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DOPPLER ASSESSMENT OF UTEROPLACENTAL BLOOD FLOW IN SCREENING FOR PREECLAMPSIA

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Review paper

Keywords: Pre-eclampsia, uterine artery Doppler, screening, prevention

Summary. Preeclampsia complicates between 4–5 percent of pregnancies and it is one of the leading causes of maternal and perinatal mortality and morbidity worldwide. One potential screening tool for identifying pregnant women at risk for developing pre-eclampsia is Doppler assessment of blood flow in uterine arteries (UtA) and some other parts of uteroplacental circulation. Studies suggest that abnormal UtA waveforms (abnormal resistance index (RI), pulsatility index (PI) or diastolic notching) reflects impaired uteroplacental blood flow due to failed second wave of trophoblastic invasion of spiral arteries, and identify women at high risk of developing preeclampsia. Still, due to high false-positive rates, low sensitivity and low positive predictive values the majority of internatinational guidelines do not recommend the use of UtA Doppler in clinical practice. Until more evidence, perinatal care should still focus on taking a detailed medical history, assessing for risk factors and measuring blood pressure at each prenatal visit and if classified as high risk, to use some other screening methods. Also, a growing amount of evidence suggests that pregnant women presenting with one recognized high risk factors or two or more moderate risk factors for developing pre-eclampsia should be offered low-dose aspirin from 12 weeks gestation in order to reduce the risk of developing preeclampsia.

Introduction

Preeclampsia is a pregnancy related condition defined as new onset hypertension after 20 weeks of gestation and coexistence of proteinuria (spot urine protein/creatinine >30 mg/mmol or >300 mg/day or ≥1 g/L (2+) on dipstick testing) or other maternal organ dysfunction including renal insufficiency (creatinine 90 umol/L or more), liver involvement (AST or ALT over 40 U/L), neurological complications (eclampsia, altered mental status, headache, scotomata), hematological complications (platelet count below 150000/mL), hemolysis or disseminated intravascular coagulation (DIC) (1). Preeclampsia is also complicated by uteroplacental dysfunction presumed by intrauterine fetal growth restriction (IUGR) and/or abnormal umbilical artery Doppler studies (1). This definition is part of classification of hypertensive disorders in pregnancy which has last been updated in year 2000 and accepted with some minor alterations by the majority of obstetric societies worldwide (2–6).

Preeclampsia complicates around 4.6 % of pregnancies (7) and it is more prevalent in first pregnancies and among women at the extremes of child bearing age (8). It is one of the leading causes of maternal and perinatal mortality and morbidity, especially in low income countries (4). Maternal morbidity includes development of stroke, eclampsia (eclamptic seizures) or organ failure as well as increased risk of development of cardiovascular diseases later in life (9,10), while perinatal morbidity includes intrauterine growth restriction, low birth weight, preterm birth and stillbirth (11).

Screening for preeclampsia

Screening and early diagnosis of preeclampsia and other hypertensive disorders in pregnancy is important since the majority of deaths and certain morbidities related to preeclampsia could potentially be avoided or alleviated. This implies that women at increased risk for developing pre-eclampsia or diagnosed with preeclampsia are provided appropriate and timely prenatal care, management, surveillance and treatment (12). A systematic review and meta-analysis published in 2016 concluded that a past history of preeclampsia, preexisting hypertension, pregestational diabetes, multifetal gestation, chronic kidney disease, and some autoimmune diseases (primary antiphospholipid syndrome (PAPS), systemic lupus erythematosus (SLE) carry the highest relative risk of developing preeclampsia (13). These six risk factors listed above, carry an absolute risk for developing preeclampsia of at least 8 percent and have been endorsed by several international guidelines (Americal College of Obstetricians and Gynecologists (ACOG), United States Preventive Services Task Force (USPSTF), Up to Date and others to define women at high risk for developing preeclampsia (14–16). Studies have shown that these women would benefit from antiplatelet therapy with low dose aspirin (LDA) started at 12 to 16 weeks gestation, which effectively and safely prevents preeclampsia and other associated complications (IUGR and preterm birth) (17). International guidelines strongly recommend the use of LDA from late first trimester to treat women at high risk of preeclampsia, but somewhat differ regarding definition of high risk factors of preeclampsia (3,15). LDA should be initiated between 12 and 28 gestational weeks (optimally before 16 gestational weeks) and continued until delivery (15,16). Of note, ACOG, USPSTF, Up to date recommend LDA of 81mg/day, while National Institute for Health and Care Exelence (NICE), World Health Organization (WHO) and Society of Obstetricians and

