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Comparison between Placental 3D Power Doppler and Uterine Artery Pulsatility Index in Early Prediction of Pre-eclampsia

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***Abstract*---**Aim of the work: To compare between placental 3D Power Doppler vascular indices and uterine artery pulsatility index in early prediction of preeclampsia. Methods: The prospective comparative observational cohort study included 200 women in their first trimester at 11–14 weeks of pregnancy divided into 2 groups. 100 women with no risk factor to develop preeclampsia (control group), 100 women with any risk factor to develop preeclampsia (case group). All women were examined by 3D abdominal ultrasound, Blood flow in placenta was examined using 3D power Doppler technique for the placental vascular indices. Uterine artery pulsatility index was also assessed. All Patients were followed up to the end of their pregnancies and their medical files reviewed to obtain whether patients developed preeclampsia and other hypertensive disorders. Results: Overall, 17 women developed pre-eclampsia while 183 women remained normotensive (7 out of 100 women in the control group and 10 out of 100 women in the case group). In both groups the women with pre-eclampsia had significantly lower placental vascular indices (vascularization index, flow index, and vascularization flow index) compared with the normotensive women. In contrast, women with pre-eclampsia in both

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groups had significantly high mean uterine pulsatility index compared with the normotensive women. However, there were no statistically significant differences between both groups regarding placental vascular indices and uterine artery pulsatility index. Conclusion: The Mean Uterine P.I was the most predictive of preeclampsia, followed by Placental V.I. and Placental V.F.I. and so they were able to predict cases while Placental FI was not found as a significant predictor.

***Keywords*---**placental vascular indices, uterine artery pulsatility index, three-dimensional Doppler ultrasound, prediction and pre-eclampsia.

Introduction

The placenta is a complex organ, rich in blood vessels, created by pregnancy to ensure the feto-maternal exchanges necessary for the nutrition and development of the product of conception (Guimar et al., 2010). Uterine and placental vascularizations are important for normal pregnancy development. Impaired trophoblastic invasion of the maternal spiral arteries and their conversion from narrow muscular vessels to wide non-vascular channels in the second trimester is responsible for defective placentation that has been implicated in the pathophysiology of preeclampsia (Kovo et al., 2013).

Because of this change, the uterine artery Doppler in normal pregnancies is characterized by low resistance and a high-flow pattern. However, in hypertensive pregnancies, incomplete trophoblast invasion results in an abnormal uterine artery Doppler pattern, which is characterized by an increased pulsatility index (PI) and an early diastolic notch (Seung et al., 2016). Abnormal placental development is associated with a few obstetrical adverse outcomes, such as preeclampsia, fetal growth restriction, preterm labor, fetal hypoxia and death (Cnossen et al., 2008).

Quantitative and qualitative assessment of placental blood flow and vascularization has become more feasible with recent advances of three dimensional power Doppler ultrasonography (3D PDUS) and 3D power Doppler histogram analysis. 3DP DUS can detect internal placental vessel features including density, caliber changes, branching and tortuosity (Hata et al., 2011). Intraplacental blood circulation is described by three vascular indices: vascularization index (VI), flow index (FI), and vascularization flow index (VFI) (Merce´ et al., 2004).

Vascularization index is the ratio of the number of color voxels to the total number of voxels in the sampled tissue, thus it represents the percentage of vascularized tissue. Flow index is the average color value of all color voxels and it describes the mean velocity of flow in the sampled tissue. The vascularization-flow index is the average color value of all color and gray voxels and describes both: the vascularization and the blood flow (De Paula et al., 2009).

Early-onset preeclampsia with pregnancy termination before 34weeks gestation is usually accompanied with intrauterine growth restriction, abnormal Doppler waveform-pattern of uterine and umbilical arteries, and adverse outcomes for both the mother and the fetus. On the other hand, late-onset preeclampsia, requiring delivery at/or after 34weeks gestation, is usually associated with low maternal morbidity, little fetal involvement and its perinatal outcomes are usually favorable. So, prediction of preeclampsia very early in pregnancy makes early prophylactic measures more effective (Park et al., 2015).

Aim of the Work

The aim of the work is to compare between the value of three-dimensional power Doppler (3D-PD) indices and uterine artery pulsatility index between 11 weeks and 14 weeks in predicting preeclampsia.

Patients and Methods

This study was conducted as comparative observational cohort study in the Obstetric Ultrasound Unit at one of the Egyptian family hospitals on patients with high-risk group (n=100) and control group (n=100). The study included patients with 11-14 weeks pregnancy, single viable intrauterine pregnancy, normal fetal morphology by ultrasound and known last menstrual period and early first trimester ultrasound confirming the date of the last period. While patients with fetal anomalies, active bleeding or threatened miscarriage and uterine malformation or uterine myoma that could interfere with the volume measurements were excluded from the study.

200 Patients were included in this study, divided into two groups. The first was a control group, 100 patients with normal obstetric history were included. The second was a high-risk group, 100 patients with any of the risk factors for preeclampsia according to the national institute for health and care excellence (NICE) were included: First pregnancy, Age 40 years or older, Pregnancy interval of more than 10 years, Body mass index (BMI) of 35 kg/m2 or more at first visit., Family history of pre-eclampsia, Multiple pregnancy., Hypertensive disease during a previous pregnancy, Chronic kidney disease, Autoimmune disease such as systemic lupus erythematosus or antiphospholipid syndrome, Type 1 or type 2 diabetes, Chronic hypertension.

