

Preeclampsia

Early and Late Preeclampsia Two Different Maternal Hemodynamic States in the Latent Phase of the Disease

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Abstract—Because early and late preeclampsia (PE) are thought to be different disease entities, we compared maternal cardiac function at 24 weeks gestation in a group of normotensive asymptomatic patients with subsequent development of early (<34 weeks gestation) and late (≥ 34 weeks gestation) PE (blood pressure $>140/90$ +proteinuria >300 mg/dL) to detect possible early differences in the hemodynamic state. A group of 1345 nulliparous normotensive asymptomatic women underwent at 24 weeks gestation uterine artery Doppler evaluation and maternal echocardiography calculating total vascular resistance. In the subsequent follow-up 107 patients showed PE: 32 patients had late and 75 had early PE. Five of 32 patients with late PE and 45 of 75 patients with early PE had bilateral notching of the uterine artery at 24 weeks (15.6% versus 60.0%; $P<0.05$). Total vascular resistance was 1605 ± 248 versus 739 ± 244 dyn \cdot s \cdot cm $^{-5}$, and cardiac output was 4.49 ± 1.09 versus 8.96 ± 1.83 L in early versus late PE ($P<0.001$). Prepregnancy body mass index was higher in late versus early PE (28 ± 6 versus 24 ± 2 kg/m 2 ; $P<0.001$). Early and late PE appear to develop from different hemodynamic states. Late PE appears to be more frequent in patients with high body mass index and low total vascular resistance; earlier forms of PE appear to be more frequent in patients with lower BMI and with bilateral notching of the uterine artery. These findings support the hypothesis of different hemodynamics and origins for early PE (placental mediated, linked to defective trophoblast invasion with high percentage of altered uterine artery Doppler) and late PE (linked to constitutional factors such as high body mass index). (*Hypertension*. 2008;52:873-880.)

Key Words: preeclampsia/pregnancy ■ hemodynamics ■ echocardiography

Preeclampsia (PE) is associated with maternal perinatal morbidity and mortality¹ and affects 5% to 7% of pregnant patients worldwide.² Hemodynamic investigations during the latent phase of PE are scarce and conflicting because of the different classifications^{3,4} used in the definition: mild, moderate, and severe, as well as early and late. The concept of early and late PE is more modern, and it is widely accepted that these two entities have different etiologies and should be regarded as different forms of the disease.^{3,4} Early-onset PE (before 34 weeks) is commonly associated with abnormal uterine artery Doppler, fetal growth restriction (FGR), and adverse maternal and neonatal outcomes.^{1,5} In contrast, late-onset PE (after 34 weeks) is mostly associated with normal or slight increased uterine resistance index, a low rate of fetal involvement, and more favorable perinatal outcomes.^{5,6} Early-onset PE and FGR are placenta-mediated diseases that share important similarities as recently demonstrated by Crispi et al,^{7,8} who reported placental growth factor (PIGF) as a useful second-trimester screening test for this form of the disease, but not for late-onset PE/FGR. Maternal echocardiography might identify at 24 weeks gestation patients who subsequently develop early severe maternal and fetal complications through the assessment of maternal hemo-

dynamics and left ventricular geometry (elevated maternal total vascular resistance [TVR] and the presence of concentric geometry)^{9–11} suggesting an involvement of the whole cardiovascular system in the placental mediated disorder. Previous data published by Bosio¹² and Easterling¹³ on the latent phase of PE are in contrast with this model (describing low TVR and high cardiac output [CO]), although the patients from those series developed late forms of PE.

Interestingly, hemodynamics and volume homeostasis in women with previous PE appear to be similar to hypertensive subjects and different from healthy parous controls,¹⁴ leading Spaanderman et al¹⁴ to propose the classification of these symptom-free subjects with a history of PE as having “latent” hypertension. Moreover, women with previous PE and a recurrent hypertensive disorder in their next pregnancy differed from those with a previous PE and an uneventful next pregnancy by a lower prepregnant plasma volume and a lower venous capacitance.¹⁵

From these considerations we hypothesized that the two disease entities (early and late PE) might develop from divergent hemodynamics (low CO-high TVR for early, and high CO-low TVR for late PE) with persisting cardiovascular differences also after pregnancy.

