Prognostic Role of Uterine Artery Doppler in Patients with Preeclampsia

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Key Words

Preeclampsia · Uterine artery Doppler · Perinatal outcome, adverse

Abstract

Objectives: To evaluate the predictive capacity of umbilical, cerebral and uterine artery Doppler in women admitted for preeclampsia (PE). **Methods:** 190 consecutive singleton pregnancies admitted with PE were included. Umbilical, cerebral and uterine artery Dopplers were performed. The association with adverse perinatal outcome was evaluated from 2 × 2 tables and multivariately by logistic regression. **Results:** A total of 82 (43%) women had an abnormal uterine artery Doppler on admission, being more prevalent in early-onset (<32 weeks) than in the late-onset PE (62 vs. 27%, $p < 0.05$). In both early- and late-onset forms, uterine artery Doppler showed a greater capacity than umbilical and middle cerebral artery Doppler for predicting adverse perinatal outcome. **Conclusion:** Uterine artery Doppler was the best predictive parameter for perinatal outcome in pregnancies with PE and may be included as a primary surveillance test.

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Introduction

Preeclampsia (PE) affects about 2–3% of pregnancies and is a major contributor to maternal mortality with an estimated 50,000 deaths/year worldwide [1]. PE is also associated with increased perinatal morbidity [2] and mortality [3].

In recent years, it has been established that early- and late-onset PE are associated with different biochemical and clinical features [4]: whereas the early-onset form is almost invariably associated with placental insufficiency and growth restriction, the late-onset form is more prevalent and, in general, placental involvement is minimally present. In patients with early-onset PE, expectant management improves neonatal outcome in selected cases, decreasing neonatal care intensive unit admittance and neonatal respiratory distress [5, 6]. Also in selected cases, mild PE could be managed in an outpatient regimen until term [7], providing a reassuring maternal and fetal assessment. While the criteria of maternal risk on which the selection of cases for expectant management could be based are well defined [7, 8], fetal criteria are not as well established.

Umbilical artery (UA) and middle cerebral artery (MCA) Dopplers are standard parameters in the manage-

ment of pregnancies at risk of placental insufficiency [9]. Uterine artery (UtA) Doppler has been widely studied for the prediction of PE and intrauterine growth restriction, reflecting the involvement of a defective trophoblastic invasion. However, it has scarcely been evaluated as a prognostic tool at the onset of PE [10–12]. Only recently, it has been reported that women with late-onset PE show a higher risk of perinatal complications if uterine resistance is increased [13]. Also, preeclamptic women with abnormal uterine flow are at higher risk of recurrence during their next pregnancy [14]. The role of UtA Doppler in identifying pregnancies at risk of fetal morbidity in both early and late forms of PE has not been investigated. It is also unknown if its prediction capacity is superior to that of UA and MCA Doppler.

This study aimed to evaluate the prediction capacity of UA, MCA and UtA Doppler in women admitted for PE.

Material and Methods

Population

Between January 2002 and December 2008 a cohort was created of 190 women with singleton pregnancies and PE who were admitted to a referral hospital in Barcelona (Spain). PE was defined according to the International Society Study of Hypertension in Pregnancy as a resting blood pressure of $\geq 140/90$ mm Hg on 2 occasions at least 4 h apart, and the presence of proteinuria (≥ 0.3 g/dl) or a 2+ urine dipstick, beyond 20 weeks of pregnancy in previously normotensive women.

Measurements

On admission, all women underwent blood and urine workup according to current recommendations [7, 8]. Doppler examination was also performed on hospital admission using a Voluson 730 Pro or Voluson 730 Expert (GE Medical Systems, Milwaukee, Wisc., USA) equipment. All the scans were performed by 1 of 6 experienced observers. UtA Doppler was carried out by identifying the vessel in an oblique scan with the sample volume distal to the crossing with the external iliac artery. Pulsatility indexes (PIs) of the left and right arteries were measured and the mean PI was calculated. The UA Doppler flow spectrum was recorded from a free-floating portion of the umbilical cord. The MCA Doppler was recorded in a transverse view of the fetal brain, with the Doppler gate placed on the vessel about 1 cm distal to the circle of Willis. In all these vessels, the pulsed Doppler gate was placed over the whole width of the vessel once it had been ensured that the angle was $<30^\circ$. Angle correction was then applied and the signal updated until 3 similar consecutive waveforms were obtained. Gestational age was calculated according to the crown-rump length at first trimester ultrasound [15]. The UtA Doppler investigation on admission and the last UA and MCA Doppler investigation within 1 week before delivery were considered for the analysis.

