

Second trimester uterine artery Doppler ultrasound as a screening test for adverse pregnancy outcome

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Summary

One main goal of antenatal care is to improve the outcome of pregnancy in terms of perinatal morbidity and perinatal mortality by identifying women at risk of complications such as preeclampsia, intrauterine growth retardation, placental abruption and intrauterine death. The association between pre-eclampsia, intrauterine growth retardation and increased uterine artery resistance measured by Doppler ultrasound has been described and subsequently color Doppler waveform analysis of the uterine arteries has been used as a screening test for adverse pregnancy outcome. The results were conflicting and often disappointing due to differences in gestational age at the time of examination in the selected study populations and due to a lack of standardized analysis of the uterine artery waveform. In low-risk populations uterine artery Doppler waveform analysis remains a test with relatively low positive predictive values reflecting the low prevalence of pregnancy complications in an unselected population. Patients with bilateral notching at 24 weeks of gestation represent a group at risk for preeclampsia, intrauterine growth retardation and adverse pregnancy outcome.

Key words: Uterine artery Doppler; Adverse pregnancy outcome; Notching.

One main goal of antenatal care is to improve the outcome of pregnancy in terms of perinatal morbidity and perinatal mortality by identifying women at risk of complications such as preeclampsia (PIH), intrauterine growth retardation (IUGR), placental abruption and intrauterine death. Historically continuous wave Doppler has been used as an indirect method of investigating blood flow changes in different vessels [1, 2]. Today it is possible to accurately assess the uteroplacental circulation with good reproducibility by means of pulsed color Doppler ultrasound. Physiologically, the uterine circulation changes during the first half of pregnancy from one of high resistance to one of low resistance and this process is characterized by the so-called trophoblast invasion into the muscular wall of the spiral arteries. This modification usually begins in the first trimester around the sixth week and continues until the 22nd-24th week of gestation [3]. The Doppler flow velocity waveform of a non-pregnant uterine artery is characterized by a high-resistance waveform with an early diastolic notch. At 20 weeks of gestation this has normally changed to a low-resistance waveform with loss of the diastolic notch [4, 5]. Increased resistance in the uterine arteries at that time is believed to reflect a failure of trophoblast invasion into the muscular spiral arteries. More than a decade ago, the association between preeclampsia, intrauterine growth retardation and increased uterine artery resistance measured by Doppler ultrasound was described and subsequently color Doppler waveform analysis of the uterine arteries has been used as a screening test for adverse pregnancy outcome [6-9]. The results were conflicting and often disappointing due to differences in gestational age at the time of examination and in the selected study populations and due to a lack of standardized analysis of the uterine artery waveform [1-6].

In low-risk populations uterine artery Doppler waveform analysis remains a test with relatively low positive predictive values (up to 50%) reflecting the low prevalence of pregnancy complications in an unselected population. In an early continuous wave Doppler study of the uterine circulation between the 16th and 24th week of gestation Harrington *et al.* showed a significant association between an abnormal resistance index ($RI > 95$ th percentile) and the subsequent development of PPIH or IUGR with a specificity of 95% and a relatively low sensitivity of 25% [12]. By introducing colour flow imaging, the use of a diastolic notch as the definition of an abnormal flow velocity waveform and a three-stage test (20, 24, 26 weeks) the same authors increased the sensitivity of the test (76%) with a progressive improvement of the specificity (from 86% to 97%) and of the positive predictive value (from 13% to 44%) [12]. North *et al.* examined nulliparous women at 19-24 weeks of gestation. They found a sensitivity of 51% with a positive predictive value of 29% for the subsequent development of preeclampsia by using the placental side ratio between peak systolic (A) and early diastolic (C) blood flow velocities (A: C ratio) in order to consider the placental posi-

tion for uterine artery examination [13]. More recently, Harrington and co-workers reported a positive predictive value of 53.6% for any complication of pregnancy (preeclampsia, intrauterine growth retardation, placental abruption, stillbirth or neonatal death) for a bilateral notch at 24 weeks of gestation in 1,326 unselected women and a sensitivity of 81.2% for the development of preeclampsia requiring delivery before 34 weeks and 57.6% for intrauterine growth retardation with positive predictive values of 27% (PIH), 31.2% (IUGR) and 37.5% (any complication). These authors used a second-stage color Doppler evaluation of the uterine circulation in case of abnormal flow velocity waveforms at 20 weeks of gestation [14].

