and Pourcelot ratio. *Br J Obstet Gynaecol* 1988;95:581-8.
- Cook CM, Connelly AJ, Trudinger BJ. Doppler assessment of the umbilical circulation. *Semin Ultrasound CT MR* 1989;10:417-27.
- Trudinger B, Cook CM, Thompson R, Giles W, Connelly A. Low-dose aspirin improves fetal weight in umbilical placental insufficiency. *Lancet* 1988;2:214-5.
- Rochelson B, Schulman H, Farmakides G, Bracero L, Ducey J, Fleischer A, et al. The significance of absent end-diastolic velocity in umbilical artery velocity waveforms. *Am J Obstet Gynecol* 1987;156:1213-8.
- Rochelson BL, Schulman H, Fleischer A, Farmakides G, Bracero L, Ducey J, et al. The clinical significance of Doppler umbilical artery velocimetry in the small for gestational age fetus. *Am J Obstet Gynecol* 1987;156:1223-6.
- Ferrazzi E, Vegni C, Bellotti M, Borboni A, Della PS, Barbera A. Role of umbilical Doppler velocimetry in the biophysical assessment of the growth-retarded fetus. Answers from neonatal morbidity and mortality. *J Ultrasound Med* 1991;10:309-15.
- Ferrazzi E, Bellotti M, Vegni C, Barbera A, Della PS, Ferro B, et al. Umbilical flow waveforms versus fetal biophysical profile in hypertensive pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1989;33:199-208.

23. Fong KW, Ohlsson A, Hannah ME, Grisar S, Kingdom J, Cohen H, et al. Prediction of perinatal outcome in fetuses suspected to have intra-uterine growth restriction: Doppler US study of fetal cerebral, renal, and umbilical arteries. *Radiology* 1999;213:681–9.
24. Schreuder AM, McDonnell M, Gaffney G, Johnson A, Hope PL. Outcome at school age following antenatal detection of absent or reversed end diastolic flow velocity in the umbilical artery. *Arch Dis Child Fetal Neonatal Ed* 2002;86:F108–14.
25. Vossbeck S, de Camargo OK, Grab D, Bode H, Pohlandt F. Neonatal and neurodevelopmental outcome in infants born before 30 weeks of gestation with absent or reversed end-diastolic flow velocities in the umbilical artery. *Eur J Pediatr* 2001;160:128–34.
26. Montenegro N, Santos F, Tavares E, Matias A, Barros H, Leite LP. Outcome of 88 pregnancies with absent or reversed end-diastolic blood flow (ARED flow) in the umbilical arteries. *Eur J Obstet Gynecol Reprod Biol* 1998;79:43–6.
27. Salafia CM, Pezzullo JC, Minior VK, Divon MY. Placental pathology of absent and reversed end-diastolic flow in growth-restricted fetuses. *Obstet Gynecol* 1997;90:830–6.
28. Karsdorp VH, van Yugt JM, van Geijn HP, Kostense PJ, Arduini D, Montenegro N, et al. Clinical significance of absent or reversed end diastolic velocity waveforms in umbilical artery. *Lancet* 1994;344:1664–8.
29. Tannirandorn Y, Phaosavasdi S. Significance of an absent or reversed end-diastolic flow velocity in Doppler umbilical artery waveforms. *J Med Assoc Thai* 1994;77:81–6.
30. Wilson DC, Harper A, McClure G. Absent or reversed end diastolic flow velocity in the umbilical artery and necrotizing enterocolitis. *Arch Dis Child* 1991;66:1467.
31. McParland P, Steel S, Pearce JM. The clinical implications of absent or reversed end-diastolic frequencies in umbilical artery flow velocity waveforms. *Eur J Obstet Gynecol Reprod Biol* 1990;37:15–23.
32. Woo JS, Liang ST, Lo RL. Significance of an absent or reversed end diastolic flow in Doppler umbilical artery waveforms. *J Ultrasound Med* 1987;6:291–7.
33. Trudinger BJ, Cook CM. Umbilical and uterine artery flow velocity waveforms in pregnancy associated with major fetal abnormality. *Br J Obstet Gynaecol* 1985;92:666–70.
34. du Plessis JM, Hall DR, Norman K, Odendaal HJ. Reversed end diastolic flow velocity in viable fetuses: is there time to wait for the effect of corticosteroids before delivery? *Int J Gynaecol Obstet* 2001;72:187–8.