Intervention:
After taking informed written or verbal consent and explaining the whole procedure the recruited patients were subjected to the following:
Careful and detailed history: Personal history: Name, age, occupation, residence, contact number and special habits of medical importance. Menstrual history: First day of last menstrual period for accurate estimation of gestational age and antenatal care. Obstetric history: Previous history of preeclampsia, pregnancy-induced hypertension or placental insufficiency. Past history**:** History of any medical disorder (Hypertension, diabetes, thrombophilia or renal disease) and surgical history.

Examination of the patients:

- General examination
- Abdominal examination

3D Power Doppler:
Acquisition of the images used for the determination of vascularization indices were obtained at the time of the first-trimester visit.
"Scans were performed by the same experienced sonographer using a Voluson P8 Expert ultrasound machine (GE Healthcare, USA) equipped with a 3.5 MHz transabdominal probe and 3D power Doppler technology".

Blood flow in placenta was examined using 3D power Doppler technique. The whole placenta was put inside the region of interest, then the power Doppler was applied to the whole placenta then analyzed with the virtual organ computer-aided analysis program (VOCAL; GE) to obtain the vascularization index (VI) (VI; the ratio between color voxels and total voxels expressed in percentages), flow index (FI) (FI; the sum of the color voxels' signal intensity divided by the number of color voxels, quantified between 0 and 100), and vascularization flow index (VFI) (VFI; the sum of color voxels' signal intensity divided by the total tissue voxels, quantified between 0 and 100).

Uterine artery pulsatility index:
The participants were asked to empty the bladder before the examinations and were placed in the dorsal lithotomy position. The left and right Uterine arteries were examined at the level of the internal cervical os by color and pulsed Doppler trans-vaginally and the mean PI was recorded.

Follow-up:
Patients were followed up to the end of their pregnancies and their medical files reviewed to obtain the outcome data. The outcome data were whether patients developed preeclampsia and other hypertensive disorders. Preeclampsia and other hypertensive disorders were defined using guidelines of the American College of Obstetricians and Gynecology (The American Congress of Obstetricians and Gynecologists, 2013). Preeclampsia was defined as (Roberts et al, 2013):

- Blood pressure: greater than or equal to 140 mmHg systolic, or greater than or equal to 90 mmHg diastolic on two occasions at least 4 hours apart after 20 weeks of gestation.
- Proteinuria of at least +1 on urine dipstick.

Statistical analysis:

Recorded data were analyzed using the statistical package for social sciences, version 20.0 (SPSS Inc., Chicago, Illinois, USA). Quantitative data were expressed as mean± standard deviation (SD). Qualitative data were expressed as frequency and percentage.

The following tests were done:

- Independent-samples t-test of significance was used when comparing between two means.
- Chi-square (χ^2) test of significance was used in order to compare proportions between qualitative parameters.
- Fisher's exact test: was used to examine the relationship between two qualitative variables when the expected count is less than 5 in more than 20% of cells, while Fisher's exact test is more accurate than the chi-squared test when the expected numbers are small.
- Receiver operating characteristic (ROC curve) analysis was used to find out the overall predictivity of parameter in and to find out the best cut-off value with detection of sensitivity and specificity at this cut-off value.
  - Sensitivity = (true +ve)/ [(true +ve) + (false –ve)].
  - Specificity = (true –ve) / [(true –ve) + (false +ve)].
  - PPV = (true +ve) / [(true +ve) + (false +ve)].
  - NPV = (true –ve)/ [(true –ve) + (false –ve)].
  - Accuracy = (TP+TN)/[TP+FP+TN+FN]
- Multivariate logistic regression Odds Ratios (OR) with 95% confidence intervals were computed to assess the overall association between each possible variable and the occurrence of preeclampsia.
- The confidence interval was set to 95% and the margin of error accepted was set to 5%. So, the p-value was considered significant as the following:
- Probability (P-value)
  - P-value <0.05 was considered significant.
  - P-value <0.001 was considered as highly significant.
  - P-value >0.05 was considered insignificant.

Results

Table 1
Comparison between high risk group and control group according to their demographic data regarding age and BMI and parity

Demographic data	High-risk Group (n=100)	Control Group (n=100)	Test	p-value
Age (years)				
Range	20-45	20-39	t=1.855	0.065
Mean±SD	33.48±8.69	31.39±7.17		
BMI [wegith/(ht)^2]				
Range	24-37	23-34	t=1.927	0.055
Mean±SD	31.02±4.34	29.86±4.17		
Parity				
Range	0-2	1-3	z=7.386	<0.001**
Median (IQR)	1 (0-1)	2 (1-2)		
Nulliparous	55 (55%)	0 (0%)	*FE*=73.129	<0.001**
Multiparous	45 (45%)	100 (100%)		

Using: t-Independent Sample t-test; z-Mann-Whitney test; FE: Fisher's Exact
*P-value>0.05 NS; *p-value <0.05 S; **p-value <0.001 HS*

The two groups were comparable in age with the mean Age ±SD in the high risk Group and Control Group was 33.48±8.69 and 31.39±7.17 respectively, there is no statistically significant difference between the two groups with (p-value 0.065). Also, this table shows that they were comparable in BMI with the mean BMI±SD in each of High risk Group and Control Group was 31.02±4.34 and 29.86±4.17 respectively, there is no statistically significant difference between the two groups with (p-value 0.055). However, results shows that there was a highly statistically significant difference between two groups according to parity (p<0.001). The highest value was found in Control Group 2 (1-2) compared to High-risk Group 1 (0-1).

