

## REVIEW

## Doppler flowmetry in preeclampsia

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**Abstract:** The purpose of this study was to summarize the new published data on the Doppler flowmetry in preeclampsia.

**Methods:** We summarize the new published data on the Doppler flowmetry in uteroplacental, fetoplacental and fetal circulation in preeclampsia. The present review summarized the results of clinical research on the Doppler flowmetry in the screening of risk of preeclampsia, in the diagnosis of preeclampsia and in the fetal risk in preeclampsia (Ref. 19). Full Text (Free, PDF) [www.bmj.sk](http://www.bmj.sk).

**Key words:** Doppler flowmetry, preeclampsia.

Early detection preeclampsia onset can prevent life – threatening conditions in both, the mother and the fetus, respectively eclampsia and later cardiovascular diseases in the mother, and fetal intrauterine growth restriction or death of the fetus. Recent research in Doppler sonography and placental angiogenesis enhanced our possibilities in this process.

### Preeclampsia

Preeclampsia (PE) is a pregnancy – specific heterogeneous systemic disorder, affecting both the mother and the fetus. Maternal syndrome is characterised with hypertension, proteinuria and edema, causing fetal syndrome, i.e. growth restriction and chronic hypoxia of the fetus. Premature delivery or abruptio placentae may also occur. PE develops in about 10 % of pregnancies and is a leading cause of perinatal morbidity and mortality. Although the cause of PE remains unknown, genetic, immunologic and inflammatory factors are considered. In the pathophysiology of PE impaired trophoblastic invasion and endothelial cell damage plays a crucial role. From this point of view, PE is a two-stage disease. Failure of blastocyst nidation at the beginning of pregnancy (1st stage), causes hypoxic changes in endothelium in

the second half of pregnancy (2nd stage). On the other hand, two clinical entities of PE are

possible. Early-onset PE with severe course, causing early vasoconstriction of spiral arteries and late-onset PE with mild course with late atherosclerotic changes in spiral arteries.

### Doppler flowmetry and preeclampsia

In physiological pregnancies trophoblast invasion transforms the high-resistance spiral arteries into a low-impedance uteroplacental circulation. This vascular transformation remains incomplete in PE.

Sonography is world-wide the method of choice for non-invasive examination of pregnancy. B-scan or 3D/4D ultrasound can detect structural characteristics of the fetus and other components of gestational sac. However, there are some limitations of this examination (6). Especially, in the sonography of placenta, depiction of placental structures alone with the evaluation of the placenta is insufficient. Sonography can visualize structural changes of trophoblast and placenta during pregnancy (5). On the other hand, functional changes of placenta are of great interest for obstetricians. From this point of view, Doppler flowmetry is a suitable non-invasive method for the evaluation of pathological hemodynamic changes not only in uteroplacental circulation, but also in subsequently altered fetoplacental and fetal circulation.

Doppler velocimetry indices include pulsatility index (PI), resistance index (RI) and systolic/diastolic velocity ratio (S/D ratio).  $PI = (PSV - EDV)/TAMV$ ,  $RI = (PSV - EDV)/PSV$  and  $S/D \text{ ratio} = PSV/EDV$ , where PSV means peak systolic velocity, EDV end-diastolic velocity and TAMV time-averaged maximum velocity.

Uteroplacental circulation represents a. uterina (Aut). Lower AutPI or lower diastolic flow in first half of pregnancy, in addition to diastolic notch in second half of pregnancy are pathological patterns of shallow implantation and poor dilatation of spiral arteries in PE. Lower diastolic flow is due to vasoconstriction of spiral arteries, postsystolic notch reflects increased resistance in spiral arteries after the ejection phase of cardiac cycle.

Fetoplacental circulation is imaged by a. umbilicalis (Aum). Insufficient flow between placenta and fetus in the second half

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of the pregnancy in PE is characterised by lower diastolic flow, amputation of diastolic flow or reversed flow in diastole (ADF/RF). Sometimes, a cumulated term, absent and/or reversed end-diastolic flow (ARED) is used.

Fetal circulation is mainly represented by a. cerebri media (ACM). Fetal cerebral circulation is the best marker to predict fetal outcome (7). Higher diastolic flow in this vessel, represented by a higher ACM PI, is a sign of a brain sparing effect, physiological response of fetal cerebral circulation to intrauterine oxygen deprivation in PE. Prolonged cerebral hypoxia leads to pathological fall in diastolic flow, resulting in intrauterine fetal death. In cases of low diastolic flow in ACM, when it is not clear if this pattern is due to normal or pathological flow, diagnosis can be confusing. The situation is complicated by the fact, that no specific Doppler flow pattern in the fetus is characterized with PE.