Gynecologists of Canada (SOCG) recommend 75mg/day (18). There is less consensus regarding criteria that confer moderate risk for developping preeclampisa. ACOG, USPSTF and Up to date recommend intiation of LDA for preeclampsia prevention to women with two or more moderate risk factors which include nulliparity, obesity (body mass index >30 kg/m2), family history of preeclampsia in mother or sister, age ≥35 years, sociodemographic characteristics (African American race, low socioeconomic level) and personal risk factors (ie. previous pregnancy with low birth weight or small for gestational age infant, previous adverse pregnancy outcome [eg, stillbirth], interval >10 years between pregnancies) (14–16). Moderate risk factors endoursed by NICE include age ≥40 years, first pregnancy, multiple gestation, >10 years between pregnancies, body mass index ≥35 kg/m^2 at presentation, family history of preeclampsia. Presence of 2 or more indicate initiation of LDA (19). All pregnant women should be screened for these high and moderate risk factors for development of preeclampisa at the first prenatal visit and managed accordingly. Transfer to secondary or tertiary health care centers, prophylactic administration of steroids for fetal lung maturation in pre-term pregnancies are just two of many other interventions that can be implemented in order to improve management of pregnant women at risk for pre-eclampsia.

Many different laboratory tests have also been proposed for screening for preeclampsia, but none of them have achieved satisfying sensitivity or specificity to be included in routine prenatal care. These include various angiogenic modulators and growth factors (PIGF, VEGF, sFIt-1), maternal serum analyses concentrations (pregnancy-associated plasma protein A) and abnormalities in cell-free DNA quantifications which all lack adequate statistical and clinical relevance (20–23).

Uteroplacental blood flow and risk of developing preeclampsia

In the past 30 years a great amount of research on ultrasound Doppler has confirmed the association between increased blood flow resistance in uteroplacental circulation i.e. uterine arteries and its branches and elevated risk of development of obstetric complications related to uteroplacental insufficiency (24,25). These mainly include hypertensive disorders of pregnancy, notably preeclampsia, but also intrauterine growth restriction, small for gestational age babies, Hemolysis, ELevated liver function test and Low Platelets (HELLP) syndrome, placental abruption and others (26,27). Increased resistance in uterine artery is a reflection of impaired uteroplacental blood flow. This is a consequence thought to occur secondarily to failed second wave of trophoblastic invasion of spiral arteries resulting in abnormal placental formation (28,29). In normal pregnancies, placental trophoblast cells invade the inner third of the myometrium and change highly resistant spiral arteries (as terminal branches of uterine arteries) into low-resistance vessels. This vascular remodeling is reflected by high diastolic velocity and continuous flow during diastolic part of cardiac cycle in uterine artery Doppler studies (30,31). In women who develop adverse pregnancy outcomes attributed to uteroplacental insufficiency, myometrial arterioles are only partially invaded which is termed failed trophoblastic invasion of spiral arteries. Spiral arteries do not loose their endothelial lining and musculoelastic tissue and their mean external diameter becomes only half of that of corresponding vessels in the normal placental bed (32). Such spiral arteries have an abnormally narrow lumen resulting in high resistance to blood flow, resulting in abnormally high resistance in proximal parts of uteroplacental circulation (i.e. uterine arteries (UtA) and impaired placental blood flow.

Most often studied Doppler abnormalities of UtA waveforms are elevated UtA resistance index (RI) and pulsatility index (PI). There are several definitions of their abnormality but most commonly used ones, RI ≥ 0.58, PI ≥ 1.60 or both above 90th centile were suggested as they were shown to represent a higher risk of: preterm birth before 32 weeks of gestation, development of severe preeclampsia, intrauterine growth restriction, HELLP syndrome, oligohydramnios presence, placental insufficiency and placental abruption (27). Other abnormalities of UtA waveforms related to adverse pregnancy outcomes due to impaired uteroplacental circulation is presence of mid-trimester diastolic notching (33), or presence of peak systolic over end diastolic velocities ratio (A:B ratio) > 90th centile, which was found to be significantly associated with development of preeclampsia and small for gestational age infants (33). In the majority of studies, all UtA Doppler indices perform similarly when evaluated in the second trimester (34,35), but a systematic review and meta analysis including almost 80,000 women concluded that pulsatility index, alone or combined with notching was most predictive Doppler index and it is the only one possibly of use in clinical practice (36). The majority of above mentioned research has been performed in pregnancies between 17 and 22 gestational weeks, defined as the period of second wave of trophoblastic invasion. However, studies have reported this association to be present as early as in the first trimster, i.e. at 12 weeks gestation (37,38).