Table 2
Comparison between high risk group and control group according to their 3D power Doppler regarding Vascularization Index (VI), Flow Index (FI) and Vascularization flow index (VFI)

3D power Doppler	High-risk Group (n=100)	Control Group (n=100)	t-test	p-value
Vascularization Index (VI)	8.69±1.45	9.07±1.55	1.790	0.075
Flow Index (FI)	42.55±7.11	44.40±8.11	1.715	0.088
Vascularization flow index (VFI)	3.58±0.86	3.80±0.86	1.809	0.072

Using: t-Independent Sample t-test; p-value>0.05 NS

The two groups were comparable in V.I with the mean V.I.±SD in each of High risk Group and Control Group was 8.69±1.45 and 9.07±1.55 respectively, there is no statistically significant difference between the two groups with (p-value 0.075). Also, this table shows that they were comparable in F.I. with the mean F.I.±SD in each of High risk Group and Control Group was 42.55±7.11 and 44.40±8.11 respectively, there is no statistically significant difference between the two groups with (p-value 0.088). Moreover, this table also shows that both groups were comparable in V.F.I with the mean V.F.I.±SD in each of High risk Group and Control Group was 3.58±0.86 and 3.80±0.86 respectively, there is no statistically significant difference between the two groups with (p-value 0.072).

Table 3
Comparison between high risk group and control group according to their uterine artery PI

Uterine Artery	High-risk Group (n=100)	Control Group (n=100)	t-test	p-value
Pulsatility Index (PI)	1.63±0.43	1.54±0.43	1.480	0.141

Using: t-Independent Sample t-test; p-value>0.05 NS

Both groups were comparable in Uterine Artery with the mean P.I.±SD in each of High risk Group and Control Group was 1.63±0.43 compared to 1.54±0.43 respectively, there is no statistically significant difference between the two groups with (p-value 0.141).

Table 4
Comparison between high risk group and control group according to preeclampsia

Preeclampsia	High-risk Group (n=100)	Control Group (n=100)	χ^2	p-value
Preeclampsia	10 (10%)	7 (7%)	0.257	0.612
Normotensive	90 (90%)	93 (93%)		

Using: χ^2 Chi-square test; p-value>0.05 NS
Relative risk 1.429 C.I. 95% (0.566-3.604)

The table clarifies that development of Preeclampsia was comparable in each of High risk group (10 patients "10 %") compared to (7 patients "7 %") in the control group, there is no statistically significant difference between the two groups with (p>0.05 non-significant).

Table 5
Comparison between preeclampsia group and normotensive group according to Vascularization Index, Flow Index, Vascularization flow index and Pulsatility index in high risk group

	Preeclampsia Group (n=10)	Normotensive Group (n=90)	t-test	p-value
3D power Doppler				
Vascularization Index (VI)	7.19±0.79	9.59±1.71	4.371	<0.001**
Flow Index (FI)	37.86±5.05	45.23±5.16	4.293	<0.001**
Vascularization flow index (VFI)	2.69±0.66	4.27±1.05	4.645	<0.001**
Uterine Artery				
Pulsatility Index (PI)	2.12±0.55	1.13±0.30	8.975	<0.001**

*Using: t-Independent Sample t-test; **p-value <0.001 HS*

There was a statistically significant difference between two groups according to Vascularization Index (VI) (p<0.001). The highest value was found in Normotensive Group (9.59±1.71) compared to Preeclampsia Group (7.19±0.79). Also, this table shows that there was a statistically significant difference between two groups according to Flow Index (FI) (p<0.001). The highest value was found in Normotensive Group (45.23±5.16) compared to Preeclampsia Group (37.86±5.05).

Moreover, results shows that, there was a statistically significant difference between two groups according to Vascularization flow Index (VFI) (p<0.001). The highest value was found in Normotensive Group (4.27±1.05) compared to Preeclampsia Group (2.69±0.66). Regards uterine artery (PI), Table shows that there was a statistically significant difference between two groups according to Pulsatility Index (PI) (p<0.001). The highest value was found in Preeclampsia Group (2.12±0.55) compared to Normotensive Group (1.13±0.30).