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Table 1. Main Maternal and Fetal/Neonatal Complications Subsequently Developed in the Study Group

Complications Occurred in the Study Group	n 226/1345
Maternal complications	139
Late preeclampsia	30
Early preeclampsia	61
Evolution toward moderate-severe GH with induced preterm delivery <34 wks	35
Abruptio placenta	5
HELLP syndrome (2 patients), coagulation abnormalities (3 patient), thrombocytopenia (3 patient)	8
Maternal and fetal/neonatal complications	37
Late preeclampsia and FGR	2
Early preeclampsia with FGR	14
Evolution towards moderate-severe GH and FGR with induced preterm delivery <34 wks	19
HELLP syndrome and neonatal death	2
Fetal/neonatal complications	50
FGR	34
Admittance to NICU	13
Perinatal death	3
Total complications	226

To test this hypothesis we compared maternal TVR and left ventricular morphology at 24 weeks gestation and 1 year postpartum in a group of asymptomatic normotensive high risk patients (nulliparous women with bilateral notching of the uterine artery at 20 to 22 weeks gestation) with subsequent development of early and late-onset PE.

Methods

Patient Selection

A total of 1688 normotensive high risk nulliparous women referred to the outpatient clinic of Tor Vergata University for the finding of bilateral notching of the uterine artery between 20 to 22 weeks gestation were recruited between 1999 and 2007; all of the patients were submitted to uterine artery Doppler and maternal echocardiography at 24 weeks gestation. Exclusion criteria were: (1) undetermined gestational age; (2) tobacco use; (3) twin pregnancies; (4) maternal heart disease; (5) preexisting maternal chronic medical problems; (6) chromosomal or suspected ultrasound fetal abnormalities; and (7) persistence of elevated blood pressure values ($\geq 140/$

90 mm Hg) at the 1-year follow-up visit. Approval of the university ethics committee was obtained, and written informed consent was collected from all of the patients. Patients were followed until term to verify the fetoneonatal and maternal outcomes. The criteria of the International Society for the Study of Hypertension in Pregnancy were used to define PE.¹⁶ PE was diagnosed if a previously normotensive woman had 2 consecutive (4 hours apart) diastolic blood pressure measurements of ≥ 90 mm Hg after the 20th week of gestation, and proteinuria >300 mg in a 24-hour urine specimen. PE was classified as early (gestational age <34 weeks at clinical onset) or late (≥ 34 weeks). FGR was defined as a birthweight below the 10th percentile¹⁷ for gestational age associated to Doppler PI of the umbilical artery before delivery above the 95th centile. The latest parameter was included to avoid the misclassification of small for gestational age babies due to constitutional factors as previously reported.¹⁸

Fetal and Uterine Artery Ultrasound Examination

For all of the ultrasound examinations, a 3.5-MHz sector ultrasound transducer interfaced to a Toshiba Xario (Toshiba Medical Systems Corp) or a Technos Esaote (Esaote Biomedica) ultrasound machine was used. Patients underwent uterine artery color Doppler examination at 24 weeks gestation, as previously described,^{10,11,19-21} and bilateral notching was noted. Fetal biometry and estimated fetal weight were assessed.

Echocardiographic Evaluation

The M-mode, 2D, and Doppler echocardiographic investigation, evaluating TVR, systolic, diastolic, and morphological parameters of the left ventricle, was performed within 24 hours from the diagnosis bilateral notching. The M-mode, 2D, and Doppler echocardiographic evaluations were performed with the patient in lateral position in harmonic imaging with a Toshiba Xario or a Technos Esaote ultrasound machine. Left ventricular end-diastolic and end-systolic diameters and interventricular septum and posterior wall diastolic thicknesses were detected according to the recommendation of the American Society of Echocardiography.²² Left ventricular mass (LVM) in grams was calculated by the Devereux formula.²³

Left Ventricular Geometric Pattern

LVM index (LVMi) was then calculated as follows: $LVMi = LVM/m^2.7$, where m was the height of the patient in meters.²⁴ Relative wall thickness (RWT) was calculated as the ratio of (interventricular septum diastolic thickness + posterior wall diastolic thickness)/left ventricular end-diastolic diameter.

Systolic Function

Stroke volume (SV) was calculated as the product of aortic valve area (AVA) and the aortic flow-velocity time integral, as previously described.¹⁹ CO was calculated as the product of SV and heart rate derived from electrocardiographic monitoring.