35. Trudinger BJ, Cook CM, Giles WB, Ng S, Fong E, Connelly A, et al. Fetal umbilical artery velocity waveforms and subsequent neonatal outcome. *Br J Obstet Gynaecol* 1991;98:378–84.
36. Bekedam DJ, Visser GH, van der Zee AG, Snijders RJ, Poelmann-Weesjes G. Abnormal velocity waveforms of the umbilical artery in growth retarded fetuses: relationship to antepartum late heart rate decelerations and outcome. *Early Hum Dev* 1990;24:79–89.
37. Brar HS, Platt LD. Reverse end-diastolic flow velocity on umbilical artery velocimetry in high-risk pregnancies: an ominous finding with adverse pregnancy outcome. *Am J Obstet Gynecol* 1988;159:559–61.
38. Neilson JP, Alfirevic Z. Doppler ultrasound for fetal assessment in high risk pregnancies. *Cochrane Database Syst Rev* 2000;CD000073.
39. Newnham JP, Patterson LL, James IR, Diepeveen DA, Reid SE. An evaluation of the efficacy of Doppler flow velocity waveform analysis as a screening test in pregnancy. *Am J Obstet Gynecol* 1990;162:403–10.
40. Makikallio K, Tekay A, Jouppila P. Yolk sac and umbilicoplacental hemodynamics during early human embryonic development. *Ultrasound Obstet Gynecol* 1999;14:175–9.
41. Yarlagadda P, Willoughby L, Maulik D. Effect of fetal heart rate on umbilical arterial Doppler indices. *J Ultrasound Med* 1989;8:215–8.
42. Mehalek KE, Rosenberg J, Berkowitz GS, Chitkara U, Berkowitz RL. Umbilical and uterine artery flow velocity waveforms. Effect of the sampling site on Doppler ratios. *J Ultrasound Med* 1989;8:171–6.
43. Joern H, Rath W. Correlation of Doppler velocimetry findings in twin pregnancies including course of pregnancy and fetal outcome. *Fetal Diagn Ther* 2000;15:160–4.
44. Hofstaetter C, Dubiel M, Gudmundsson S. Two types of umbilical venous pulsations and outcome of high-risk pregnancy. *Early Hum Dev* 2001;61:111–7.
45. Reed KL, Chaffin DG, Anderson CF. Umbilical venous Doppler velocity pulsations and inferior vena cava pressure elevations in fetal lambs. *Obstet Gynecol* 1996;87:617–20.
46. Gudmundsson S. Importance of venous flow assessment for clinical decision-making. *Eur J Obstet Gynecol Reprod Biol* 1999;84:173–8.
47. Gudmundsson S, Gunnarsson GO, Hokegard KH, Ingemarsson J, Kjellmer I. Venous Doppler velocimetry in relationship to central venous pressure and heart rate during hypoxia in the ovine fetus. *J Perinat Med* 1999;27:81–90.
48. Hofstaetter C, Gudmundsson S, Dubiel M, Marsal K. Ductus venosus velocimetry in high-risk pregnancies. *Eur J Obstet Gynecol Reprod Biol* 1996;70:135–40.
49. Gudmundsson S, Tulzer G, Huhta JC, Marsal K. Venous Doppler in the fetus with absent end-diastolic flow in the umbilical artery. *Ultrasound Obstet Gynecol* 1996;7:262–7.
50. Kiserud T. The ductus venosus. *Semin Perinatol* 2001;25:11–20.
51. Reed KL, Chaffin DG, Anderson CF, Newman AT. Umbilical venous velocity pulsations are related to atrial contraction pressure waveforms in fetal lambs. *Obstet Gynecol* 1997;89:953–6.
52. Gagnon R, Lamb T, Richardson B. Cerebral circulatory responses of near-term ovine fetuses during sustained fetal placental embolization. *Am J Physiol* 1997;273:H2001–8.
53. Wladimiroff JW. Behavioural states and cardiovascular dynamics in the human fetus; an overview. *Early Hum Dev* 1994;37:139–49.
54. Norwitz ER, Hoyte LP, Jenkins KJ, van der Velde ME, Ratiu P, Rodriguez-Thompson D, et al. Separation of conjoined twins with the twin reversed-arterial-perfusion sequence after prenatal planning with three-dimensional modeling. *N Engl J Med* 2000;343:399–402.
55. van den Wijngaard JA, van Eyck J, Noordam MJ, Wladimiroff JW, van Strik R. The Doppler flow velocity waveform in the fetal internal carotid artery with respect to fetal behavioural states. A longitudinal study. *Biol Neonate* 1988;53:274–8.