Coleman and co-workers reported a positive predictive value of 65% for the prediction of preeclampsia and/or intrauterine growth retardation requiring delivery before 34 weeks with a sensitivity of 92% in a high-risk population including women with a history of IUGR, PIH, essential hypertension, or autoimmune diseases like systemic lupus erythematosus, antiphospholipid syndrome or pre-existing renal disease [15].

However, these observations can not be translated into multiple gestations. Geipel and co-workers recently reported a lower sensitivity of abnormal uterine Doppler results in the detection of preeclampsia (36.4%), IUGR (28.9%) and adverse pregnancy outcome in twins (26.5%) [16].

An important point is that all the studies dealing with the analysis of flow velocity waveforms of the uterine arteries as a screening procedure consistently demonstrate a high negative predictive value of the test (98-99%). In other words, women presenting with a normal uterine Doppler at 20 to 24 weeks of gestation have a very low risk of developing preeclampsia or having a small baby [17]. This is an important message for the patients and should also be considered in the discussion about the intensity of antenatal care offered to the patients.

Screening is reasonable when an adequate treatment for the condition is available. A meta-analysis of randomized trials dealing with the effect of low-dose aspirin, concludes that low-dose aspirin could prevent preeclampsia while the results of the CLASP trial failed to show an overall benefit of aspirin [18]. Harrington and co-workers showed in their study on the effectiveness of slow-release aspirin in screen-positive patients a reduction of the overall incidence of complications associated with uteroplacental insufficiency but the incidence of preeclampsia or IUGR remained the same [19].

It can be concluded from the data, that there is still no standardized evaluation of what is called abnormal uterine circulation (notch or resistance index) and when to perform the test (20-24 weeks) in which population (low- or high-risk). The subjective analysis of the absence or presence of a diastolic notch by trained operators has good inter-observer agreement and seems to be a reliable predictor as computerized velocity waveform analysis is still experimental and cannot yet be transduced in a routine clinical setting and other ratios do not perform better [20]. The evaluation of uterine artery Doppler at 20-24 weeks of gestation can be incorporated in the fetal anomaly scan. Patients with bilateral notching at 24 weeks of gestation represent a group at risk for preeclampsia, intrauterine growth retardation and adverse pregnancy outcome. On the other hand, patients with normal flow velocity waveforms in the uterine arteries at that time of gestation constitute a low-risk group suitable for less intensive antenatal care.

Furthermore, it can be speculated, that analysis of flow velocity waveform analysis of the uterine arteries at 20-24 weeks of gestation in combination with biochemical testing (e.g., α -fetoprotein, β -human chorionic gonadotropin) might further improve the positive predictive value of the test in an university setting [21].

If we concentrate on patients with bilateral notching at 20-24 weeks, I think we have a high-risk group suitable for intensive antenatal care. Those patients might be appropriate for randomized controlled trials with administration of low-dose aspirin in the near future.

References

- [1] Campbell S., Griffin D.R., Pearce J.M., Diaz-Recasens J., Cohen-Overbeek T.E., Willson K., Teague M.: "New Doppler technique for assessing uteroplacental blood flow". *Lancet*, 1983, *1*, 675.
- [2] Trudinger B.J., Gies W.B., Cook C.M.: "Uteroplacental blood flow velocity waveforms in normal and complicated pregnancy". *Br. J. Obstet. Gynaecol.*, 1985, *39*.
- [3] Pijnenborg R., Dixon G., Robertson W.B., Brosens I.: "Trophoblastic invasion of decidua from 8-18 weeks of pregnancy". *Placenta*, 1980, *1*, 3.
- [4] Dickey R.P., Hower J.F.: "Ultrasonographic feature of uterine blood flow during pregnancy and the first 16 weeks of pregnancy". *Hum. Reprod.*, 1995, *10*, 2448.
- [5] Jurkovic D., Jauniaux E., Kurjak A., Hustin J., Campbell S., Nicolaides K.H.: "Transvaginal color Doppler assessment of the uteroplacental circulation in early pregnancy". *Obstet. Gynecol.*, 1991, *77*, 365.