Table 2. Baseline Features of the 2 PE Groups and Controls

Parameter	Controls n=1119 1	Late PE n=32 2	Early PE n=75 3	P Value
Age, y	32 \pm 5	32 \pm 4	34 \pm 4	0.046, 1 vs 3, 2 vs 3
Age >35 y, n (%)	284 (25.4)	8 (25.0)	33 (44.0)	0.03, 1 vs 3, 2 vs 3
Height, m	1.64 \pm 0.05	1.65 \pm 0.06	1.63 \pm 0.05	N.S.
Prepregnancy body mass index, kg/m ²	23 \pm 4	28 \pm 6	24 \pm 2	<0.001 , 1 vs 2, 2 vs 3
Bilateral notch of the uterine artery at 24 weeks gestation, n (%)	67 (6.0)	5 (15.6)	45 (60.0)	<0.001 , 1 vs 3, 2 vs 3, 1 vs 2
Gestational age at delivery, week	39 \pm 1	37 \pm 1	32 \pm 3	<0.001 , 1 vs 3, 2 vs 3, 1 vs 2
Neonatal weight centile	46 \pm 23	48 \pm 20	18 \pm 12	<0.001 , 1 vs 3, 2 vs 3

N.S. indicates not significant.

Table 3. Morphologic and Hemodynamic Parameters at 24 Weeks Gestation and 1 Year Postpartum

Parameter	Controls n=1119	Early PE n=75	Late PE n=32
24 weeks gestation			
Heart rate	80±11	75±14*	89±13*†
Systolic blood pressure, mm Hg	115±11	121±10*	115±13†
Diastolic blood pressure, mm Hg	62±11	70±10*	60±12†
Mean blood pressure, mm Hg	80±8	87±8*	79±9†
Total vascular resistance, dyn · s · cm ⁻⁵	990±179	1605±248*	739±244*†
Left ventricular mass, g	124±21	129±28*	168±41*†
Left ventricular mass index, g/m ^{2.7}	33±6	35±7*	43±12*†
Left ventricular diastolic diameter, cm	4.85±0.29	4.51±0.29*	5.16±0.29*†
Interventricular septum diastolic thickness, cm	0.79±0.09	0.90±0.12*	0.91±0.12*
Posterior wall diastolic thickness, cm	0.75±0.10	0.84±0.14*	0.88±0.13*
Relative wall thickness	0.32±0.05	0.39±0.06*	0.35±0.04*†
Stroke volume, mL	83±11	61±13*	102±19*†
Cardiac output, L	6.61±1.10	4.49±1.09*	8.96±1.83*†
Left atrial maximal area, cm ²	15.7±2.7	14.4±2.2*	15.6±2.1*
Left atrial minimal area, cm ²	7.6±1.52	7.8±1.9*	7.5±1.4
Left atrial fractional area change, %	52±7	46±12*	52±8
1 year postpartum			
Heart rate	74±9	75±12	78±10
Systolic blood pressure, mm Hg	119±11	123±10*	122±10*
Diastolic blood pressure, mm Hg	68±10	71±13	70±13
Mean blood pressure, mm Hg	85±9	89±10	88±11
Total vascular resistance, dyn · s · cm ⁻⁵	1361±279	1458±285*	1257±277*†
Left ventricular mass, g	97±20	115±23*	141±40*†
Left ventricular mass index, g/m ^{2.7}	26±5	30±7*	38±12*†
Left ventricular diastolic diameter, cm	4.69±0.28	4.64±0.27	4.93±0.20*†
Interventricular septum diastolic thickness, cm	0.70±0.09	0.78±0.09*	0.85±0.16*†
Posterior wall diastolic thickness, cm	0.65±0.10	0.75±0.10*	0.80±0.18*†
Relative wall thickness	0.29±0.04	0.33±0.04*	0.34±0.07*
Stroke volume, mL	71±12	68±12	74±9†
Cardiac output, L	5.10±0.97	5.03±1.07	5.75±1.00*†
Left atrial maximal area, cm ²	14.6±2.7	14.2±2.4	15.5±3.1*†
Left atrial minimal area, cm ²	8.1±1.9	8.0±1.8	7.8±1.8
Left atrial fractional area change, %	44±10	43±11	50±7*†

**P*<0.05 vs controls.†*P*<0.05 vs early PE.

TVR

At the end of the maternal echocardiographic examination, systolic and diastolic blood pressure (SBP and DBP, respectively) were measured from the brachial artery with a manual cuff. TVR was calculated in dynes · s · cm⁻⁵ according to the following formula: TVR=(MBP[mm Hg]/CO[L/min]) 80 where MBP was mean blood pressure calculated as DBP+(SBP-DBP)/3.

