New Directions of Maternal Factors and Ultrasound Markers in the Prediction of Early and Late Pre-Eclampsia

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Abstract

Pre-eclampsia (PE) is one of the hypertensive pregnancy disorders, de novo protein-uric hypertension that develops after 20 weeks of gestation and it is a systemic disorder associated with high maternal and neonatal morbidity and mortality. The aim of this study was to determine the usefulness as a screening method for early- and late-onset pre-eclampsia of a combination of a series of measurements, including maternal characteristics and UtA Doppler measured at 11 + 0 to 13 + 6 weeks of gestation and 22 to 24 weeks of gestation. This is a retrospective cohort study, during January - December 2017, of women who have had Pre-eclampsia at a tertiary referral University Hospital of Obstetrics and Gynecology "Koço Gliozheni" in Tirana, Albania. In total were 62 women with Pre-eclampsia during this period of time. Maternal and neonatal data were collected from the case notes and was done uterine artery color Doppler examination at 22-24 weeks of gestation. The ultrasound machine used was Aloka Echo Camera L. All data were calculated with SPSS 15.0. T-test, Chi-Square test, Fisher test and Correlation were used for statistical analysis. In total, 62 women with Pre-eclampsia were classified: 32% Early PE and 68% Late PE. In Doppler examination 26 % had bilateral notch at uterine artery, 12 % notch at AU Dexter, 15 % notch at AU Sinister and 47,1 % without notch. 58.8 % Apgar score in the first minute was 8 and

67.6 % in the fifth minute was 9. Mean Fetus Weight at Early PE 1543.18 g and at Late PE 2623.91 g and mean NICU was 37.82 days at early PE and 6.87 days at Late PE. There is a very significant correlation between Fetus Weight (g) and NICU (R=-0.84, p<0.001) also there is a significant difference between the presence of IUGR on early and Late PE (Fisher's Exact Test = 8.192, p=0.008). There is a significant difference on CPR values on early and late PE (T-test = -2.127, p=0.041).

Keywords: pre-eclampsia, maternal characteristics, screening, uterine artery Doppler

Introduction

Pre-eclampsia (PE) is one of the hypertensive pregnancy disorders, de novo proteinuric hypertension that develops after 20 weeks of gestation, which affects from 3 to 5% of pregnant women. It is a systemic disorder associated with high maternal and neonatal morbidity and mortality (Roberts JM. 2001.) In addition, PE frequently coexists with intrauterine growth restriction (IUGR, also called fetal growth restriction), placental abruption, and the need for iatrogenic preterm delivery, which are additional major causes of adverse outcomes. (Poon LC et al. 2010). Its diagnosis is based on clinical features, such as high blood pressure and proteinuria, which are the terminal events of a cascade of phenomena that are likely initiated during placental formation and development in the late first trimester of gestation (Redman CWG. 2009). Increasingly, early-onset pre-eclampsia is considered to be a more severe form of the disease than is the late-onset condition (Romero R. 2008). Many groups have focused on methods to predict pre-eclampsia in order to identify accurately pregnant women who are at risk (Nicolaides KH. 2007). Pregnancy-related HD are thought to be the consequence of impaired trophoblastic invasion of the maternal spiral arteries, resulting in maintenance of vessels of high resistance, inadequate perfusion of the placenta, tissue injury, and increased production of vasoconstrictive substances. In these cases, there are qualitative and quantitative changes in the maternal uterine artery (UA) Doppler waveforms. Maternal uterine artery (UtA) Doppler at 22–24 weeks of gestation has become the most reliable tool for prediction of pre-eclampsia; this diagnostic test has the ability to predict nearly 50% of instances of any form of the disease and approximately 85% of cases of severe or early-onset disease (Parra M et al. 2005), (Yu CK et al. 2005). However, UtA Doppler performed in the final weeks of the first trimester of gestation (11 + 0 to 13 + 6 weeks) varies much more in its predictive ability for early-onset pre-eclampsia than it does at the second-trimester scan. (Martin AM et al. 2001), (Plasencia W et al. 2007) The majority of the studies evaluated the UA Doppler in the second trimester of pregnancy, supposedly because the trophoblastic invasion of the maternal spiral arteries has finished at this point. On the other hand, there is now strong evidence demonstrating that abnormal UA Doppler in the first trimester of pregnancy is also