Definitions

Early PE was defined as that diagnosed before 32.0 weeks. Severe PE was defined as a blood pressure of $\geq 160/110$ mm Hg on 2 or more determinations, proteinuria of ≥ 5 g/24 h or the presence of maternal complications, including eclampsia and other neurological manifestations, HELLP syndrome (lactate dehydrogenase >600 IU/l, aspartate transaminase >62 IU/l, platelet count (10^9 /l) $<100,000$), acute renal failure defined as creatinine >1.2 g/dl, subcapsular hepatic hematoma, pulmonary edema and the presence of disseminated intravascular disease. Small-for-gestational age (SGA) was defined as a birth weight <10 th centile according to local customized curves [16]. Adverse perinatal outcome was defined as the presence of at least one of the following: fetal or neonatal demise, acidosis at birth (UA pH <7.10 and base excess >12 mEq/l), 5-min Apgar score <7 , and admission to the neonatal intensive unit for more than 10 days.

Management

Magnesium sulfate seizure prophylaxis was administered to all women with severe PE, as well as first and second-line antihypertensive therapy with labetalol and hydralazine, respectively, when blood pressure was persistently $\geq 160/110$ mm Hg. Corticosteroid therapy for fetal lung maturity was administered to all pregnancies less than 34 weeks of gestational age. During admission, maternal blood pressure was recorded several times per day and laboratory testing at least twice a week. Fetal assessment was performed by daily fetal heart rate monitoring and Doppler at least every 3 days. Indications for delivery were severe PE beyond 32 weeks once pulmonary maturation was completed, uncontrollable blood pressure, maternal complications (defined above), abruptio placentae or decelerative fetal heart rate (>5 decelerations of more than 30 beats/min from basal line in 30 min). In addition, beyond 28 weeks indications for delivery also included UA Doppler with absent reversed end-diastolic velocities or persistent (>12 h apart) ductus venosus Doppler with absent or reversed atrial flow. Women without severity criteria [7] were discharged and outpatient management with weekly fetal and maternal assessment was performed. In cases with mild PE, delivery was induced after 37 weeks.

Statistical Analyses

Doppler parameters were transformed into z values for gestational age [17, 18]. Best cutoffs were chosen by means of receiver operator characteristics (ROC) curve analyses. Sensitivity, specificity and positive and negative likelihood ratios (LHRs) for the prediction of adverse outcome were calculated. Multivariate analysis for the occurrence of adverse perinatal outcome was performed by logistic regression. MedCalc 8.0 (MedCalc Software, Belgium) and SPSS 14.0 (SPSS Inc., USA) were used for the statistical analyses.

Results

Table 1 details the basal characteristics of the study population at admission. In 85% (162/190) of the patients, the criteria of severity were met; and in 44% (84/190) the clinical onset was before 32 weeks. Among the early-on-

set cases, 96% fulfilled the criteria of severity, whereas only 76% of the late-onset cases fulfilled them ($p < 0.05$).

Table 2 depicts the perinatal outcome. SGA was found in 120 neonates (63.2%), with a higher incidence in early-onset PE (85 vs. 44%, $p < 0.05$). A total of 51 (26.8%) infants had adverse perinatal outcomes, including non-exclusively 12 perinatal deaths, 9 cases with 5-min Apgar score of <7 , 21 cases of UA pH <7.10 , and 20 cases that required admission to the neonatal intensive care unit for more than 10 days. Early-onset cases showed a nonsignificant trend to a higher incidence of adverse outcome (33.3 vs. 21.4%, $p = 0.06$).

ROC curve analysis showed that whereas the area under the curve was 0.69 (95% CI 0.60–0.78; $p < 0.001$) for UtA PI, it was 0.59 (95% CI 0.50–0.69; $p = 0.06$) and 0.58 (95% CI 0.48–0.68; $p = 0.09$) for UA PI and MCA PI, respectively. The best cutoff for UtA PI was the 97.5th centile, and the 95th centile for UA PI and MCA PI. Overall, a total of 82 (43%) women had UtA PI >97.5 th centile on admission. While this proportion was 62% (54/87) among early-onset PE, it was 27% (28/103) in cases with late-onset. Table 3 details the performance of Doppler parameters in predicting adverse perinatal outcome in both early- and late-onset clinical forms. Importantly, in both early- and late-onset forms, abnormal UtA Doppler showed a higher sensitivity and greater capacity for ruling in (+LHR) and out (–LHR) the occurrence of adverse outcome.