Diastolic Function

Assessment of diastolic function was obtained as previously described.^{21,25,26} The following variables were measured: peak flow velocity in early diastole (E wave velocity) and during atrial contraction (A wave velocity); E/A ratio; E and A wave time-velocity integrals; deceleration time of the E-wave (DtE) and duration of the A wave (A wave duration); isovolumetric relaxation time of the left ventricle (IVRT).

Outcome

The evolution of gestation was followed until term by an investigator, blinded as to the results of maternal echocardiography. We considered for the study only the two main outcomes: early-onset (before 34 weeks gestation) and late-onset-PE (≥34 weeks gestation) and excluded the other complications from the analysis.

Postpartum Control

All patients had a clinical and echocardiographic examination 1 year after delivery.

Statistical Analysis

Patients were classified as normal outcome and early and late onset PE. Values are expressed as mean±SD. Comparisons between groups were performed using the 1-way ANOVA with Student-

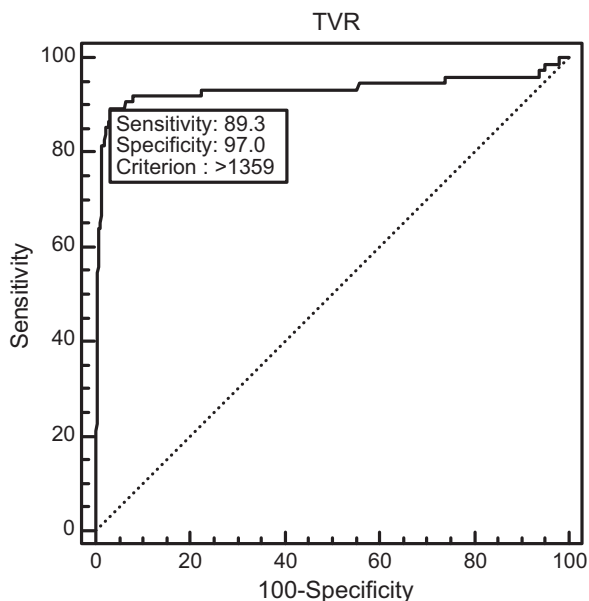


Figure 1. This ROC curve reports the cut-off value of TVR for the prediction of early PE ($>1359 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$). Sensitivity, specificity, positive, and negative predictive values were 89.3%, 97.0%, 66.3%, and 99.3%, respectively. It is interesting to note that this value is similar to that previously reported by Vasapollo et al⁹ in a similar population.

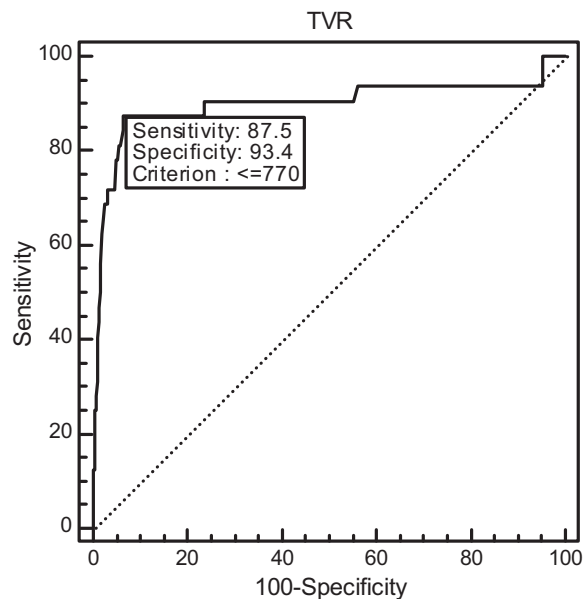


Figure 2. This ROC curve reports the cut-off value of TVR for the prediction of late PE ($\leq 770 \text{ dyn} \cdot \text{s} \cdot \text{cm}^{-5}$). Sensitivity, specificity, positive, and negative predictive values were 87.5%, 93.4%, 26.2%, and 99.6%, respectively.