Table 6
Comparison between preeclampsia group and normotensive group according to Vascularization Index, Flow Index, Vascularization flow index and Pulsatility index in control group

	Preeclampsia Group (n=7)	Normotensive Group (n=93)	t-test	p-value
3D power Doppler				
Vascularization Index (VI)	7.85±0.79	10.48±1.71	4.790	<0.001**
Flow Index (FI)	41.37±5.05	49.43±5.16	4.695	<0.001**
Vascularization flow index (VFI)	2.94±0.66	4.66±1.05	5.057	<0.001**
Uterine Artery				
Pulsatility Index (PI)	1.97±0.55	1.05±0.30	8.340	<0.001**

*Using: t-Independent Sample t-test; **p-value <0.001 HS*

There was a statistically significant difference between two groups according to Vascularization Index (VI) (p<0.001). The highest value was found in Normotensive Group (10.48±1.71) compared to Preeclampsia Group (7.85±0.79). Also, this table shows that, there was a statistically significant difference between two groups according to Flow Index (FI) (p<0.001). The highest value was found in Normotensive Group (49.43±5.16) compared to Preeclampsia Group (41.37±5.05).

Moreover, results shows that, there was a statistically significant difference between two groups according to Vascularization flow Index (VFI) (p<0.001). The highest value was found in Normotensive Group (4.66±1.05) compared to Preeclampsia Group (2.94±0.66). Regards uterine artery (PI), Table shows that, there was a statistically significant difference between two groups according to Pulsatility Index (PI) (p<0.001). The highest value was found in Preeclampsia Group (1.97±0.55) compared to Normotensive Group (1.05±0.30).

Table 7
Comparison between preeclampsia group and normotensive group according to Vascularization Index, Flow Index, Vascularization flow index and Pulsatility index in all women's

	Preeclampsia Group (n=17)	Normotensive Group (n=183)	t-test	p-value
3D power Doppler				
Vascularization Index (VI)	7.52±0.79	10.04±1.71	4.590	<0.001**
Flow Index (FI)	39.62±5.05	47.33±5.16	4.491	<0.001**
Vascularization flow index (VFI)	2.82±0.66	4.47±1.05	4.851	<0.001**
Uterine Artery				
Pulsatility Index (PI)	2.05±0.55	1.09±0.30	8.703	<0.001**

*Using: t-Independent Sample t-test; **p-value <0.001 HS*

There was a statistically significant difference between two groups according to Vascularization Index (VI) (p<0.001). The highest value was found in Normotensive Group (10.04±1.71) compared to Preeclampsia Group (7.52±0.79). This table shows also that, there was a statistically significant difference between

two groups according to Flow Index (FI) (p<0.001). The highest value was found in Normotensive Group (47.33±5.16) compared to Preeclampsia Group (39.62±5.05).

Results also shows that, there was a statistically significant difference between two groups according to Vascularization flow Index (VFI) (p<0.001). The highest value was found in Normotensive Group (4.47±1.05) compared to Preeclampsia Group (2.82±0.66). Table shows that, there was a statistically significant difference between two groups according to Pulsatility Index (PI) (p<0.001). The highest value was found in Preeclampsia Group (2.05±0.55) compared to Normotensive Group (1.09±0.30).

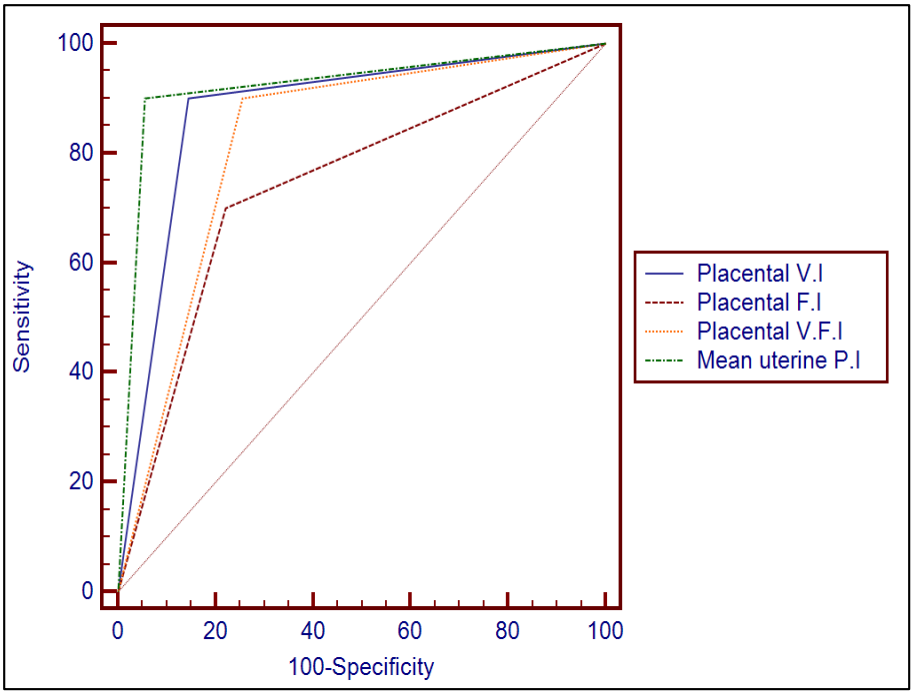

Figure 1. Receiver-operating characteristic (ROC) curve for early prediction of preeclampsia using the placental 3D power Doppler and uterine artery pulsatility index in High-risk Group

	Cut-off	Sen.	Spe.	PPV	NPV	AUC [95% C.I.]	p-value
Placental V.I	8.03	90%	85.6%	58.9%	98.0%	0.878 [0.797 to 0.935]	<0.001**
Placental F.I	39.72	70%	77.7%	45.9%	95.9%	0.739 [0.641 to 0.822]	0.024*
Placental V.F.I	3.53	90%	74.4%	48.1%	96.5%	0.822 [0.733 to 0.891]	<0.001**
Mean uterine P.I	1.54	90%	94.4%	64.3%	99.8%	0.922 [0.851 to 0.966]	<0.001**

Receiver operator characteristics (ROC) curves were constructed for placental vascular indices and uterine artery PI as early predictors of preeclampsia in included High-risk Group. Placental and uterine artery indices were significant discriminative as denoted by the significantly large area under the curves (AUCs); with PI being the most significant discrimination, with p-value <0.001 highly significant prediction of preeclampsia.