Multivariate regression analysis including standard severity criteria of PE showed (table 4) that abnormal UtA was the only parameter that significantly and independently predicted adverse perinatal outcome, with an OR of 4.17 (95% CI 1.97–8.81; $p < 0.001$). On stratification for early- and late-onset clinical forms, the ORs were 3.34 (95% CI 1.05–10.6; $p = 0.04$) and 5.18 (95% CI 1.63–16.47; $p = 0.005$), respectively.

Discussion

Our study demonstrates that UtA Doppler on admission for PE is superior to UA and MCA Doppler in identifying those cases at higher risk of adverse perinatal outcome. In addition, we found that none of the standard severity criteria for PE were significantly associated with this adverse outcome.

UtA Doppler is a validated noninvasive surrogate of trophoblastic invasion [19] and placental perfusion [20]. Thus, neonates of preeclamptic women with abnormal

Table 1. Characteristics of the study population

<i>Basal characteristics</i>	
Maternal age, years	31.5 (5.2)
Body mass index	26.9 (7)
Primiparity, %	62.6
Smoking, %	22
<i>Risk factors for preeclampsia</i>	
Body mass index >30 , %	38
Diabetes mellitus, %	2.6
Autoimmune disease, %	3.2
Thrombophilia, %	3.7
Dyslipidemia, %	4.7
Previous preeclampsia, %	8.4
<i>Characteristics on admission</i>	
Gestational age at onset, weeks	32.4 (4)
Early-onset preeclampsia (<32 weeks), %	44
Diastolic blood pressure, mm Hg	105 (10)
Systolic blood pressure, mm Hg	172 (20)
24-hour proteinuria, g	2.3 (2.5)
Severity criteria, %	85
Data expressed as mean (standard deviation) or proportions.	

Table 2. Perinatal outcome of the study population

Gestational age at delivery, weeks	33.5
Admission to delivery interval, days	9
Birth weight, g	1,833
Emergent CS for fetal distress, %	20
Admission to NICU for >7 days, %	20
SGA, %	63.1
Acidosis at birth, %	11.3
5-Min Apgar score <7 , %	4.8
Perinatal mortality, %	6.3
Stillbirth, %	2.1
Neonatal death, %	4.3
Data expressed as mean (standard deviation) or proportions.	
CS = Cesarean section; NICU = neonatal intensive care unit; SGA = small-for-gestational age.	

UtA Doppler are likely to have been exposed to more severe intrauterine hypoxia secondary to placental insufficiency, which explains the association with adverse outcome. The fact that UtA Doppler was more predictive than UA Doppler could speculatively be explained because the latter has been demonstrated to become abnormal only in advanced stages of placental dysfunction [21, 22]. Also, regional brain perfusion studies in IUGR fetuses showed that brain hypoxia is present long before

Table 3. Prediction of Doppler parameters for adverse perinatal outcome

	Se	Sp	+LHR	–LHR	OR	95% CI	p
Overall							
Abnormal UtA	67	65	1.93	0.51	3.80	1.92–7.48	<0.001
Abnormal UA	45	63	1.23	0.87	1.42	0.74–2.72	0.29
Abnormal MCA	47	65	1.33	0.82	1.63	0.85–3.13	0.14
Early-onset							
Abnormal UtA	79	47	1.48	0.44	3.34	1.18–9.41	0.02
Abnormal UA	62	41	1.06	0.92	1.16	0.46–2.88	0.76
Abnormal MCA	62	52	1.29	0.73	1.75	0.71–4.36	0.23
Late-onset							
Abnormal UtA	50	79	2.38	0.63	3.77	1.40–10.15	0.06
Abnormal UA	23	79	1.08	0.98	1.1	0.35–3.43	0.86
Abnormal MCA	27	74	1.05	0.98	1.07	0.37–3.1	0.9

Se = Sensitivity; Sp = specificity; LHR = likelihood ratio; CI = confidence interval; OR = odds ratio; UtA = uterine artery; UA = umbilical artery; MCA = middle cerebral artery.