Newman-Keuls correction for multiple comparisons, whereas the intragroup comparison between pregnancy and postpartum data were performed using the ANOVA for repeated measurements. The Mann-Whitney *U* test was used for nonnormally distributed data. Because of the strong predictive power of TVR for complications found in previous reports,^{9–11} we built separate Receiver-operator characteristic (ROC) curves to find the best cut off value for early and late PE, respectively. We also built a ROC curve for the prediction of late PE through BMI. To test intraobserver and interobserver variability, 2 independent observers measured data on videotape recordings from 20 randomly selected patients. The same data were than remeasured on tape after 1 month by 1 of the 2 observers.

Results

Three hundred forty-three patients were excluded from the study because of missing data for pregnancy outcome (185 patients), follow-up drop outs (148 patients), and persisting high blood pressure values at the follow up visit (10 patients). Of the 1345 remaining patients, 226 (16.80%) had a maternal or fetal complications (Table 1): 107 patients (7.95%) had early or late PE either isolated or associated to FGR; 119 (8.85%) patients had other maternal or fetal complications; 1119 women had normal outcome of pregnancy and were considered as controls. Table 2 reports the main features of the controls and early and late PE group. Early PE showed an increased percentage of patients >35 years old, a higher prevalence of bilateral notching at 24 weeks gestation, a lower gestational week at delivery, and a lower neonatal weight centile compared to both controls and late PE. Patients with late PE showed a higher prepregnancy BMI compared to both the normal outcome and early PE groups. The prevalence of bilateral notching of the uterine artery at 24 weeks was higher compared to the normal outcome and lower compared to early PE.

Table 3 shows the main hemodynamic features of the 3 groups at 24 weeks gestation and at 1 year postpartum follow-up. During pregnancy (Table 3) late PE was characterized by the highest LVMi, and CO, and lowest TVR compared to early PE and controls. In the postpartum (Table 3) early PE showed intermediate LVMi as compared to late PE and controls, with the highest value of TVR. Late PE was characterized by the lowest value of TVR, larger diameter of the left ventricle, with the highest CO. RWT was increased in both early and late PE when compared to controls.

Intragroup comparisons in controls showed significantly ($P<0.001$) higher HR, LVM and LVMi, LVDd, IVSd and PW thickness, RWT, SV, and CO, whereas TVR was lower during pregnancy compared to the postpartum values.

Intragroup comparisons in the late PE showed a significantly ($P<0.001$) higher HR, LVM and LVMi, LVDd, IVSd and PW thickness, RWT, SV, and CO in pregnancy compared to the postpartum values, whereas the SBP, DBP, MBP, and TVR were significantly lower. LA fractional area change (FAC) remained unchanged.

Intragroup comparisons in the early PE showed a significantly ($P<0.001$) higher LVM and LVMi, IVSd and PW thickness, RWT, and TVR in pregnancy compared to the postpartum values, while the SV and the CO were lower.

Figures 1 and 2 show the cut-off values for TVR, sensitivity, and specificity for the prediction of these complications.

The overall sensitivity, specificity, positive and negative predictive value for detection of early and late PE using a cut-off value of >1359 and $\leq 770 \text{ dyne} \cdot \text{s} \cdot \text{cm}^{-5}$ were 92.5%, 90.5%, 48.3%, and 99.2%, respectively.

Figure 3 shows the best cut off of BMI for the prediction of late PE.

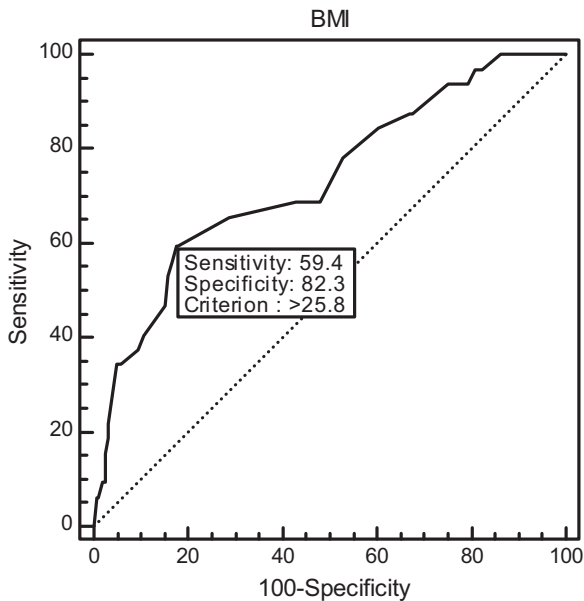


Figure 3. This ROC curve reports the cut-off value of prepregnancy BMI for the prediction of late PE (>25.8 kg/m²). Sensitivity, specificity, positive, and negative predictive values were 59.4%, 82.5%, 8.3%, and 98.7%, respectively.