associated with abnormalities in trophoblast invasion. 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. (Von Dadelszen P et al. 2003), (Huppertz B. 2008). Early-onset PE (before 34 weeks) is commonly associated with abnormal uterine artery Doppler, fetal growth restriction (FGR), and adverse maternal and neonatal outcomes. (Ness RB et. al. 2006), (Murphy DJ et al. 2000), (Walker JJ. 2000). 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. (Ness RB. 2006), (Sibai B. 2005). Early-onset PE and FGR are placenta-mediated diseases (Crispi F et al. 2006) 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 risk factors: age, parity, previous obstetric history, etc. Maternal echocardiography might identify at 24 weeks gestation patients who subsequently develop early severe maternal and fetal complications through the assessment of maternal hemodynamics suggesting an involvement of the whole cardiovascular system in the placental mediated disorder. (Vasapollo B et al. 2008), (Valensise H et al. 2006), (Novelli GP et al. 2003), (Bosio PM et al. 1999). The abnormal placentation that characterizes pre-eclampsia is associated with an increased resistance in the utero-placental circulation. Ultrasonography evidence of this resistance includes the presence of a diastolic 'notch' in the Doppler waveform of the uterine artery or an increase in that vessel's pulsation index (PI). (Campbell S et al. 1983) Being an objectively measured continuous variable, the latter is preferable to the somewhat subjective assessment of 'notching'. (Lees C. 2010) It has been suggested that Doppler studies might be most predictive if performed in a sequential fashion in both the first and second trimesters. (Napolitano R et al. 2012) However, such an approach would preclude the early initiation of prophylaxis. Other potential ultrasonography parameters for the prediction of pre-eclampsia include 3D power Doppler assessment of placental volume and vascularity, maternal MCA Doppler indices (Belfort M et al. 2012). Further research will determine whether any of these is superior to uterine artery Doppler analysis.

Materials and Methods

This is a retrospective cohort study, during January - December 2017, of women who have had Pre-eclampsia at a tertiary referral University Hospital of Obstetrics and Gynecology "Koço Gliozheni" in Tirana, Albania. In total were 62 women with Pre-eclampsia during this period of time. Maternal demographic characteristics, ultrasonography measurements (uterine artery color Doppler examination at 22-24 weeks of gestation) and neonatal data were collected from the case notes (medical records and were recorded in a computer database). The ultrasound machine used was Aloka Echo Camera L. All ultrasound examinations were performed by an obstetrician. PE cases were managed by medical team, obstetric consultants. Data were collected on patient age, parity, gestational age at time of delivery, history of previous PE, mean arterial pressure and Doppler ultrasound parameters. Neonatal

evaluation included neonatal birth weight, Apgar score at 1 and 5 minutes, neonatal gender, generality admission to the neonatal intensive care unit. All data were calculated with SPSS 15.0. T-test, Chi-Square test, Fisher test and Correlation were used for statistical analysis.

Results and Discussions

In total, 62 women with Pre-eclampsia were classified: 32% Early PE (before 34 weeks) and 68% Late PE (after 34 weeks). At the table Nr.1 we can see that the mean age of mothers with PE was 32.65 years old, Std. deviation = 5.851 years. 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. 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 hemodynamic data. The mean age of mother at Early PE was 34.45 years old and at Late PE was 31.78 years old. (Table nr.2).

Parity was also a maternal characteristic that could interfere in the trophoblastic invasion of the maternal spiral arteries in the present study. Pre-eclampsia is more common among women who: has had a baby (50% second parity, 14.7% third parity, 2.9 % multiparity). At the Table Nr.1 are summarized the neonatal complications, like as: Low Birth Weight (mean 2200-2300 g) and some of them IUGR. It has also been observed that women carrying male fetuses (62%) are at slightly greater risk for PE than are women carrying female fetuses (38%). We can admit that 29 % of women of PE have had previous PE in their pregnancies.