According to a reveiw by Papageorghiou et al., increased impedance to flow in UtA in pregnancies attending routine antenatal care identifies about 40% of asymptomatic women who will subsequently develop preeclampsia and following a positive test, the likelihood of developing pre-eclampsia is increased by about 6 times (39). On the other hand, women with normal UtA Doppler at 20 weeks' gestation have a low risk of developing obstetric complications related to uteroplacental insufficiency (40). A study by Coomarasamy *et al.* suggests that prophylactic LDA therapy before 16 gestational weeks in women identified as being at risk of developing preeclampsia using UtA Doppler assessment results in a significant reduction in preterm preeclampsia (41). A systematic review and meta analysis

by Cnossen *et al.* describes that increased UtA pulsatility index with notching is predictive of developing preeclampsia and has a positive likelihood ratio 21.0 among high risk patients and 7.5 among low risk patients (36). Another meta analysis by Kleinrouweler *et al.* supports adding UtA Doppler measurements to other patients characteristics (blood pressure or BMI) in identification of women at risk for preeclampsia (42).

Despite these significant associations and two above mentioned meta analyses from 2008 and 2013 supporting the use of UtA Doppler in clinical practice; (36,42) WHO, Up to Date and some other studies emphasize that UtA Doppler ultrasound should not be used in routine second trimester antenatal care as a screening method due to high false-positive rates (43,44). UtA Doppler has low positive predictive values being between 4 and 29%.(29,45) In a study of Irion et al., UtA Doppler abnormalities had low sensitivities ranging from 26% to 34% and low positive predictive values form 7% to 28% for predicting preeclampsia, low birthweight and prematurity in low risk nuliparous women (34). Also, in a study by Li *et al.,* only one third of women with preeclampsia showed signs of increased UtA vascular impedance in the third trimester (46). On the other hand, UtA Doppler waveform analysis may be useful in selected high risk populations. In women identified to be at high risk for pre-eclampsia and/or SGA babies, UtA Doppler waveform performed between 22 and 24 weeks gestation, i.e. after second wave of trophoblast invasion; predicted severe adverse pregnancy outcomes and was better than clinical risk assessment in prediction of preeclampsia and SGA babies (29). UtA Doppler studies have also been shown to have a higher accuracy in identifying patients who will subsequently develop early rather than late-onset pre-eclampsia, which might be a focus in future research (47,48).

Up to Date points out that all these data need to be interpreted with caution, as studies of UtA Doppler velocimetry for prediction of preeclampsia are difficult to compare because investigators have used different Doppler sampling techniques and different definitions of abnormal flow velocity waveform, have assessed different populations with differing, gestational age at examination, and criteria for diagnosis of preeclampsia (44). Recent ACOG recommendations define women at high or moderate risk for developing preeclampsia that would benefit from LDA therapy and do not include UtA Doppler assessment (14).

The debate whether to use UtA Doppler in routine prenatal care for screening for obstetric complications related to uteroplacental insufficiency remains inconclusive.

Conclusion

Doppler assessment of blood flow in uteroplacental circulation is a potential screening tool for selecting pregnant women at high risk for developing some adverse pregnancy outcomes, including preeclampsia. However, results from studies are inconclusive as well as recommendations for clinical use and further research is mandatory to estimate and entirely comprehend different screening methods (49). It should always be kept in mind that preeclampsia cannot reliably be predicted in the general as well as high risk population, and perinatal care should still focus on taking a detailed medical history, assessing for risk factors and measuring blood pressure at each prenatal visit (44,50). There is a growing amount of evidence and recommendations suggesting that pregnant women presenting with one recognized high risk factors or two or more moderate risk factors for developing pre-eclampsia should be offered low dose aspirin from 12 weeks gestation to reduce the risk of developing preeclampsia.