There is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve, while, significant difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I was the most predictive of preeclampsia, followed by Placental V.I. and Placental V.F.I. and so they were able to predict cases and there are slight differences between them.

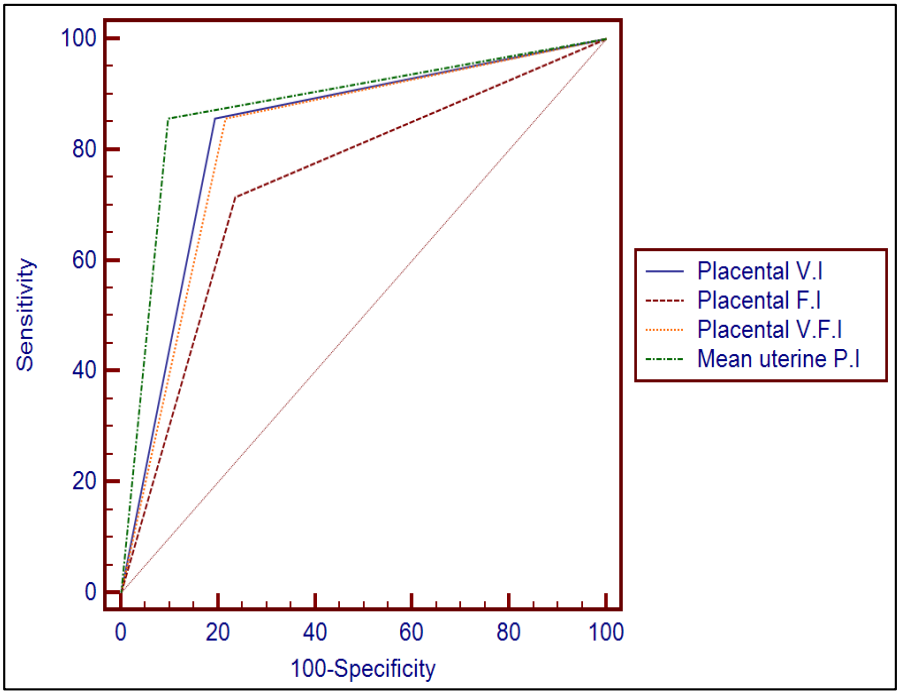

Figure 2. Receiver-operating characteristic (ROC) curve for early prediction of preeclampsia using the placental 3D power Doppler and uterine artery pulsatility index in control group

	Cut-off	Sen.	Spe.	PPV	NPV	AUC [95% C.I.]	p-value
Placental V.I	8.89	85.7%	80.7%	45%	98.7%	0.832 [0.744 to 0.899]	<0.001**
Placental F.I	43.95	71.4%	76.3%	28.5%	97.3%	0.739 [0.641 to 0.822]	0.016*
Placental V.F.I	3.91	85.7%	78.5%	33.1%	98.6%	0.821 [0.732 to 0.891]	<0.001**
Mean uterine P.I	1.39	85.7%	90.3%	50%	98.8%	0.880 [0.800 to 0.937]	<0.001**

Receiver operator characteristics (ROC) curves were constructed for placental vascular indices and uterine artery PI as early predictors of preeclampsia in included control group. Placental and uterine artery indices were significant discriminative as denoted by the significantly large area under the curves (AUCs); with PI being the most significant discrimination, with p-value <0.001 highly significant prediction of preeclampsia.

There is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve, while, significant

difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I was the most predictive for preeclampsia, followed by Placental V.I. and Placental V.F.I. and so they were able to predict cases and there are slight differences between them.