### Indications for Doppler flowmetry in preeclampsia

After Sohn 2004 there are three indications for this examination (15):

- 1) To anticipate or screen for the risk of PE by examining the uteroplacental vessels in the first or second trimester.
- 2) To confirm the diagnosis of PE in the second half of pregnancy by finding changes characteristic of PE in the uteroplacental bed, such as a notch or corresponding increases in resistance, correlating with a poorly developed placental vascular bed.
- 3) Evaluation of the fetal or fetoplacental vessels to exclude any risk for the fetus. The examination determines how the fetus is coping with the changes resulting from the PE.

### Doppler flowmetry in the screening of risk of preeclampsia

In the first and second trimester of gestation high resistance flow, determined by Doppler flowmetry indices, such as Aut PI and Aut RI, can detect later development of PE. On the other hand, application of this method for screening of all pregnancies in order to detect risk of PE is questionable.

Melchiorre et al 2008 found significantly higher Aut RI at 11–14 weeks in women who subsequently developed preterm PE in opposite to those with a normal outcome.

This findings support, but not prove, a rigid separation between the etiology of early- and late-onset PE. Finally, this data do not support routine introduction of first trimester Doppler flowmetry into clinical practice (9).

Plasencia et al 2008 measured Aut PI at 11+0 to 13+6 weeks and 21+0 to 24+6 weeks of gestation. They detected that the decrease in Aut PI between these two examinations is steeper in pregnancies with a normal outcome than in those developing PE. Authors conclude that effective screening for PE can be achieved by the Doppler measurement of Aut PI at 11+0 to 13+6 weeks and the change in PI between 11+0 to 13+6 weeks and 21+0 to 24+6 weeks (12).

Detti et al 2006, in addition, focused on abnormal Doppler flow indices and the possibility to detect first trimester IUGR in

cases, when the last menstrual period and conception time are accurately known (3).

Teixeira et al 2008 evaluated Ductus venosus Doppler flowmetry in the first trimester from the view of trophoblastic migration, partially by PE. Their findings suggest that the first wave of trophoblastic migration may begin at a CRL of 63 mm. Investigation of pulsatility index for vein behavior in early pregnancy may be useful as a screening method to evaluate whether placental implantation is adequate (17).

Parra et al (2006) detected by the examination at 11 to 14 and 22 to 25 weeks a significantly increased Aut PI, plasma levels of soluble fms-like tyrosine kinase 1 (sFlt1), PAI-1/PAI 2 ratio and F-2 isoprostane in women who subsequently developed PE compared with control pregnancies. This study demonstrated early changes in markers of impaired placentation, anti-angiogenic state, oxidative stress and endothelial dysfunction suggesting that these derangements may play a role in the pathogenesis of PE. Aut PI is the best test to predict PE at 23 weeks of gestation (10).

### Doppler flowmetry in the diagnosis of preeclampsia

In the second half of pregnancy Doppler flowmetry is used in cases of clinically existing PE. It is opposite to the first half of pregnancy, when only risk of PE can be established. The main signs in Doppler signal patterns by PE are increases of Aut PI and the Aut protodiastolic notch. On the other hand, this sign does not occur in all cases of PE. In these cases of PE, combination of Doppler flowmetry and circulating angiogenic factors levels are recommended. Generally, combination of sonography and blood examination of special serum substances, markedly improve the sonographic diagnosis, i.e.  $\beta$ -hCG in tubal pregnancy (4).

Yu et al (2008) showed an inverse significant association between the gestational age at delivery and prevalence of small for gestational age (SGA) babies and between the gestational age at delivery and prevalence of mean Aut PI in PE. They conclude, that Doppler ultrasound assessment of the uterine arteries is more effective in identifying PE requiring preterm than term delivery (19).

Stepan et al (2008) examined endoglin, a cell-surface coreceptor for transforming growth factor in patients with Doppler flow patterns of PE at 19–24 gestation weeks. Soluble endoglin levels were elevated in second – trimester pregnancies with abnormal uterine perfusion in women who experienced PE. This examination is more accurate than Doppler sonography in predicting early-onset complications of pregnancy (16).

Crispi et al (2008) investigated Aut PI and PIGF at 20–24 gestation weeks in patients with early-onset and late-onset PE. Sensitivity for early-onset PE was for Aut PI 47.4 % and for PIGF 84.4 %. When combining Aut PI and PIGF, sensitivity for early-onset PE was 89.5 %. Conversely, sensitivity for late-onset PE was below 11 % for all parameters analyzed (2).

Espinoza et al (2007) examined the relationship between Aut PI and plasma concentrations of placental growth factor (PIGF) in association with PE. In patients with abnormal Doppler flow-

metry (increased Aut PI, notch) low maternal plasma concentration of PIGF (less than 280 pg/mL) in the second trimester is associated with a high risk for early-onset PE (8).