The mean arterial pressure is calculated by dividing the sum of the systolic and twice the diastolic blood pressures by three and is thus easily measurable. As we can see that the mean systolic blood pressure is 160 mm Hg (for Early PE 167.7 and for Late PE 156.3 mm Hg) and mean diastolic blood pressure is 96.5 mm Hg (for Early PE 99.55 and for Late PE 95 mm Hg). (Table Nr.1 and Nr.3, Fig. Nr.1).

The utility of Doppler analysis of the uterine artery in predicting pre-eclampsia has been extensively studied initially in the mid-second trimester and more recently in early pregnancy. The abnormal placentation that characterizes pre-eclampsia is associated with an increased resistance (RI) in the utero-placental circulation. Ultrasonography evidence of this resistance includes the presence of a diastolic 'notch' in the Doppler waveform of the uterine artery or an increase in that vessel's pulsation index (PI). In our study, the mean UA RI was calculated in both trimesters of pregnancy.

We considered abnormal values greater than 0.85 and 0.77 in the first and second trimester, respectively. Being an objectively measured continuous variable, the latter is preferable to the somewhat subjective assessment of 'notching'. At the table Nr.3

we can see that mean CPR at Early PE is 1.3 (around 1) and at Late PE 1.79. We can see that in Doppler examination 26% had bilateral notch at uterine artery, 12 % notch at AU Dexter, 15 % notch at AU Sinister and 47,1 % without notch (figure nr.2).

PE is associated with an increase in preterm birth and neonatal outcome. Fetal intrauterine growth retardation (IUGR + PE 38 %), Low birth weight (< 2500 g), low Apgar score which needs admission in neonatal intensive care unit. Mean Fetus Weight at Early PE 1543.18 g and at Late PE 2623.91 g and mean days that neonatal had stayed in the Intensive Care Unit was 37.82 days at early PE and 6.87 at Late PE. (Table Nr.2) In the figure Nr.4 we can see that 58.8 % APGAR score in the first minute was 8 and 67.6 % in the fifth minute was 9. From the table nr.4. we can see that exist a very significant correlation between Fetus Weight (g) and NICU, Apgar min 1 and Apgar min 5. The lower fetus weight, higher is NICU (R=-0.84). On the other side the lower fetus weight, lower is the APGAR min 1 and min 5 (R=0.574 and R=0.688). Also as higher the APGAR min 1 and min 5 as lower the NICU. There is a significant difference between the presence of IUGR on early and Late PE. As we can see from figure nr.5 the presence of IUGR is higher on early PE (Fisher's Exact Test = 8.192, df=1, p=0.008 (2-sided). There is a significant difference on CPR values on early and late PE (T-test = -2.127, p=0.041). (see the tab. Nr. 5)

Conclusion

Abnormal uterine artery Doppler studies in the first and second trimester combining with maternal factors are useful to predict PE in low-risk pregnant women and have been associated with subsequent adverse pregnancy outcomes including preeclampsia, fetal growth restriction, and perinatal mortality. Early PE showed: an increased percentage of patients >35 years old, an increased PI and an elevated RI of uterine artery Doppler, a higher prevalence of bilateral notching at 24 weeks gestation, a lower gestational week at delivery, a lower neonatal weight centile and some days at the NICU.

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Table Nr.1 Maternal and Neonatal parameters

	Minimum	Maximum	Mean		Std. dev.
	Statistic	Statistic	Statistic	Std. Error	Statistic
Maternal Age	18	45	32.65	1.003	5.851
Parity	1	4	1.88	0.132	0.769
Maternal Weight(kg)	66	127	83.82	1.941	11.318
Maternal Height(cm)	153	169	161.53	0.643	3.752
SBP	140	190	160.00	2.214	12.910
DBP	75	110	96.47	1.204	7.020
PI UA	0.70	1.39	1.0318	0.03527	0.20567
PI MCA	0.60	2.80	1.6597	0.09690	0.56504
CPR	0.70	3.59	1.6388	0.11498	0.67046
Fetus Weight (g)	975	3600	2274.26	130.236	759.398
APGAR Min 1	2	9	7.8529	0.20740	1.20937
APGAR Min 5	6	9	8.6176	0.11182	0.65202
NICU	0	62	16.88	3.453	20.137