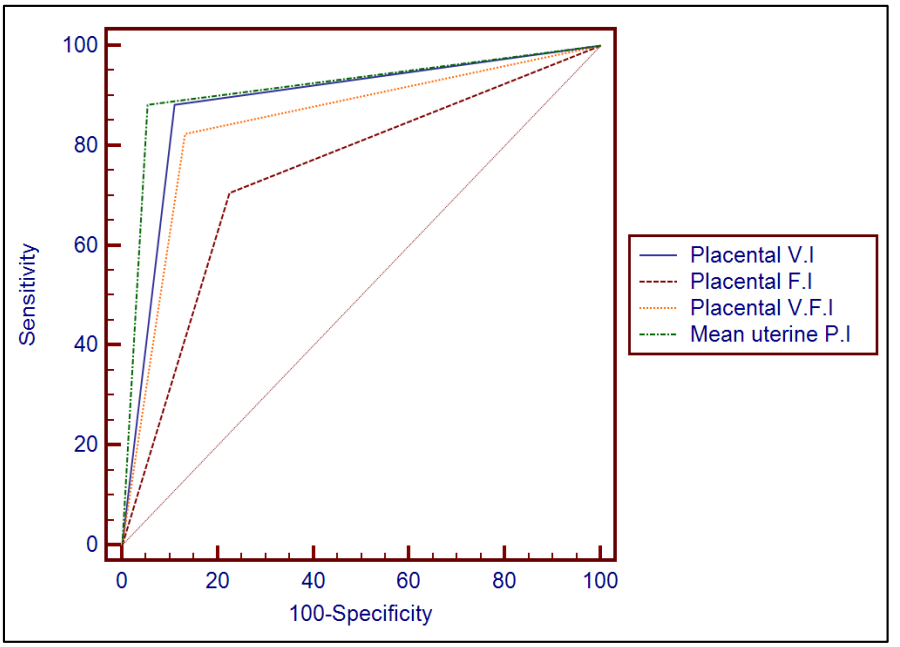

Figure 2. Receiver-operating characteristic (ROC) curve for early prediction of preeclampsia using the placental 3D power Doppler and uterine artery pulsatility index in all women

	Cut-off	Sen.	Spe.	PPV	NPV	AUC [95% C.I.]	p-value
Placental V.I	8.46	88.2%	89.1%	42.9%	98.8%	0.887 [0.794 to 0.979]	<0.001**
Placental F.I	41.83	70.6%	77.0%	22.2%	96.6%	0.741 [0.610 to 0.871]	<0.001**
Placental V.F.I	3.72	82.4%	86.9%	36.8%	98.1%	0.846 [0.737 to 0.955]	<0.001**
Mean uterine P.I	1.47	88.2%	91.8%	50.0%	98.8%	0.914 [0.823 to 1.000]	<0.001**

Receiver operator characteristics (ROC) curves were constructed for placental vascular indices and uterine artery PI as early predictors of preeclampsia in included all women. Placental and uterine artery indices were significant discriminative as denoted by the significantly large area under the curves (AUCs); with PI being the most significant one, with p-value <0.001 highly significant prediction of preeclampsia.

There is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve, while, significant difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I was the most predictive of preeclampsia, followed by Placental V.I. and Placental V.F.I. and so they were able to predict cases and there are slight differences between them.

Table 8
Pairwise comparison of ROC curves

Placental V.I ~ Placental F.I	
Difference between areas	0.146
Standard Error[c]	0.0491
z statistic	2.966
Significance level	P = 0.0030
Placental V.I ~ Placental V.F.I	
Difference between areas	0.0403
Standard Error[c]	0.0299
z statistic	1.349
Significance level	P = 0.1774
Placental V.I ~ Mean uterine P.I	
Difference between areas	0.0273
Standard Error[c]	0.00842
z statistic	3.243
Significance level	P = 0.0612
Placental F.I ~ Placental V.F.I	
Difference between areas	0.105
Standard Error[c]	0.0417
z statistic	2.525
Significance level	P = 0.0116
Placental F.I ~ Mean uterine P.I	
Difference between areas	0.173
Standard Error[c]	0.0496
z statistic	3.484
Significance level	P = 0.0005
Placental V.F.I ~ Mean uterine P.I	
Difference between areas	0.0677
Standard Error[c]	0.0310
z statistic	2.181
Significance level	P = 0.092

p-value>0.05 NS; p-value <0.05 significant

There is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve, while, significant difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I the most predictive of preeclampsia, followed by Placental V.I. and Placental V.F.I. so, they were able to predict cases and there are slight differences between them.

Table 9
Regression model for prediction of Preeclampsia using placental 3D power Doppler and uterine artery pulsatility index

	Odds ratio	95% C.I.		p-value
		Lower	Upper	
Placental V.I	0.319	0.154	0.658	<0.001**
Placental F.I	0.645	0.301	1.383	0.511
Placental V.F.I	1.948	0.936	2.174	0.027*
Mean uterine P.I	5.198	1.596	16.925	<0.001**

Multivariate analysis revealed that significant early predictors of preeclampsia were Placental V.I, Placental V.F.I and Mean uterine P.I. with (95% CI)Odds ratios (OR) were [0.319 (0.154 0.658) with p-value <0.001**; 1.948 (0.936 2.174) with p-value 0.027* and 5.198 (1.596 16.925) with p-value <0.001**] respectively, while Placental FI was not found as a significant predictors.

Discussion

Analysis of the study results showed the absence of any statistically-significant difference between women who subsequently developed preeclampsia and women with unaffected pregnancies as regards general demographic data including age and maternal weight. However, there was a highly statistically significant difference between the two groups according to parity (p<0.001). The highest value was found in Control Group 2 (1-2) compared to High-risk Group 1 (0-1). This is because the primigravida was considered as a risk factor for developing pre-eclampsia in our study.

Luo et al. (2007), reported that the nulliparous women are at risk of pre-eclampsia 2.42 times higher than multiparous women through a meta-analysis that comprised 26 studies. There was no statistically significant difference between both groups regards vascularization (VI), flow (FI), vascularization flow (VFI) indices and uterine artery (PI). In our study, vascularization, flow and vascularization flow indices were found to be significantly lower in patients who developed preeclampsia in both groups denoting the impaired vascular invasion at the maternal-placental interface.