Savvidou et al (2006) correlated abnormal Aut Doppler flow (diastolic notch) and sFlt-1 at 23–25 weeks of gestation. Maternal serum concentration of sFlt-1 in pregnancies with FGR was increased but this increase was not evident in pregnancies with impaired placentation that subsequently developed into FGR or PE (13).

Piazzze et al (2007), on the other hand, correlated Aut RI and mean platelets volume (MPV) in third trimester pregnancies. MPV was significantly higher in women with altered Aut Doppler velocimetry compared with those with normal Doppler profiles. In the group with altered Aut Doppler velocimetry, pregnancies complicated by PE showed a MPV value higher than pregnancies affected by IUGR. Mean Aut RI values were significantly related to MPV in both PE and IUGR group. This study showed that periodical monitoring of MPV can be associated to Doppler velocimetry in order to improve the management of pregnancies with Aut Doppler velocimetry alterations (11).

### Doppler flowmetry in the fetal risk in preeclampsia

In PE long-term deficiency in the placental supply can lead to intrauterine fetal growth restriction, chronic fetal oxygen deprivation and finally, to acute fetal hypoxia with the danger of intrauterine fetal death. However, IUGR is detectable by ultrasound biometry of the fetus and recognition of acute fetal hypoxia by CTG is possible. In this situation, Doppler flowmetry in chronic poor blood supply from the placenta to the fetus can be performed by Aut and to the brain by ACM.

Acharya et al (2005) constructed new reference ranges for all three commonly used Aum Doppler indices, Aum PI, Aum RI and Aum S/D ratio. Longitudinally established percentiles of Doppler indices from this study showed a continuous reduction throughout the second half of pregnancy without any plateau or increased near term, as reported previously. There was a significant negative association between Doppler indices and placental weight and neonatal birth weight, but not with gender. This new reference ranges are more appropriate for serial evaluation of fetal hemodynamics (1).

Schlembach et al (2007) correlated levels of angiogenic growth factors with Doppler flowmetry by PE and IUGR. Aum PI was significantly higher in women with IUGR than in those with PE. Maternal sFlt-1 levels were higher in women with PE than in those with IUGR. PIGF levels in the umbilical vein were below the detection limit in nearly all samples of IUGR fetuses and lower than in those with PE. Maternal PIGF levels were inversely correlated with PI values of both vessels. No correlation could be found in the serum of the umbilical artery for all growth factors and for vascular endothelial growth factors (VEGF) in all compartments. The correlations between maternal and fetal angiogenic factor serum levels and Doppler flowmetry indices of uterine and umbilical arteries in PE and IUGR reflect the severity of the disorders, especially for the fetus (14).

Turan et al (2008) evaluated arterial and venous Doppler abnormalities from the onset of placental insufficiency in IUGR. They identified three patterns of progression:

1) Mild placental dysfunction that remained confined to the Aum/ACM. The Aum became abnormal at a median of 32 weeks of gestation but the PI never exceeded 3SD above normal. Progression took a median of 33 days, requiring delivery at a median of 35 weeks.

2) Progressive placental dysfunction. Initially normal Aum PI at 29 weeks of gestation increased beyond 3SD, progressing to abnormal ACM, ARED Aum, abnormal Ductus venosus flow, umbilical vein pulsation in 9-day intervals requiring delivery by 33 weeks.

3) Severe early-onset placental dysfunction. Markedly elevated Aum PI established by 27 weeks of gestation was associated with rapid (7-days intervals) progression to abnormal venous Doppler with median delivery at 30.6 weeks. Authors conclude that the characteristics of cardiovascular manifestations in IUGR are determined by the gestational age at onset and the severity of placental disease. Recognition of these factors is critical for planning fetal surveillance in IUGR (18).

### Conclusions

Doppler flowmetry may help in the screening of risk of PE in high-risk patients by the measurements of Aut PI in early gestation at 11–14 weeks. On the other hand, valid results are only possible in the cases of early-onset PE. In late-onset PE, no early hemodynamic changes occur.

In the diagnosis of preeclampsia altered uterine flow patterns with protodiastolic notch at 20–24 weeks of gestation are detectable in patients who later develop PE. Validity of diagnosis increases when combining Aut Doppler flowmetry with serum levels of angiogenic factors evaluation.

In the fetal risk in preeclampsia abnormal umbilical flow patterns, especially by serial measurements, in combination with fetal biometry chronic placental dysfunction with IUGR can be detected. ARED in umbilical artery flow and abnormal fetal Doppler velocimetry in ACM and Ductus venosus are markers of acute oxygen deprivation.

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