- [6] Campbell S., Pearce J.M.F., Hackett G., Cohen-Overbeek T., Hernandez C.: "Qualitative assessment of utero-placental blood flow: early screening tests for high-risk pregnancies". *Obstet. Gynecol.*, 1986, 68, 649.
- [7] Bower S., Bewley S., Campbell S.: "Improved prediction of preeclampsia by using the two stage screening of uterine arteries using the early diastolic notch and color Doppler imaging". *Obstet. Gynecol.*, 1993, 82, 78.
- [8] Valensise H., Bezzeccheri V., Rizzo G., Tranquilli A.L., Garzetti G.G., Romanini C.: "Doppler velocimetry of the uterine artery as a screening test for gestational hypertension". *Ultrasound Obstet. Gynecol.*, 1993, 3, 18.
- [9] Bewley S., Cooper D., Campbell S.: "Doppler investigation of uteroplacental blood flow in the second trimester: a screening study for pre-eclampsia and intrauterine growth retardation". *Br. J. Obstet. Gynaecol.*, 1991, 198, 871.
- [10] Jacobson S.L., Imhof R., Manning N., Mannion V., Little D., Rey E., Redman C.: "The value of Doppler assessment of the uteroplacental circulation in predicting pre-eclampsia or intra-uterine growth retardation". *Am. J. Obstet. Gynecol.*, 1990, 162, 110.
- [11] Bower S., Schuchter K., Campbell S.: "Doppler ultrasound screening as part of routine antenatal scanning: prediction of pre-eclampsia and intrauterine growth retardation". *Br. J. Obstet. Gynaecol.*, 1993, 100, 989.
- [12] Harrington K.F., Campbell S., Bewley S., Bower S.: "Doppler velocimetry studies of the uterine artery in the early prediction of pre-eclampsia and intra-uterine growth retardation". *Eur. J. Obstet. Gynecol. Reprod. Biol.*, 1991, 42, 14.
- [13] North R.A., Ferrier C., Long D., Townend K., Kincaid-Smith P.: "Uterine artery Doppler flow velocity waveforms in the second trimester for the prediction of pre-eclampsia and fetal growth retardation". *Obstet. Gynecol.*, 1994, 83, 378.
- [14] Harrington K., Cooper D., Lees C., Hecher K., Campbell S.: "Doppler ultrasound of the uterine arteries: the importance of bilateral notching in the prediction of pre-eclampsia, placental abruption or delivery of a small-for-gestational-age baby". *Ultrasound Obstet. Gynecol.*, 1996, 7, 182.
- [15] Coleman M.A.G., McCowan L.M.E., North R.A.: "Mid-trimester uterine artery Doppler screening as a predictor of adverse pregnancy outcome in high-risk women". *Ultrasound Obstet. Gynecol.*, 2000, 15, 7.
- [16] Geipel A., Berg C., Germer U., Katalinic A., Krapp M., Smrcek J., Gembruch U.: "Doppler assessment of the uterine circulation in the second trimester in twin pregnancies: prediction of pre-eclampsia, fetal growth restriction and birth weight discordance". *Ultrasound Obstet. Gynecol.*, 2002, 20, 541.
- [17] Aquilina J., Harrington K.: "Pregnancy hypertension and uterine artery Doppler ultrasound". *Curr. Opinion Obstet. Gynecol.*, 1996, 8, 435.
- [18] CLASP (Collaborative Low-dose Aspirin Study in Pregnancy): "A randomised trial of low-dose aspirin for the prevention and treatment of pre-eclampsia among 9364 pregnant women". *Lancet*, 1994, 343, 619.
- [19] Harrington K., Kurdi W., Aquilina J., England P., Campbell S.: "A prospective management study of slow-release aspirin in the palliation of uteroplacental insufficiency predicted by uterine artery Doppler at 20 weeks". *Ultrasound Obstet. Gynecol.*, 2000, 15, 13.
- [20] Irion O., Masse J., Forest J.C., Moutquin J.M.: "Peak systolic over protodiastolic ratio as an objective substitute for the uterine artery notch". *Br. J. Obstet. Gynecol.*, 1996, 103, 993.
- [21] Valensise H.: "Uterine artery Doppler velocimetry as a screening test: where we are and where we go". *Ultrasound Obstet. Gynecol.*, 1998, 12, 81.

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