In the control group (no risk factor):
Women who developed preeclampsia the mean VI was 7.85±0.79 compared with 10.48±1.71 in women who did not develop preeclampsia (p<0.001). The mean FI was 41.37±5.05 in women who developed preeclampsia and 49.43±5.16 in unaffected women (p<0.001) and the mean VFI was 2.94±0.66 in women who developed preeclampsia and 4.66±1.05 in unaffected women (p<0.001).

In the case group (with any risk factor):
Women who developed preeclampsia the mean VI was 7.19±0.79 compared with 9.59±1.71 in women who did not develop preeclampsia (p<0.001). The mean FI was 37.86±5.05 in women who developed preeclampsia and 45.23±5.16 in unaffected women (p<0.001) and the mean VFI was 2.69±0.66 in women who developed preeclampsia and 4.27±1.05 in unaffected women (p<0.001). Low VI values are interpreted as a decrease in the number of vessels within the placenta. The decreased

FI values can be viewed as a reduction in placental blood flow by increasing placental resistance. VFI low values show a decrease in the number of vessels in the placenta, as well as a reduction of blood flow at this level. The three indices being reduced show that there is a reduction in speed, intensity and placental blood perfusion (Demers et al., 2015).

These data are consistent with the current knowledge of the pathophysiology of the placenta mediated disorders. Several authors have studied first-trimester placental vascularization and uterine artery PI for the prediction of preeclampsia.

Demers and his colleagues in their cohort study of 1,034 pregnant women who were prospectively assessed using three-dimensional ultrasound between 10 weeks and 6 days and 13 weeks and 6 days in predicting preeclampsia and small for gestational age. 3D power Doppler disclosed that women with preeclampsia or small for gestational age were associated with a significantly lower VI, FI and VFI, in the first trimester compared with women with term deliveries without any complications (all $p < 0.05$). The comparison of mean values in the normal group and the preeclamptic group was:

VI 6.4 (4.0–9.1) and 4.0 (1.1–6.0)
FI 45.1 (41.3–48.9) and 41.7 (34.6–46.5)
VFI 2.9 (1.8–4.3) and 1.4 (0.4–2.5) *(Demers et al., 2015).*

In 2010, *Hafner and colleagues* also demonstrated a correlation between placental volume and placental vascular indices and unfavorable pregnancy outcomes. 3D power Doppler vascularization index (VI) and flow index (FI) of the entire placenta and the neighboring myometrium were measured in the first trimester in 383 women with singleton pregnancies during a period of three months. In addition they measured placental volume. They found that preeclampsia was seen in 10 cases, gestational hypertension in 7 cases, preterm delivery in 13cases and SGA in 41cases with the mean values of the VI and VFI were significantly lower in the pregnancies that developed preeclampsia but not in gestational hypertension or SGA or preterm labor (Hafner et al., 2010).

Also, in the same context, our results were matched with those of Dar and his co-worker (2010) who prospectively studied 277 women at 10 weeks 4 days to 13 weeks 6 days. All first trimester 3DPD flow indices were significantly lower in patients who subsequently developed preeclampsia as compared with unaffected pregnancies (mean ± SD): Pre-eclampsia VI = 17.0 ± 7.2 Vs no pre-eclampsia VI = 23.7 ± 10.6 ($P < 0.001$). Pre-eclampsia FI = 47.0 ± 6.9 Vs no preeclampsia FI = 52.6 ± 8.3, ($P < 0.001$). Pre-eclampsia VFI = 8.3 ± 3.8 vs no preeclampsia VFI = 12.9 ± 7.1 ($P < 0.002$) (Dar et al., 2010).

We also compared our study to that of Costa and his colleagues who conducted a study on 26 women with normalpregnancy and 17 women with PE where they concludedsimilar results to ours as they found that VI, FI and VFI werelower in PE compared to normal pregnancy (Costa et al., 2010). On the other hand, Moreira Neto and Ramos conducted a prospective, observational study using 3D powerDoppler to evaluate the placental perfusion in 96 pregnantwomen who came to do the ultrasound routine between 11 and14 weeks. The placental vascular index (VI), flow

index (FI),blood vessels and blood flow index (VFI) by three-dimensionalDoppler histogram were calculated. All patients repeated theexam between 16 and 20 weeks. The outcome was scored asnormal or pre-eclamptic. The study results showed that placentalvascular indices including VI, FI and VFI were significantlylower in pre-eclamptic placentas compared with controls in thestudy performed in the second trimester ($p < 0.001$). There was*not any statistical difference* in the patients examined in the firsttrimester (Neto and Ramos, 2016).

Moreover, one of the most recent studies by Soliman et al. (2019) revealed high and remarkable differences between pre-eclamptic and normal women in both placental VI and VFI ($p = 0.03$). However, there was no significant observed difference in the placental FI. Uterine artery Doppler assessment is regarded as a promising screening tool for the prediction of pre-eclampsia in the first trimester (Zhong et. al. 2010). It has been used to identify the at-risk population between 11 and 14 weeks of pregnancy (Townsend et. al. 2016). In our study, uterine artery (UtA) pulsatility index (PI) was found to be significantly higher in patients who developed preeclampsia in both groups.