Table Nr.2: Mother's Age

	PE	Mean	Std. Deviation	Std. Error Mean
Age	Early PE	34.45	6.758	2.038
	Late PE	31.78	5.308	1.107

Table nr.3. Blood Pressure, Doppler Parameters, Fetus Weight and NICU

PE		SBP	DBP	PI UA	PI MCA	CPR	Fetus Weight (g)	NICU
Early PE	Mean	167.73	99.55	1.1245	1.5100	1.3027	1543.18	37.82
	Std. Dev	14.029	6.105	.16299	.60656	.42800	446.667	16.424
Late PE	Mean	156.30	95.00	.9874	1.7313	1.7996	2623.91	6.87
	Std. Dev	10.789	7.071	.21216	.54323	.71241	615.864	12.715
Total	Mean	160.00	96.47	1.0318	1.6597	1.6388	2274.26	16.88
	Std. Dev.	12.910	7.020	.20567	.56504	.67046	759.398	20.137

Tab. Nr. 4. The correlation between Fetus Weight (g) and NICU, APGAR min 1 and min 5.

		Fetus Weight (g)	APGAR min 1	APGAR min 5	NICU
Fetus Weight(g)	Pearson Correlation	1	.574(**)	.688(**)	-.841(**)
	Sig. (2-tailed)		.000	.000	.000
APGAR min 1	Pearson Correlation	.574(**)	1	.810(**)	-.659(**)
	Sig. (2-tailed)	.000		.000	.000
APGAR min 5	Pearson Correlation	.688(**)	.810(**)	1	-.800(**)
	Sig. (2-tailed)	.000	.000		.000
NICU	Pearson Correlation	-.841(**)	-.659(**)	-.800(**)	1
	Sig. (2-tailed)	.000	.000	.000	

Tab. Nr.5. CPR values on early and late PE

	PE	Mean	Std. dev	Std. Error Mean
CPR	Early PE	1.3027	.42800	.12905
	Late PE	1.7996	.71241	.14855

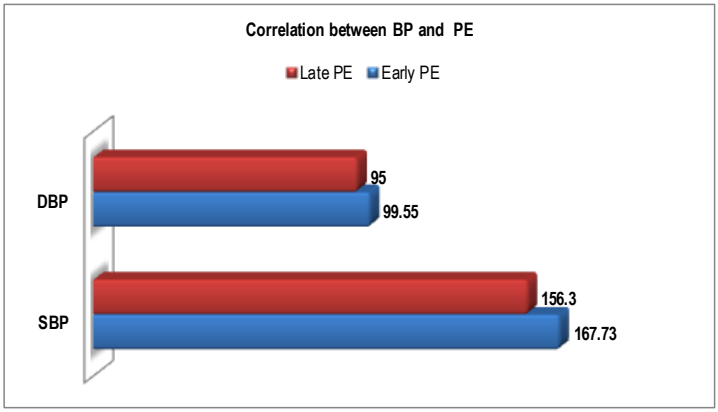
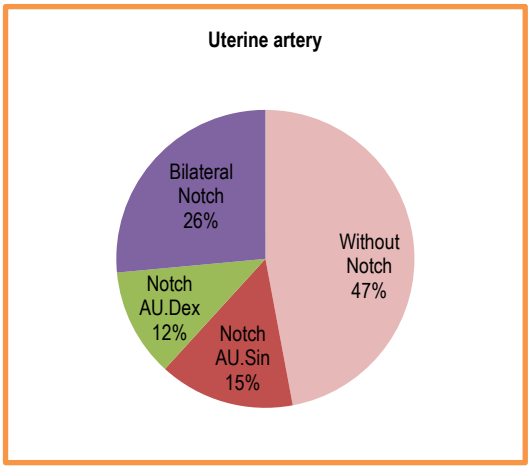