Table 4. Regression analysis of severity criteria for the prediction of adverse perinatal outcome

	OR	95% CI	p
Blood pressure $\geq 160/110$ mm Hg	0.72	0.35–1.49	0.37
Prodromic neurological symptoms	1.53	0.72–3.23	0.27
AST >62 UI/l	0.6	0.19–1.86	0.37
LDH >600 mg/dl	0.94	0.38–2.29	0.88
Creatinine >1.2 mg/dl	0.84	0.07–10.55	0.89
24-Hour proteinuria >5 g/dl	1.67	0.57–4.94	0.35
Platelet count ($10^9/l$) $<100,000/l$	0.50	0.14–1.77	0.28
SGA	1.12	0.52–2.42	0.77
Abnormal mean UtA PI	4.17	1.97–8.81	<0.001
Abnormal UA PI	1.65	0.55–2.75	0.38
Abnormal MCA PI	1.73	0.87–2.59	0.25

UtA = Uterine artery; PI = pulsatility index; UA = umbilical artery; MCA = middle cerebral artery; AST = aspartate transaminase; LDH = lactate dehydrogenase; SGA = small-for-gestational age; CI = confidence interval.

significant changes in MCA are observed [23]. In keeping with this, Geerts and Odendaal [24] found that in severe PE, umbilical and cerebral Doppler parameters were not associated with adverse outcome, once adjusted for fetal size. On the contrary, our multivariate analysis that included SGA as a covariate confirmed the significant and independent value of UtA Doppler in predicting adverse outcome. In a group of 115 preeclamptic women, Simanaviciute and Gudmundsson [25] found that cerebral to uterine Doppler better predicted the necessity to deliver

prematurely than abnormal Doppler alone in either the UA or UtA. However, the authors did not report these results separately for early- and late-onset cases. Besides the interval between examination and delivery (mean 4.5 weeks) prevents strong conclusions from being drawn. In line with our results, Ghi et al. [13] found in late-onset PE that abnormal UtA was strongly associated with adverse perinatal outcome, but in this study the comparison of this predictive capacity with that of UA and MCA Doppler was not addressed.

The severity of PE is defined by biochemical and clinical maternal parameters [7], being essentially focused on maternal wellbeing. Interestingly, a survey including 18 experts [26] aimed at identifying tests (among 33 tests which included items of history, examination, and investigations) that could be clinically relevant in predicting maternal and fetal complications in women with PE, revealed that ‘ultrasound including Doppler studies’, un-specifically, was not rated among the potentially most useful predictors. Consistent with our findings, some previous studies [27, 28] have also suggested that presumed intrauterine stress reflected by the severity of maternal disease did not accurately predict neonatal outcome. It is therefore, of importance to define parameters that could better predict perinatal outcome. In our study, abnormal UtA Doppler at the onset of PE was the only parameter that significantly and independently predicted adverse perinatal outcome.

In keeping with the concept that early- and late-onset PE are associated with different biochemical and clinical features [4], we have found that while more than half

of the early-onset cases of PE had an abnormal UtA Doppler, only one quarter of the cases of late-onset had this Doppler sign. These findings conferred to the UtA Doppler a different potential role for each clinical form. In early PE, where efforts are made to prolong the pregnancy to allow fetal maturation, the UtA performs better in ruling out the occurrence adverse outcome, allowing the safe prolongation of pregnancy. Our results do not support including abnormal UtA as an indication for early delivery. On the other hand, in late-onset PE, UtA Doppler is better at defining at-risk fetuses in whom the recommended outpatient management for mild PE [7] could pose an unnecessary risk. Ghi et al. [13] have recently reported how in late-onset PE UtA accounts for most cases of adverse outcome.

One of the limitations of our study is that most cases (85%) met the criteria of severity and it could be argued that our sample represents a population of preeclamptic women referred to a tertiary hospital rather than the overall population of preeclamptic women. This could

have increased the sensitivity, specificity and LHRs of all the diagnostic tests, but could not explain the differences between them. Another limitation is that second-trimester Doppler was not available for analysis. This could have enabled knowing whether preeclamptic women with abnormal Doppler at onset correspond to those with abnormal flow in the second trimester. This could mean that an adverse outcome secondary to PE could be predicted earlier by second-trimester Doppler. However, Soregaroli et al. [29] reported that about half of the women with abnormal UtA Doppler at 24 weeks had normalization of Doppler indices by 34 weeks. As the proportion of abnormal Doppler in the second trimester [30] is the same as the proportion found in our study at clinical onset, one could speculatively conclude that some women convert from normal to abnormal and vice versa during the third trimester.

Our findings contribute to the premises for future studies evaluating management strategies based on UtA Doppler results at the clinical onset of PE.

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