In the control group (no risk factor):
The mean uterine artery (UtA) pulsatility index (PI) was 1.97±0.55 compared with 1.05±0.30 in women who did not develop preeclampsia ($p<0.001$). In the case group (with any risk factor):
The mean uterine artery (UtA) pulsatility index (PI) was 2.12±0.55 compared with 1.13±0.30 in women who did not develop preeclampsia ($p<0.001$). High (UtA) pulsatility index (PI) measured by Doppler's ultrasound means an indirect measure of placental vascular resistance which is usually increased in cases of incomplete transformation of uterine spiral arteries (Papageorghiou et. al. 2004).
The uterine artery Doppler results in our study are in agreement with Khalil et al., 2010 who were investigating the predictive values of first-trimester uterine artery PI and RI in assessments of at-risk women for pre-eclampsia.
They found that PI and RI increased significantly in the presence of pre-eclampsia. They concluded that the mean value of PI and pulse-wave analysis could help in the prediction of pre-eclampsia in women at increased risk (Khalil et al., 2010).
Also, in the same context, our results were matched with those of Demers et al. (2019) out of 4,676 participants with completed follow-up, 232 (4.9%) developed PE, including 202 (4.3%) term and 30 (0.6%) preterm PE. Mean UtA-PI decreased with gestational age between 11 and 13 6/7 weeks ($p < 0.001$).

- Patients did not develop PE: mean uterine PI 1.6
- Patients developed term PE: mean PI 1.6 ($p < 0.12$)
- Patients developed preterm PE: mean PI 2.2 ($p < 0.001$)

We also compared our study to that of Salem and Ammar (2018) who conducted a study on 270 women with normalpregnancy and 30 women with PE where they concludedsimilar results to ours as they found that:

Pre-eclampsia PI = 2.4 ± 0.2 Vs no pre-eclampsia PI = 1.4 ± 0.4 ($P < 0.001$)

In a study by Gomaa et al. (2015), they found that at 11–13 weeks of pregnancy the mean PI of uterine arteries was significantly higher in pre-eclamptic (2.46 ± 0.28)

than in normal women (1.435 ± 0.45), and this is similar to our results. In our study (both groups) receiver operator characteristics (ROC) curves were constructed for placental vascular indices and uterine artery PI as early predictors of preeclampsia. Placental and uterine artery indices were good predictors as denoted by the significantly large area under the curves (AUCs); with PI being the most significant discrimination, with p-value <0.001 highly significant prediction of preeclampsia.

There is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve, while, significant difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I was the most predictive for preeclampsia, followed by Placental V.I. and Placental V.F.I. and so they were able to predict cases and there are slight differences between them.

In the control group (no risk factor):
The area under the ROC curve for theprediction of preeclampsia was 0.83, 0.73, 0.82 and 0.88 for VI, FI, VFI and PI respectively.

In the case group (with any/ risk factor):
The area under the ROC curve for theprediction of preeclampsia was 0.87, 0.73, 0.82 and 0.92 for VI, FI, VFI and PI respectively.

This result was matched with those of Dar and his co-workers (2010) who studied 277 women enrolled, 24 developed preeclampsia. The 3DPD indices were lower in women who developed preeclampsia. The area under the receiver-operating characteristics curve for the prediction of preeclampsia was 78.9%, 77.6%, and 79.6% for VI, FI, and VFI, respectively (Dar et al., 2010). Also it was matched with those of Odibo and colleagues. They found that the mean values of the VI and VFI were significantly lower in the pregnancies that developedpreeclampsia with the area under the ROC curve for theprediction of preeclampsia was 0.71, 069 and 0.70 for VI, FI andVFI respectively (Odibo et al., 2011).

Song et al. (2019) reported that the PI was the best candidate for pre-eclampsia prediction with an AUC of 0.987 which was close to our results. Moreover, Erdoğdu et al. (2014) conducted a study at the same stage of pregnancy (11–14 weeks), to investigate the role of uterine artery Doppler in the prediction of pre-eclampsia during the first trimester. They determined the uterine artery PI value by the ROC curve. They had report that AUC was 0.83($p < 0.001$).

Pairwise comparison of ROC curves of this study revealed that there is no statistically significant difference between (Placental V.I, Placental V.F.I and Mean uterine P.I) regarding area under the curve. While there is a significant difference of AUC compared Placental F.I. with (p-value <0.05), this indicates that the Mean Uterine P.I was the most predictive for preeclampsia, followed by Placental V.I. and Placental V.F.I.

Conclusions

In conclusion, 3D power Doppler assessment of placental vascularization and uterine artery pulsatility index may provide new insights into normal and abnormal feto-

placental hemodynamics. 3D power Doppler and Uterine artery PI emerge as a valuable noninvasive tools to study patho-physiological changes that occur in the uteroplacental circulation early in pregnancy.

It appears that during the first trimester, patients who subsequently develop adverse pregnancy outcomes like preeclampsia have lower 3D power Doppler indices in this key space. Also, they have higher uterine artery PI. Using this methodology has the potential to improve screening for preeclampsia in the future.

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