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DOPLERSKA ANALIZA UTEROPLACENTARNOG PROTOKA U PROBIRU ZA PREEKLAMPSIJU

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Pregledni članak

Ključne riječi: Preeklampsija, dopler uterine arterije, prevencija

Sažetak. Preeklampsija je poremećaj koji zahvaća 4–5% trudnoća i predstavlja jedan od vodećih uzroka majčinog i perinatalnog mortaliteta i morbiditeta diljem svijeta. Kvalitetan probir i rano prepoznavanje trudnica s povećanim rizikom od razvoja preeklampsije od velike su važnosti zbog mogućnosti izbjegavanja ili ublažavanja povećanog mortaliteta i morbiditeta koji ju prate. Najšire prihvaćena metoda rane dijagnostike preeklampsije predstavlja mjerenje krvnog tlaka na svakom antenatalnom pregledu, ali uz znatno reduciranu mogućnost ranog probira. Anamnestički podaci koji svrstavaju trudnice u skupinu s visokim rizikom za razvoj preeklampsije su: razvoj preeklampsije u prethodnoj trudnoći, arterijska hipertenzija ili šećerna bolest prije trudnoće, višeplodna trudnoća, kronična bubrežna bolest i određene autoimune bolesti (sistemski eritemski lupus i antifosfolipidni sindrom).

Jedna od brojnih metoda probira jest korištenje ultrazvučne tehnologije, odnosno analize protoka uteroplacentarne cirkulacije doplerom. Dokazana je povezanost između povišenog otpora u uterinim arterijima i povećanog rizika od razvoja patoloških stanja trudnoće povezanih s uteroplacentarnom insuficijencijom, poput hipertenzivnih poremećaja u trudnoći (naročito preeklampsije), zastoja u rastu ploda, HELLP sindroma, abrupcije posteljice i drugih. Povišen otpor protoku krvi u uterinoj arteriji odraz je poremećaja protoka krvi u njenom distalnom vaskularnom bazenu koji je posljedica abnormalne placentacije, odnosno nepotpune invazije trofoblasta u spiralne arterije. Istražene su različite promjene doplerskog vala uterine arterije poput indeksa otpora (s graničnom vrijednosti RI ≥ 0,58), indeksa pulsatilnosti (s graničnom vrijednosti PI ≥ 1,60) i postojanja dijastoličkog ureza. Neovisno o izmjerenim vrijednostima, većina istraživanih parametara pokazala je sličnu uspješnost u ranom probiru. Brojna istraživanja pokazuju kako se patološki doplerski zapis uterine arterije u drugom tromjesečju trudnoće povezuje s razvojem preeklampsije, dok njen uredan zapis s relativno velikom sigurnošću otklanja postojanje rizika od razvoja patoloških stanja povezanih s uteroplacentarnom insuficijencijom. Unatoč navedenom, većina međunarodnih društava u svojim smjernicama i dalje ne preporuča rutinsko korištenje ultrazvučne doplerske tehnike uterine arterije u kliničkom radu zbog njene relativno niske osjetljivosti (do 35%), niske pozitivne prediktivne vrijednosti (između 7 i 30%) te velikog broja lažno pozitivnih rezultata.

U skladu s navedenim, rasprava treba li koristiti tehniku doplera uterine arterije kao metodu probira drugog tromjesečja u razvoju preeklampsije ostaje i dalje otvorena te su potrebna dodatna istraživanja u svrhu potpune procjene njene učinkovitosti. Razvoj preeklampsije i dalje se ne može pouzdano predvidjeti niti u općoj, niti u visoko rizičnoj populaciji, te se antenatalna skrb u ovom pogledu i dalje temelji na kvalitetno uzetoj anamezi, procjeni čimbenika rizika i mjerenju krvnog tlaka prilikom svakog pregleda. Raste broj istraživanja i preporuka koje ukazuju kako bi trudnice koje imaju jedan od visoko rizičnih čimbenika, ili dva ili više srednje rizičnih čimbenika, trebale profilaktički primati male doze acetilsalicilne kiseline od 12. tjedna trudnoće, a u svrhu smanjenja rizika od razvoja preeklampsije.