Figure 4 shows CO plotted against MBP for each patient with isometric lines of TVR.

Table 4 shows the main diastolic features of the 3 groups at 24 weeks gestation and at 1 year postpartum follow-up. During pregnancy (Table 4) late PE was characterized by the longest DtE and the lowest E/A ratio, compared to early PE and controls. IVRT, E wave, and A wave were similar when comparing late PE and controls, whereas early PE showed the shortest DtE, the longest IVRT with the lowest values of the A wave parameters when compared with both controls and

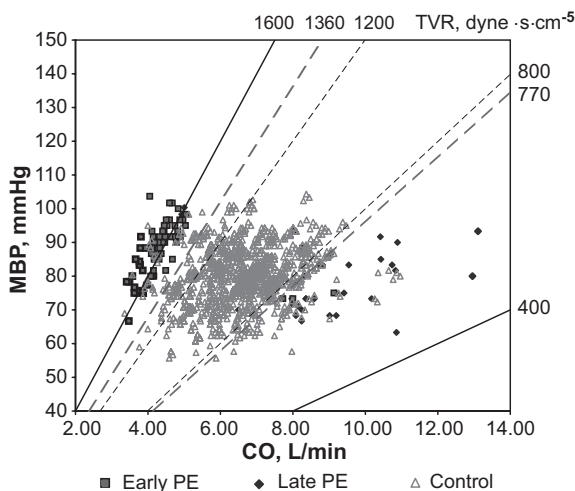


Figure 4. Scatter plot of MBP vs CO detected for each subject at 24 weeks in the asymptomatic phase. Isometric lines of TVR were built so that it is evident the distribution of each group within the lines of TVR. Controls (open triangles) are mostly concentrated between the isometric lines 770 and 1360 dyn · s · cm⁻⁵. Patients with subsequent early PE (closed squares) are grouped in an area above the isometric line of 1360 dyn · s · cm⁻⁵, whereas patients with subsequent late PE (closed rhombi) are distributed under the isometric line of 770 dyn · s · cm⁻⁵.

Table 4. Parameters of Diastolic Function at 24 Weeks Gestation and 1 Year Postpartum

Parameter	Controls n=1119	Early PE n=75	Late PE n=32
24 weeks gestation			
E wave velocity, cm/s	86±11	102±17*	86±12†
E wave time-velocity integral, cm	15±6	16±7	14±4
DtE, ms	274±40	190±62*	292±21*†
A wave velocity, cm/s	75±8	63±9*	79±5†
A wave time-velocity integral, cm	9±2	7±2*	10±3
A wave duration, ms	147±11	131±17*	149±9†
IVRT, ms	76±9	93±8*	79±5†
E/A ratio	1.17±0.23	1.68±0.50*	1.09±0.15*†
1 year postpartum			
E wave velocity, cm/s	95±15	89±17*	86±18*
E wave time-velocity integral, cm	15±5	16±7	14±5
DtE, ms	211±57	224±58*	252±58*†
A wave velocity, cm/s	65±9	72±12*	73±15*
A wave time-velocity integral, cm	7±1	7±2	8±2
A wave duration, ms	129±17	134±17	139±14
IVRT, ms	84±9	94±11*	84±6†
E/A ratio	1.53±0.47	1.26±0.26*	1.21±0.27*

*P<0.05 vs controls.
†P<0.05 vs early PE.

late PE. In the postpartum (Table 4) early and late PE patients showed lower E wave, and E/A ratio compared to controls. DtE was longer in late versus Early PE and controls and IVRT showed the longest value in early PE.

Intragroup comparisons in controls showed significantly (P<0.05) higher E wave velocity, shorter DtE, lower A wave velocity, time-velocity integral, and duration, longer IVRT, and higher E/A ratio in the postpartum compared to pregnancy.

Intragroup comparisons in the early PE showed a significantly (P<0.05) longer DtE, lower E wave velocity, higher A wave velocity, and lower E/A ratio in the postpartum compared to pregnancy.