56. Wladimiroff JW, Tonge HM, Stewart PA. Doppler ultrasound assessment of cerebral blood flow in the human fetus. *Br J Obstet Gynaecol* 1986;93:471–5.
57. Connors G, Hunse C, Gagnon R, Richardson B, Han V, Rosenberg H. Perinatal assessment of cerebral flow velocity wave forms in the human fetus and neonate. *Pediatr Res* 1992;31:649–52.
58. Potts P, Connors G, Gillis S, Hunse C, Richardson B. The effect of carbon dioxide on Doppler flow velocity waveforms in the human fetus. *J Dev Physiol* 1992;17:119–23.
59. Gagnon R, Lamb T, Richardson B. Cerebral circulatory responses of near-term ovine fetuses during sustained fetal placental embolization. *Am J Physiol* 1997;273:H2001–8.
60. Kopecky EA, Ryan ML, Barrett JF, Seaward PG, Ryan G, Koren G, et al. Fetal response to maternally administered morphine. *Am J Obstet Gynecol* 2000;183:424–30.
61. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Oepkes D, et al. The use of ultrasonography and Doppler in the prediction of fetal haemolytic anaemia: a multivariate analysis. *Br J Obstet Gynaecol* 1994;101:680–4.
62. Mari G, Deter RL, Carpenter RL, Rahman F, Zimmerman R, Moise KJ Jr, et al. Noninvasive diagnosis by Doppler ultrasonography of fetal anemia due to maternal re-cell alloimmunization. Collaborative Group for Doppler Assessment of the Blood Velocity in Anemic Fetuses. *N Engl J Med* 2000;342:9–14.
63. Divakaran TG, Vaughn J, Clark TJ, Khan KS, Whittle MJ, Kilby MD. Noninvasive techniques to detect fetal anemia due to red blood cell alloimmunization: a systematic review. *Obstet Gynecol* 2001;98:509–17.
64. Mari G, Detti L, Oz U, Zimmerman R, Duerig P, Stefos T. Accurate prediction of fetal hemoglobin by Doppler ultrasonography. *Obstet Gynecol* 2002;99:589–93.
65. Morrow RJ, Adamson SL, Lewin M, Bull SB, Ritchie JW. The influence of spontaneous accelerations of fetal heart rate on umbilical artery velocity waveforms. *Am J Obstet Gynecol* 1989;160:995–7.

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66. Spencer JA, Price J, Lee A. Influence of fetal breathing and movements on variability of umbilical Doppler indices using different numbers of waveforms. *J Ultrasound Med* 1991;10:37–41.
 67. Adamson SL, Morrow RJ, Langille BL, Bull SB, Ritchie JW. Site-dependent effects of increases in placental vascular resistance on the umbilical arterial velocity waveform in fetal sheep. *Ultrasound Med Biol* 1990;16:19–27.
 68. Kurjak A, Dudenhausen JW, Hafner T, Kupesic S, Latin V, Kos M. Intervillous circulation in all three trimesters of normal pregnancy assessed by color Doppler. *J Perinat Med* 1997;25:373–80.
 69. Campbell S, Vyas S, Nicolaides KH. Doppler investigation of the fetal circulation. *J Perinat Med* 1991;19:21–6.
 70. Surat DR, Adamson SL. Downstream determinants of pulsatility of the mean velocity waveform in the umbilical artery as predicted by a computer model. *Ultrasound Med Biol* 1996;22:707–17.
 71. Gagnon R, Johnston L, Murotsuki J. Fetal placental embolization in the late-gestation ovine fetus: alterations in umbilical blood flow and fetal heart rate patterns. *Am J Obstet Gynecol* 1996;175:63–72.
 72. Trudinger BJ, Stevens D, Connelly A, Hales JR, Alexander G, Bradley L, et al. Umbilical artery flow velocity waveforms and placental resistance: the effects of embolization of the umbilical circulation. *Am J Obstet Gynecol* 1987;157:1443–8.
 73. Joern H, Funk A, Goetz M, Kuehlwein H, Klein A, Fendel H. Development of quantitative Doppler indices for uteroplacental and fetal blood flow during the third trimester. *Ultrasound Med Biol* 1996;22:823–35.
 74. Woolf SH, Battista RN, Angerson GM, Logan AG, Eel W. Canadian Task Force on the Periodic Health Exam. Ottawa: Canada Communication Group; 1994. p. xxxvii.