Fig. Nr. 1. Sistolic and Diastolic Blood Pressure



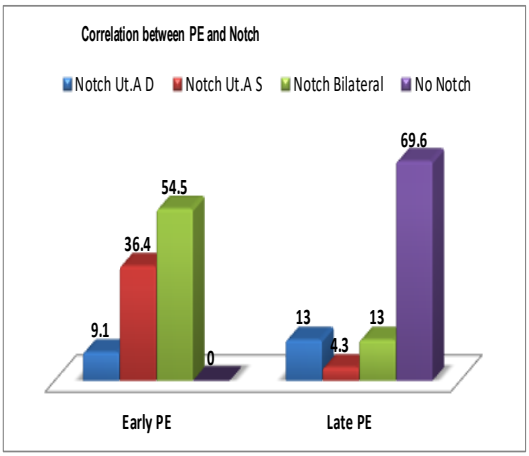
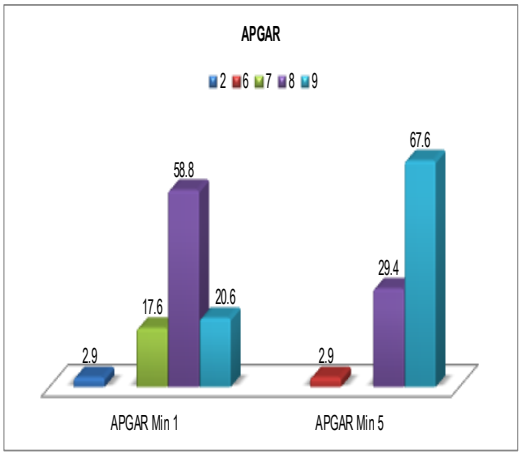


Fig. Nr.2. Doppler of Uterine Artery Fig. Nr.7. Doppler of Uterine Artery



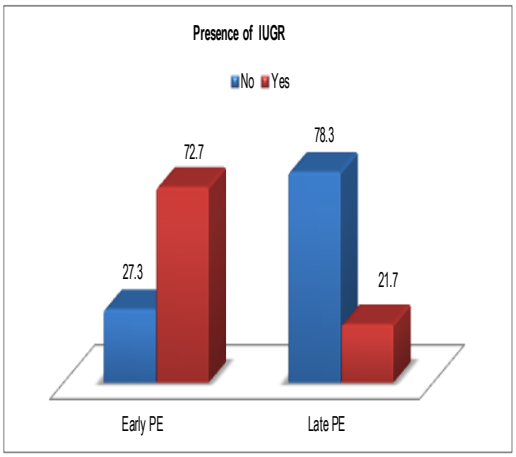


Fig. Nr.4. APGAR minute 1 & 5Fig. Nr.5. The presence of IUGR

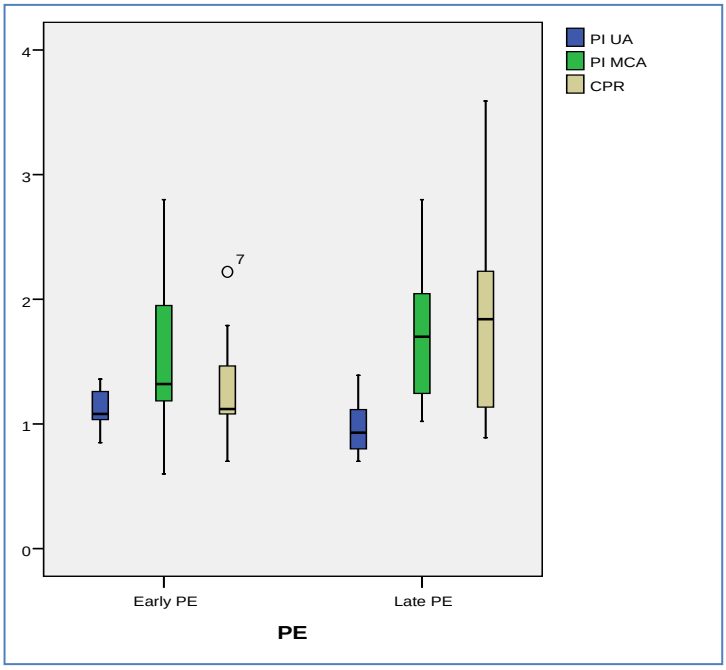


Fig. nr. 6. The values of PI UA, PI MCA, CPR on early and Late PE