Intragroup comparisons in the Late PE showed a significantly (P<0.05) shorter DtE, lower A wave time-velocity integral, and duration, and longer IVRT in the postpartum compared to pregnancy.

Inter- and Intraobserver Variability

Intra- and interobserver variability in terms of coefficient of variation (CV) and regression coefficient are reported. For the interventricular septum thickness, the CVs were 7.2% (r=0.98) and 7.4% (r=0.97) for intra- and interobserver error respectively. For the posterior wall thickness (PWT) they were 8.0% (r=0.98) and 8.1% (r=0.96), for the left ventricular diastolic diameter they were 5.0% (r=0.98) and 7.6% (r=0.97), for the left ventricular systolic diameter they were 7.1% (r=0.98) and 7.6% (r=0.96), for the LVM they were 8.4% (r=0.95) and 8.8% (r=0.94).

Discussion

Early (before 34 weeks) and late (≥34 weeks) onset PE probably recognize different etiologies and therefore develop

through different models of maternal cardiovascular adaptation in the latent phase of the disease and in the postpartum. The novel finding of this study is the identification of two drastically different hemodynamic states at 24 weeks gestation preceding the appearance of early and late PE: early PE appears to be linked mainly to failed placental vascular remodeling and expresses through a high TVR-low CO response, whereas late PE might be more linked to maternal constitutional factors and is characterized by a low TVR-high CO.

Uterine Artery Doppler

Late PE has been reported to be associated with normal or slightly altered uterine artery Pulsatility Index;⁴ early PE is more often associated with altered uterine artery Doppler.⁴ Our results are in accordance with these observations because we found a significantly higher percentage of bilateral notching in the early PE group (60.0%). On the other hand, the percentage of bilateral notching in the late-PE was significantly higher than controls (15.6% versus 6.0%), suggesting a placental involvement in a confined number of patients. Another interesting result is that patients with subsequent normalization of the uterine artery Doppler at 24 weeks gestation are at risk for complications when the cardiac response appears to be abnormal: in fact, in the early preeclampsia group “only” 60% had a persisting bilateral notch denoting that also when we have a subsequent normalization the complication might occur when TVR is altered.

Age

It was interesting to see how maternal age was different in the two groups of preeclampsia: early onset PE are older with a higher percentage of women over 35 years than late onset PE and controls. Although it is well known that an age more than 35 years is linked to a higher risk for preeclampsia, the importance of age in early and late preeclampsia has not been clearly reported so far. An intriguing hypothesis could be that an older age might negatively influence the placental process, but this should be confirmed on larger numbers with the whole set of hemodynamical data.

Prepregnancy BMI

Among the maternal factors that may contribute to the development of late-PE, prepregnancy BMI seems to play a crucial role. In our study late PE shows the highest values of BMI. Many of the maternal hemodynamic and cardiac morphological differences among late and early PE and controls might be explained by this anthropometric feature. In fact, in the late PE group the higher LVM, SV, and CO and lower TVR, not only during pregnancy, but also at 1 year follow-up, might reside in the high BMI of this group. This is in accordance with several observations showing an expanded intravascular volume associated with obesity, which is related to an increased venous return to the heart, increased CO, and increased blood flow to kidneys and other organs in normal and hypertensive patients.²⁷

In the past we reported^{9–11} different maternal cardiovascular features in the preclinical phase of PE from those found by Bosio¹² and Easterling.¹³ We described high TVR-low CO whereas Bosio¹² and Easterling¹³ observed low TVR-high CO.

We can explain this difference considering that Bosio's¹² and Easterling's¹³ series were mainly characterized either by higher BMI (27 kg/m²) or weight (80.5 kg) versus the controls; high BMI and obesity might per se cause a hemodynamic state with low TVR-high CO.²⁷ Moreover, in these studies the main complication was late PE (mean gestational age at delivery: 36 weeks and 39 weeks in the Bosio's¹² and Easterling's¹³ series, respectively), without FGR. Our series, instead, mainly showed early PE with a BMI of 24 kg/m² often associated to FGR, the latest characterized by a hypovolemic state^{18,20,28} with high TVR and low CO.^{18,20,29} In the past, similar results on hypertensive patients with high TVR and lower birthweight were found by Easterling et al.³⁰ We may hypothesize that Bosio's¹² and Easterling's¹³ series and our previous studies^{9–11} were describing two different disease entities: one determined by maternal factors (late PE), and the other of placental origin (early PE).

In the present study the hemodynamics found at 24 weeks gestation in patients subsequently developing late PE appears to be similar to that described by Bosio¹² and Easterling.¹³ Moreover, neither our late PE nor Bosio's¹² and Easterling's¹³ showed FGR.

TVR in Pregnancy

Another important result is the prediction of late PE by TVR: in contrast with early PE, where high TVR appears to predict this complication⁹ (confirmed also by the present study; Figure 1), late PE is predicted by TVR ≤ 770 dyne (Figure 2). These data are in accordance with those published by Easterling et al.,¹³ showing lower TVR values at 20 to 25 weeks in patients with subsequent late PE versus controls. It is interesting to note that some of the early PE patients are in the low TVR area, whereas some of the late PE are in the high TVR area (Figure 4), testifying to the complex pathophysiology of PE in which factors favoring the early or late appearance of the disease might interact differently.

Diastolic Function in Pregnancy

Diastolic function differs among early PE, late PE, and controls. In particular, A wave velocity and time-velocity integral values suggest that atrial contribution is increased in both controls and late PE, whereas it seems to fail in early PE. This is also confirmed by the atrial FAC around 50% in controls and late PE, and lower in early PE. DtE and IVRT in late PE resembles the physiological response to pregnancy as obtained in this study and previous reports.²⁶ Although the interpretation of these results might be controversial, these parameters might suggest a more altered diastole in early compared to late PE patients in which the latest (late PE) achieve the goal of increasing the diastolic filling of the left ventricle despite a more hypertrophied ventricle, whereas the former (early PE) fail in this attempt.

Morphometry of the Left Ventricle

The early PE group shows increased relative wall thickness and small left ventricular diameter at 24 weeks gestation versus both controls and late PE. These features resemble a concentric geometric pattern of the left ventricle suggesting an underfilling state with pressure overload. On the contrary the late PE group shows the largest diameter of the left

ventricle with an intermediate relative wall thickness as compare to controls and early PE. This identifies a hypertrophized ventricle with high CO, interpretable as an overfilling state without pressure overload.

Postpartum

Because, as previously reported by Agatisia et al,³¹ women with previous PE exhibit impaired endothelial function 1 year postpartum, it should not surprise to find different left ventricular morphometric patterns in formerly preeclamptic women as compared to controls. In fact, in early and late PE are both characterized 1 year postpartum by a higher RWT and a more hypertrophized ventricles versus controls, late PE showing a larger LV diameter. DtE and IVRT, instead, show a totally different behavior from pregnancy to the postpartum in early PE (with an increased time of DtE and an unchanged IVRT) as compared to both controls and late PE (in which DtE becomes shorter and IVRT longer).

The behavior of TVR after pregnancy in late and early PE is different. In the first group there is an elevation of TVR value, although it remains lower than controls; on the contrary, in the second group there is a drop of TVR value as previously described.¹⁰ It is interesting to note the similarity of the hemodynamics characterized by an underfilling state as previously described in patients with previous PE^{14,15} with our early PE group, whereas late PE women at 1 year postpartum show a low TVR-high CO state associated to higher BMI.

The most surprising result is related to the persistence of these diverging hemodynamics in the two groups (high TVR in formerly early PE, and low TVR in formerly late PE), suggesting that both late and early PE might be at increased risk for cardiovascular diseases later in life with drastically different hemodynamic pathways.

Perspectives

A possible interpretation of the data from this study might be that the early PE patients have an earlier low TVR stage compared to late PE, so that at 24 weeks they already have crossed over to the high TVR phase of the disease; this possible interpretation needs further longitudinal data from early pregnancy to be clarified, although this hypothesis would not explain why 1 year postpartum formerly early PE still show high TVR and formerly late PE have low TVR. At this stage, considering the postpartum data, the present study seems to support the view that early and late PE develop from two different hemodynamics. Early preeclampsia appears to be more related to the evolution of an extremely altered cardiovascular response probably triggered by a placental disorder. Late preeclampsia seems to be more linked to maternal constitutional factors.

The implication of these findings might lead to different preventive strategies and pharmacological interventions in early and late PE in the future.

Disclosures

None.

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